Journal of Medical Ultrasound (2017) **25**, 150—156

Chinese Taipei Society of Ultrasound in Medicine

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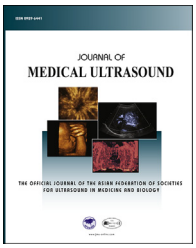

ORIGINAL ARTICLE

Ultrasonographic Evaluation of Lower Extremity Entheseal Sites in Diabetic Patients Using Glasgow Ultrasound Enthesitis Scoring System Score

Sibel Caglar Okur [1]*, Yasemin Pekin Dogan [1], Murat Mert [2], Ozge Aksu [1], Ozer Burnaz [1], Nil Sayiner Caglar [1]

[1] *Physical Medicine and Rehabilitation Unit, Istanbul Training and Research Hospital, and* [2] *Department of Orthopedics and Traumatology, Yeni Yüzyıl University, Istanbul, Turkey*

Received 29 September 2016; accepted 1 March 2017
Available online 6 May 2017

KEYWORDS
diabetes mellitus,
enthesitis,
Glasgow Ultrasound Enthesitis Scoring System,
lower limb,
ultrasound

Abstract *Objective:* The prevalence of musculoskeletal complications in diabetes mellitus (DM) increases with the duration of disease and with poor glycemic control. Our aim was to evaluate lower extremity musculoskeletal complications in patients with DM using the Glasgow Ultrasound Enthesitis Scoring System, and to reveal the relationship between clinical and sonographic findings.
Materials and methods: A total of 67 patients (25 men, 42 women) with DM were included in the study. All the diabetic patients were selected if they did not have any symptom of musculoskeletal system in the lower extremities. They were divided into four groups. Ultrasonographic assessment was performed according to the Glasgow Ultrasound Enthesitis Scoring System with an Esaote MyLab 5 device equipped with a 5—13 MHz linear transducer. Correlation between diabetes duration and lower extremity enthesopathy scores were evaluated.
Results: There was a significant correlation between duration of DM and total Glasgow Ultrasound Enthesitis Scoring System scores ($p < 0.001$). In addition, duration of DM was significantly correlated with enthesophyte scores and erosion scores (both $p < 0.001$). There was a significant difference among Groups 1—4 for the mean enthesophyte score and mean erosion score (both, $p < 0.001$).

Conflicts of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be a potential conflict of interest. Sibel Caglar Okur, Yasemin Pekin Dogan, Murat Mert, Ozge Aksu, Ozer Burnaz, Nil Sayiner Caglar declare that they have no conflicts of interest.

* Correspondence to: Dr Sibel Caglar Okur, Istanbul Training and Research Hospital, Kasap Ilyas Mh. Org. Abdurraman Nafiz Gurman Cd, Fatih, Istanbul PK: 34098, Turkey.
E-mail address: sibelcaglarokur@gmail.com (S.C. Okur).

http://dx.doi.org/10.1016/j.jmu.2017.03.011

Conclusion: Musculoskeletal ultrasonography is an effective, inexpensive, and useful tool without radiation for evaluating diabetic patients for the early diagnosis of musculoskeletal complications.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, which results from defects in insulin secretion, insulin action, or both [1]. DM impacts the connective tissue and causes various changes in periarticular and articular structures. Both increase in DM incidence and extension of living period in DM patients lead to a more common observation of musculoskeletal problems in these patients. Metabolic disorders such as protein glycosylation, microvascular anomalies, and collagen accumulation in the skin and periarticular structures may be the reason of changes in the musculoskeletal system [1—6]. Many studies inspected the musculoskeletal complications of DM patients. An increase in enthesopathic complications, such as diabetic cheiroarthropathy in the upper extremity, Dupuytren's contracture, adhesive capsulitis on shoulder, flexor tenosynovitis and carpal tunnel syndrome, diffuse idiopathic skeletal hyperostosis on the spine, diabetic muscle infarcts at the lower extremity, patellar tendinitis and bursitis, Achilles tendinopathy, plantar fasciitis, and epin calcanei, was observed [3—8]. The frequency of osteoarthritis for both minor and major joints was found to be higher particularly in Type 2 DM patients compared with controls as well as earlier development and higher severity [9—12]. Prolongation of the diabetes period increases the strength of complications [13—15].

The prevalence of tendinopathies is increased in patients with DM compared with euglycemic controls [6,16—20]. Several studies have shown increased thickness and stiffness of the plantar fascia and Achilles tendon in Type 2 DM patients [9,16]. Furthermore, a small number of radiological studies assessed quadriceps and patellar tendons, and showed the influence of diabetic status [21—23]. A few case presentations indicating spontaneous quadriceps tendon rupture were reported for DM patients [24,25]. DM affects bursas, enthesis zones, and periosteumeum together with tendons, and it may cause damage [15,24,26].

Conventional radiography, ultrasonography, and magnetic resonance imaging are used to diagnose tendinopathies, bursitis, and other morphologic pathologies of musculoskeletal system. Musculoskeletal ultrasonography is a widely available and inexpensive imaging tool, and demonstrates fluid collections, soft tissue lesions, and bone surface lesions with sensitivity comparable with magnetic resonance imaging. Sonographic examination is more sensitive and specific than clinical examination for the detection of enthesitis and tendon involvement [26—29].

The Glasgow Ultrasound Enthesitis Scoring System (GUESS) is a validated and useful tool for quantifying ultrasonographic findings (Table 1). It is composed of assessments of degenerative changes such as tendon thickness, existence of enthesitis, bursitis, or erosions [27].

DM is an endocrinologic disorder that has been shown to increase the risk of musculoskeletal diseases such as tendinopathies, bursitis, erosions, and enthesitis. We aimed to investigate the correlation between DM duration and lower extremity musculoskeletal findings with using an ultrasonographic scoring system.

In our study, we examined the relation between clinical features of DM participants such as diagnosis duration, sex, body mass index, fasting blood glucose and glycosylated hemoglobin (HbA1c) levels, and GUESS scores, which can provide demonstration of involvements of frequently effected lower extremity enthesal sites with ultrasonography.

Materials and methods

This study was carried out from March 7, 2015 to March 30, 2016 in the outpatient clinics of physical medicine and

Table 1 Glasgow Ultrasound Enthesitis Scoring System.

Superior pole of the patella—quadriceps tendon enthesis
Quadriceps tendon thickness >6.1 mm
Suprapatellar bursitis
Superior pole of patella erosion
Superior pole of patella enthesophyte
Inferior pole of the patella—proximal patellar ligament enthesis
Patellar ligament thickness >4 mm
Inferior pole of patella erosion
Inferior pole of patella enthesophyte
Tibial tuberosity—distal patellar ligament enthesis
Patellar ligament thickness >4 mm
Infrapatellar bursitis
Tibial tuberosity erosion
Tibial tuberosity enthesophyte
Superior pole of the calcaneus—Achilles tendon enthesis
Achilles tendon thickness >5.29 mm
Retrocalcaneal bursitis
Posterior pole of calcaneus erosion
Posterior pole of calcaneus enthesophyte
Inferior pole of the calcaneus—plantar aponeurosis enthesis
Plantar aponeurosis thickness >4.4 mm
Inferior pole of calcaneus erosion
Inferior pole of calcaneus enthesophyte

Each item scores 1 point. The total possible score for both lower extremities is 36.

rehabilitation clinic at Istanbul Training & Research Hospital.

Study design and population

Patients with DM who were followed up at the endocrinology and metabolism clinics of Istanbul Training and Research Hospital formed our study group.

The inclusion criteria were as follows:

- Having diagnosis of Type 2 DM for a minimum of 3 years
- Age >18 years
- Body mass index <25 kg/m^2
- Not having any of the musculoskeletal symptoms of pain, limitation of range of motion, erythema, swelling, or edema in the lower limbs

Participants with a diagnosis duration of DM of <3 years; with a history of lower extremity operations; who were exposed to any trauma that might damage the anatomic structure of the lower extremities; with Type 1 DM; who have another endocrinologic disease (thyroid disorders, mucopolysaccharidosis, etc.); who have chronic kidney disease and are undergoing dialysis treatment; with diabetic complications such as retinopathy, nephropathy, or neuropathy; and whose body mass index is 25 kg/m^2 and higher were not included in the study.

The present study has been approved by the Local Ethics Committee (IRB number DI-123-912-423).

Imaging study

Sonographic examinations were performed by an experienced physiatrist trained in musculoskeletal ultrasonography using an Esaote Biomedica MyLab 5 system (Esaote SpA, Genoa, Italy) equipped with a 5–13 MHz linear transducer. All sonographic examinations were performed by this same clinician who did not have any clinical information about the participants' disease durations.

Sonographic evaluations and scoring were performed according to the GUESS, which includes evaluation of the quadriceps tendon, patellar ligament, Achilles tendon, plantar fascia thickness, enthesophytes and erosions at the origin, and attachment sites of the tendons listed above. Suprapatellar, infrapatellar, and retrocalcaneal bursae were also evaluated. Examination of the superior pole of the patella (quadriceps tendon insertion), inferior pole of the patella (patellar ligament origin), and patellar ligament insertion at the tibial tuberosity was performed with the patient in the supine position with the knees flexed at 30°. For the examination of the Achilles tendon and plantar aponeurosis, the patient was in the prone position with the feet hanging over the edge of the examination table at 90° flexion.

Bony erosion was defined as discontinuity of the cortex with a defect; an enthesophyte was defined as a bony prominence at the end of normal bone contour. Thickness of ligaments, fascias, and tendons was measured at the point of maximum thickness proximal to the bony insertion. The following GUESS values were used for tendon/ligament thickening: 6.1 mm for quadriceps tendon, 4 mm for proximal and distal patellar ligament, 5.3 mm for Achilles tendon, and 4.4 mm for plantar fascia. Bursitis was defined as a well-circumscribed, localized anechoic or hypoechoic compressible area at the site of an anatomical bursa. Tendon thickness and the presence or absence of bony erosion, enthesophyte, and bursitis were recorded for each site. One point was scored for each abnormal entheseal site, with a maximum score of 18 for each lower limb examined (Table 1). The total GUESS score was calculated as the sum of scores of both lower limbs, with a maximum score of 36 [27] (Figures 1–4).

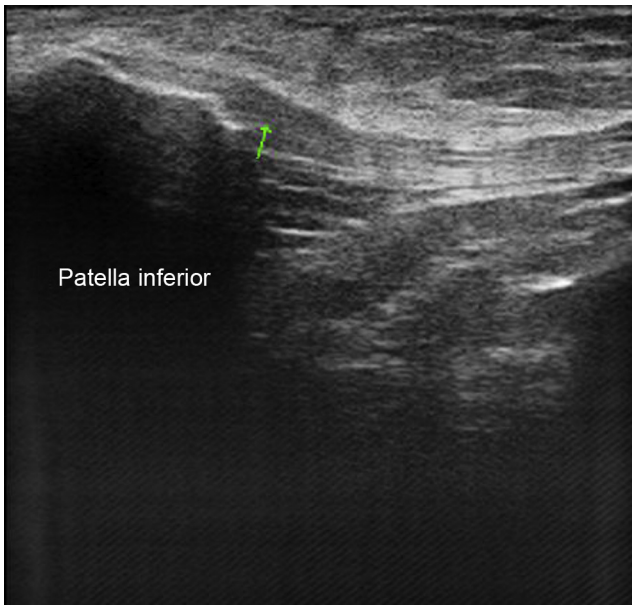

Figure 1 Inferior pole of the patella—proximal patellar ligament enthesis: enthesophyte at the inferior pole of the patella and thickening of the patellar tendon.

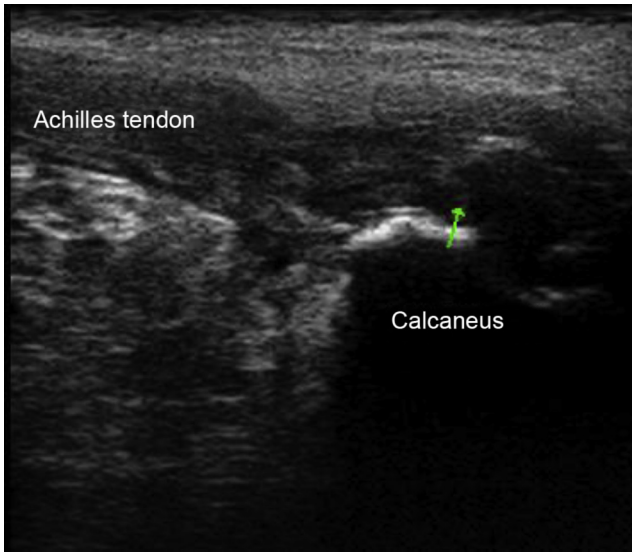

Figure 2 Superior pole of the calcaneus—Achilles tendon enthesis: enthesophytes at the posterior of the calcaneus, erosions, and thickening of the tendon.

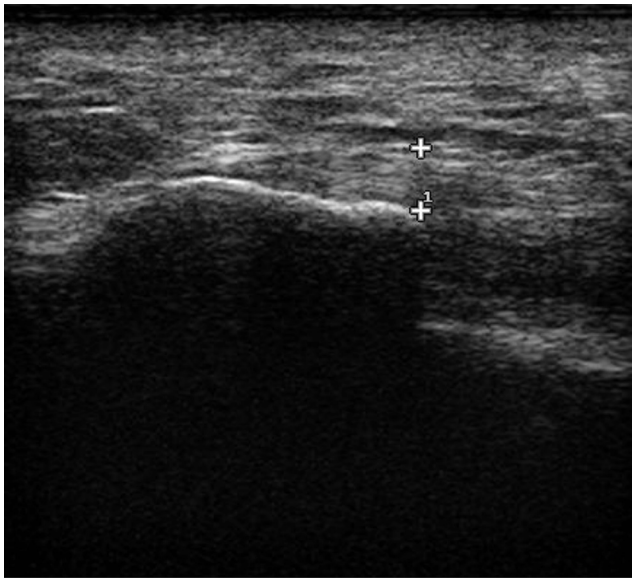

Figure 3 Inferior pole of the calcaneus—plantar aponeurosis enthesis: thickening of the plantar fascia.

Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were described by numbers or percentages for categorical variables, and by means, medians, or standard deviations for continuous variables. More than two independent groups of continuous variables are compared with one-way analysis of variance (ANOVA) test because normally distribution condition is provided. Student's *t*-tests were used for subgroup analysis of parametric variables. The correlation between continue parameters and GUESS score was assessed using the Pearson test. The correlation between noncontinuous parameters and GUESS score was assessed using the Spearman correlation. The significance of the difference of GUESS scores between the groups was evaluated by Tukey's *post hoc* test. The statistical alpha significance level was considered at $p < 0.001$.

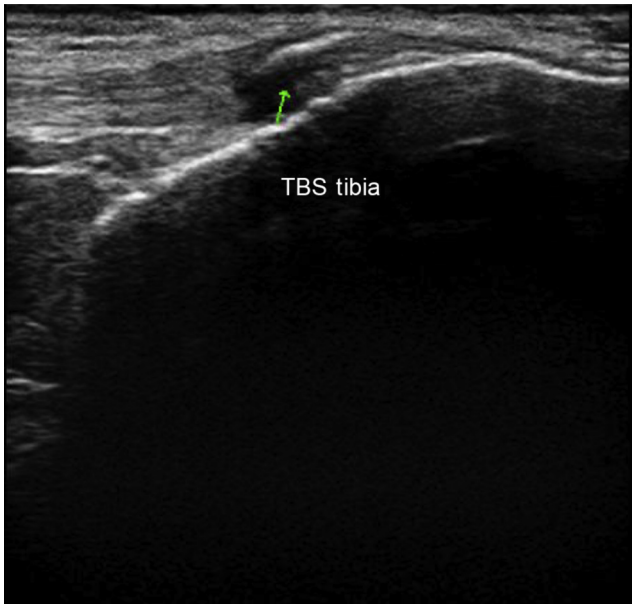

Figure 4 Tibial tuberosity—distal patellar ligament enthesis: enthesophyte at the attaching point of patellar tendon to tuberositas tibia thickening of the patellar tendon. TBS = tuberositas.

Results

A total of 67 participants (25 men, 42 women) with DM, diagnosed for at least 3 years and referred to Physical Medicine and Rehabilitation outpatient clinic, were enrolled in the study. The mean age was 55 years (minimum: 38 years; maximum: 77 years). Participants were grouped according to the duration of DM: Group 1, 3—5 years ($n = 15$); Group 2, 5—10 years ($n = 23$); Group 3, 10—15 years ($n = 15$); and Group 4, >20 years ($n = 14$). Participants' ages were comparable among the four groups, and a statistically significant difference was observed ($p < 0.001$; ANOVA test). There was a female predominance in Groups 1, 2, and 4, but there were no significant differences between the groups with respect to sex ($p > 0.001$; ANOVA test). Results are summarized in Table 2.

The lower extremities of 67 diabetic participants were evaluated with musculoskeletal ultrasound. GUESS score variables among the groups were evaluated, and the results are summarized in Table 3.

HbA1c levels were found to be significantly correlated with diabetes diagnosis duration ($p < 0.001$); while fasting blood glucose levels were not correlated.

A significant correlation was found between age and total GUESS scores of participants ($p < 0.001$), and there was a significant correlation between duration of DM and total GUESS scores. In addition, duration of DM was significantly correlated with enthesophyte and erosion scores (both $p < 0.01$). Significant differences were found among Groups 1—4 by means of enthesophyte scores and mean erosion scores (both $p < 0.01$). A comparison of GUESS scores among different groups using Tukey's test is shown in Table 4. The *post hoc* test showed statistical significance in GUESS scores increasing with diabetes duration. The most significant difference was found between Groups 1 and 4 ($p < 0.001$).

Duration of DM had no correlation with suprapatellar and retrocalcaneal bursitis, and quadriceps tendon thickness. However, we found that proximal patellar ligament, distal patellar ligament, Achilles tendon, and plantar fascia thicknesses increased in correlation with disease duration.

Discussion

As a result, we found that degenerative changes of the lower extremities are increasing with the duration of DM. Age and the levels of HbA1c were found to be positively correlated with total GUESS scores. Ultrasonographic evaluation is a reliable and inexpensive method for investigating degenerative process before clinical presentation is apparent.

Table 2 Patient characteristics.

	Duration of diabetes (y)				p^a
	3–5	5–10	10–20	>20	
No. of patients	14	23	15	14	
Sex (female/male)	9/5	15/8	8/7	9/5	>0.001
Age (min/max)	55 (38–67)	63 (48–82)	64 (56–72)	71 (66–77)	<0.001

ANOVA = analysis of variance; max = maximum; min = minimum.
[a] ANOVA test.

The prevalence of diabetes-related musculoskeletal system problems increases in direct correlation with the patient's age, DM diagnosis age, and DM duration [5,6,13,14,17]. There was a significant correlation between total GUESS scores and age in our study. Aging positively effects degenerative changes as appointed formerly. However, in our study, we formed age-matched patient groups according to the duration of DM so as to explain the increase of total GUESS scores with the duration of diabetic status.

It is believed that collagen thickening due to the deterioration of DM neoangiogenesis, nonenzymatic glycosylation of peritendinous collagen, and basal membrane damage further aggravates diabetes-related musculoskeletal system problems [10,11,13–16].

In many studies, evaluation of DM patients' Achilles tendon morphologies indicated an increase in tendon thickness and disruption in tendon morphology along with the disease time [9,16,20]. The literature includes various studies that have regionally evaluated various tendon structures, while we used the GUESS that enabled us to inspect the lower extremity ultrasonographically in many fields. The GUESS enables the evaluation and quantification of knee, ankle, and plantar zone from the point of bursitis, enthesitis, tendon thicknesses, and erosions.

Table 3 Sonographic findings at entheseal sites by duration of diabetes mellitus.

	Duration of diabetes (y)				
	3–5	5–10	10–20	>20	p^a
Total GUESS score					<0.001
Mean ± SD	3.7 ± 2.1	5.3 ± 2.3	10.1 ± 1.2	12.2 ± 2	
Min–Max	1–8	1–8	8–12	9–16	
Total enthesophyte score					<0.001
Mean ± SD	1.9 ± 0.8	2 ± 1.2	4.1 ± 1.0	4.6 ± 0.5	
Min–Max	1–3	0–5	2–5	4–5	
Total erosion score					<0.001
Mean ± SD	0.6 ± 0.8	1.4 ± 1.7	2.1 ± 1.3	3.3 ± 1.1	
Min–Max	0–2	0–4	0–4	1–5	
Quadriceps tendon thickness (mm)					>0.001
Mean ± SD	5.6 ± 0.3	5.9 ± 0.4	5.6 ± 0.7	5.4 ± 0.4	
Min–Max	5.3–6.3	4.6–6.3	4.7 ± 6.3	5.0 ± 5.8	
Proximal patellar tendon thickness (mm)					<0.001
Mean ± SD	3.7 ± 0.5	4.0 ± 0.2	4.0 ± 0.2	4.2 ± 0.3	
Min–Max	2.3–4.2	3.7–4.5	3.6–4.3	3.7–4.6	
Distal patellar ligament thickness (mm)					<0.001
Mean ± SD	3.9 ± 0.2	4 ± 0.4	4.1 ± 0.2	4.1 ± 0.2	
Min–Max	3.6–4.3	3.2–4.9	3.6–4.4	3.7–4.5	
Achilles tendon thickness (mm)					<0.001
Mean ± SD	4.9 ± 0.5	4.1 ± 0.3	4.7 ± 0.5	5.1 ± 0.7	
Min–Max	3.8–5.6	3.6–4.7	3.8–5.4	4–6.1	
Plantar fascia thickness (mm)					<0.001
Mean ± SD	4.1 ± 0.3	4.2 ± 0.3	4.4 ± 0.4	4.4 ± 0.5	
Min–Max	3.7–4.8	3.5–4.7	3.6–4.9	3.7–5.9	
Glycosylated hemoglobin					<0.001
Mean ± SD	5.8 ± 0.5	6.4 ± 0.8	6.9 ± 0.6	7.4 ± 1.1	
Min–Max	5.1–6.6	5.1–7.8	6.1–7.9	5.9–9.2	

ANOVA = analysis of variance; GUESS = Glasgow Ultrasound Enthesitis Scoring System; max = maximum; min = minimum; SD = standard deviation.
[a] ANOVA test.

Table 4 Comparison of GUESS scores between groups by Tukey's test.

Groups	Mean diff.	Q	p	95% CI of diff.
Groups 1 & 2	−4.18	3.62	<0.01**	−5.73 to −2.3
Groups 1 & 3	−3.31	2.91	<0.01**	−4.71 to −1.8
Groups 1 & 4	−5.27	4.31	<0.001***	−6.34 to −2.5
Groups 2 & 3	−1.21	0.95	<0.01**	−4.34 to −0.85
Groups 2 & 4	−3.91	2.87	<0.01**	−5.51 to −0.87
Groups 3 & 4	−1.23	0.91	<0.01**	−2.87 to −0.15

**$p < 0.01$, moderately significant.
***$p < 0.001$, highly significant.
CI = confidence interval; diff. = difference; GUESS = Glasgow Ultrasound Enthesitis Scoring System.

In our study, we found high arthropathy scores in participants with a disease duration of 5 years or longer. Arthropathy, which occurred due to accumulation of glycolyzed protein deposits around the joint, continued to increase in correlation with diabetes diagnosis period and reached the highest level in the participants with a diagnosis duration of 20 years or longer.

Batista et al [20] identified that deterioration of tendon morphology and an increase in tendon thickness correlated with the diabetes period in their studies, where they evaluated the Achilles tendon in the lower extremity. In our study, we identified an increase in the thicknesses of tendons (proximal patellar ligament, distal patellar ligament, Achilles tendon, and plantar fascia) except for quadriceps tendon [16—20]. Similar to our study, Altinel et al [23] did not identify any increase in tendon thicknesses for quadriceps tendon thickness evaluation of 41 diabetic and nondiabetic participants. It may be interpreted as follows: the structure and function of the quadriceps tendon could be less affected by the diabetic process.

Superiority of ultrasonographic inspection is its ability to show calcifications in intratendinous and intraligamenter structures. The incidence of observing intratendinosis calcifications, which can be also named as enthesophytes, increases particularly in diabetic patients with a history of 10 years or longer disease period [13,14]. We also identified enthesophytes in the Achilles tendons of four participants in Group 3 and five in Group 4.

In addition to the destruction of tendon structure, the frequency of bursitis development also increases in diabetic patients. In our study, we assessed suprapatellar, infrapatellar, and retrocalcaneal bursas. Unlu et al [21] identified deterioration in the tendon morphology and bursitis in 14 of 23 diabetic participants. We found a positive correlation between diabetes duration and bursitis frequency, which is particularly evident for suprapatellar bursitis scores. However, we could not find the same correlation for retrocalcaneal bursitis, and we have not identified any supporting data in the literature either.

Our study also showed that enthesopathy formation increased in association with the period of diabetes. The most important advantage of assessment with ultrasonography is its ability to indicate enthesophytes and tendinopathies. Early diagnostic inspection of individuals with unregulated diabetic status using ultrasonography can aid in taking preventive measures in the early period before these lesions become chronic. We found the highest total enthesophyte scores in Group 4 in our study, similar to the studies of Balint et al [27] and Abate et al [30], indicating the relationship between disease duration and enthesophyte formation.

A correlation between DM-related musculoskeletal complications and fasting blood glucose was reported in many studies in recent years [31—34]. However, while a relation was not identified between fasting blood glucose and enthesopathies in our study, we found that HbA1c levels and total GUESS scores were associated, similar to the study of Attar [35]. HbA1c levels are more valuable data compared with instant blood glucose measurements for indicating the course of long-term diabetic status. Therefore, monitoring HbA1c levels regularly may be beneficial for early diagnosis of musculoskeletal problems in unregulated diabetic patients. In addition to keeping HbA1c levels within normal limits, regular ultrasonographic follow-up of these patients may prevent permanent musculoskeletal system disorders [36].

However, not having a control group that consists of nondiabetic, age-matched participants may be considered an important restriction of our study. A control group could help us achieve more significant results about diabetes-specific musculoskeletal findings if age-related osteodegenerative changes are eliminated. Another limitation of our study was not assessing other complications of DM such as angiopathy or peripheral neuropathy, which can also affect lower extremity findings. Other comorbidities can also affect the degenerative process of tendons in DM, which we had not considered in this study.

As a result, ultrasonographic studies on musculoskeletal system complications of DM patients are relatively fewer in number in the literature. The importance of our study is that we used an ultrasonographic scoring system that assesses the lower extremity entirely in many different sites and gives a numeric result. For diabetic patients, in addition to following up laboratory parameters, mainly HbA1c, conducting regular ultrasonographic assessment particularly for those with a long disease duration may prevent permanent musculoskeletal system diseases and, as a result, reduce the incidence of pain and functional loss.

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