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Assessment of Muscluo-Tendionous Changes in Diabetes Mellitus: A Musculoskeletal Ultrasonographic study

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ABSTRACT

Background: Diabetes mellitus (DM) is a common endocrine disorder worldwide, causing multisystem comorbidities, which compromise organ functions including musculoskeletal complications that affect the quality of life up to handicapping. Ultrasound is a very sensitive tool and a strong predictor of a DM musculoskeletal (MSK) changes, aiding in early management and control of disease parameters preventing subsequent comorbidities.

Objective: This study aimed to evaluate if there is a relation between sonographic musculo-tendinous structural changes and diabetes and to correlate them with both clinical and laboratory parameters.

Patient and Methods: 40 diabetic patients and 25 healthy subjects were involved in this work. All participants underwent history taking, general and musculoskeletal examination and laboratory and ultrasonographic evaluation.

Results: 28 diabetic females and 12 diabetic males with mean age of 49.8± 13.7 years, showed statistically significant tendinous changes mainly tendon thickness compared to controls ($p<0.05$), there were statistically significant correlations between these variations and disease duration, HA1c P (0.008, <0.001) respectively.

Conclusion: Chronic diabetes is linked to the destruction of collagen fibres, and biomechanical decline of tendons. Ultrasound is sensitive and accurate dedicated, simple and noninvasive screening method for the detection of musculoskeletal changes related to diabetes. This could serve as strong screening tool of underserved, asymptomatic diabetic individuals.

Keywords: Diabetes mellitus, Muscluo-tendionous, Musculoskeletal ultrasonographic.

INTRODUCTION

Approximately 463 million people worldwide have T2DM [1]. Diabetes patients may experience a range of musculoskeletal problems throughout their lifetimes as a result of their weakened immune systems, vascular insufficiency brought on by microcirculation problems, and neurological abnormalities [2].

A frequent illness of the muscle tissue known as tendinopathy has a complex pathophysiology that is not being completely understood. It often happens as a result of overuse, metabolic abnormalities, and other tendon microinjury-related variables, one of which being diabetes as a metabolic condition. It has been proposed that microstructural problems in diabetic tendons, such as tendon thickening and decreased tendon stiffness, may start before the appearance of symptoms or macrostructural alterations [3]. One risk factor for rotator cuff injuries is DM, and those with type 2 DM are more likely to experience tendon ruptures [4]. The rotator cuff has a poor prognosis, slow healing rates, and a greater frequency of re-tears following repair [5].

DM-Related Leukocytes, antibodies, inflammatory cytokines, and the complement system are among immune system components that can be affected by hyperglycemia, which can reduce pain perception and disrupt microcirculation, leading to tendon reactive inflammation. One of the primary causes of tissue dysfunction is assumed to be an increased buildup of advanced glycation end products (AGEs) in the collagenous tissues of diabetes individuals [6].

A hyperglycemic milieu in T2DM tendon can result in changes in tendon structure because AGEs produce cross-links through a non-enzymatic interaction between sugars and the free amino groups of proteins and lipids. This alters the biomechanical characteristics of the tissue matrix [7].

Vascular endothelial growth factor, cytokines, and specific receptors for AGE (RAGE) that have been found on the membranes of chondrocytes, tenocytes, and fibroblasts are overexpressed in diabetes, which may help to explain why diabetics have an increased prevalence of lesions and inflammatory responses. In addition to the pathogenetic pathway mediated by AGEs, microvascular illness may result in tissue hypoxia, which produces oxygen free radicals and an excess of growth hormones and cytokines [8]. Additionally, T2DM complicates an already difficult healing landscape in the case of tendon injuries, and DM impairs both tendon homeostasis and repair following acute injury, both clinically and at the cellular level [9]. Unfortunately, the negative effects of diabetes persist even after the repair of rotator cuff injury, and persistent hyperglycemia impairs tendon-to-bone healing after rotator cuff repair.

Based only on clinical symptoms, it is challenging to differentiate between the MSK disorders associated with DM. For these MSK symptoms, sonography is routinely performed as a preliminary imaging scan and is useful in differentiating between the various DM-related MSK disorders [2]. Given its benefits over MRI, particularly at shoulder level, due to its ease of accessibility and usage [10].

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The purpose of the current study to provide guidance for an accurate diagnosis changes occurring in some tendons, in both upper and lower limbs, in patients with diabetes mellitus (DM) relying on sonographic imaging variations, and to evaluate associations of these changes with patients' clinical status, disease duration, glycemic control as well as laboratory parameters.

PATIENT AND METHODS

A case-control study was conducted at the Rheumatology, Rehabilitation and Physical Medicine Department, Faculty of Medicine, Benha University Hospitals on patients with diabetes mellitus. These patients presented between July 2022 and February 2023.

Inclusion criteria: Symptomatic diabetic patients especially those with a musculoskeletal complaint of shoulder pain and a subsequent shoulder movement limitation, foot pain.

Exclusion criteria: Individuals with history or concomitant diagnoses such as muscle contusion, strain, paralysis, myositis, rhabdomyolysis, statin-induced myopathy or any other myopathy that could alter the sonographic appearance of the muscle, who < 16y, pregnant women and connective tissue disorders causing arthritis.

Sixty-five volunteers, matched for age and sex, were divided into two groups for the current study.

Patients' group: 40 diabetic patients who met the American Diabetes Association Classification and Diagnosis of diabetes criteria 2019 for the diagnosis of diabetes mellitus were included in our work [11], their disease duration ranged from 1year up to 22 years. They were on (Insulin for typ1DM patients, Metformine, Sulphonylurea, TZDs, DPP4 inhibitors for Type2DM). Two types of diabetes mellitus patients have participated in the study. Two of them were categorized as type 1 DM (5%) while the rest thirty-eight were classified as type2 DM (95%). **Control group:** 25 apparently healthy participants in the control group. All subjects underwent a thorough medical history interview, comprehensive clinical examination and laboratory and radiological examinations.

Ultrasonographic examination: All Us examination from these patients were performed by well-trained MSK sonographer. For each patient a complete shoulder and Achilles tendon US were performed utilizing a 9-MHz transducer (GE LOGIQ E9 unit; General Electric Milwaukee, WI, USA) Company). Currently, A total of (4×40)160 tendons of 40 DM patients and (4×25)100 tendons of healthy controls were examined clinically and radiologically following instructions of European league Against Rheumatism (EULAR) guidelines for musculoskeletal ultrasound assessment [12]. Biceps, supraspinatus (SST), subscapularis and Achilles tendons were selected because of their easy accessibility (Figs. 1, 2 & 3).

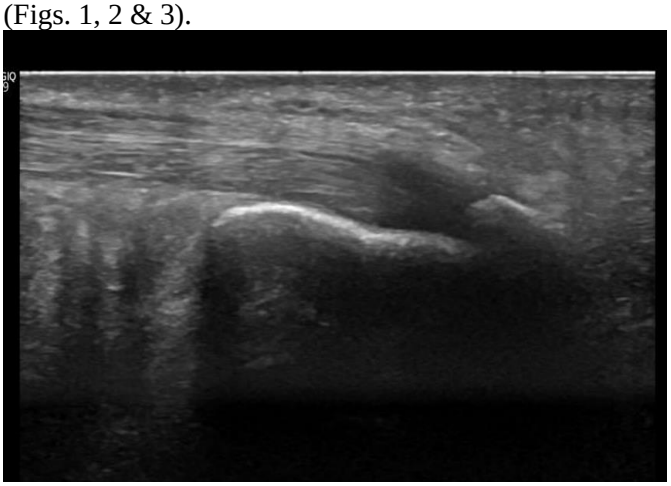

Fig. (1): Longitudinal scan of Achilles of 46 years male diagnosed as type2 DM 11 years ago, negative Thompson test on clinical examination, lab (FBS:143.1 mg/dl 2hpp:247mg/dl, HAIc. 8.9%): tendon showing calcification+1.

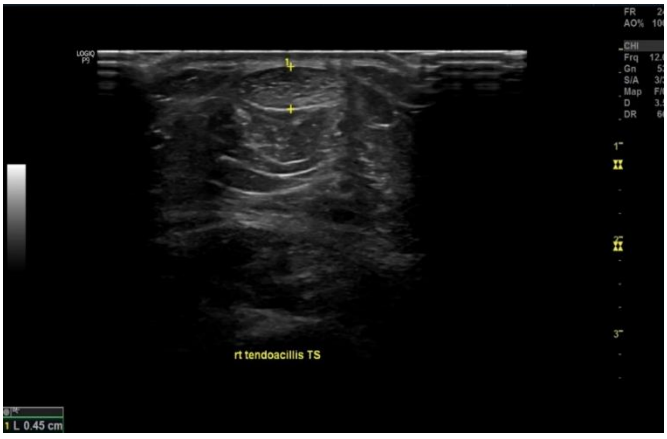

Fig. (2): Transverse scan of Tendon Achilles for measuring thickness (58 mm) of 48 years female diagnosed as type2 DM 10 years ago, negative Thompson test on clinical examination, lab (FBS :151 mg/dl 2hpp:256.3mg/dl, HAIC:9.45%).

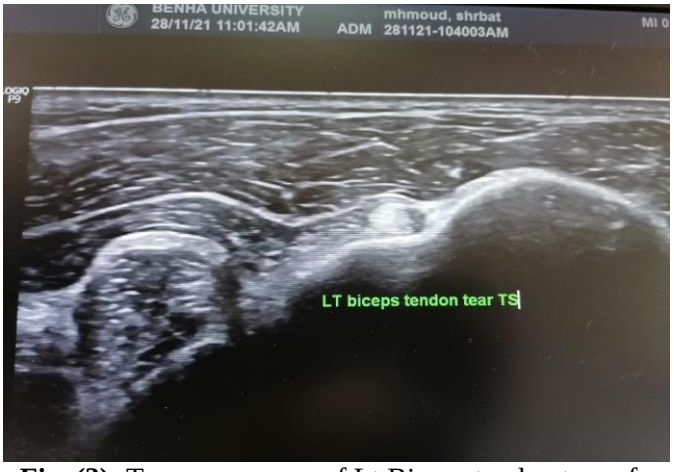

Fig. (3): Transverse scan of Lt Biceps tendon tear of 49 female diagnosed as type 2 DM 14 years ago positive Yorgason test on clinical examination, lab (FBS :169 mg/dl 2hpp:296.3mg/dl, HAIC:11.45%)

Ethical approval: This study was governed by the Helsinki Declaration on the Ethical Principles in Human Research. The study's procedure was approved by the Faculty of Medicine's, Benha University Human Subjects Research Ethics Committee. Before taking part in the study, all participants signed informed written consents.

Statistical analysis

Utilising SPSS software version 25, data management and statistical analysis were carried out. Prior to beginning the research, the normality of continuous variables was evaluated using direct data visualisation and normality tests. Means, standard deviations, or medians and ranges were used to summarise numerical data. Numbers and percentages served as a summary of categorical data. Using the Mann Whitney U test (non-parametric test), comparisons between cases and controls and between patients with and without shoulder discomfort were made. The Fisher exact test or the Chi-square test, as applicable, was used to compare categorical variables. Using the Mann Whitney U test, fasting blood sugar, 2 hours post-prandial, HA1c levels, and illness duration were compared between various ultrasonography results. Spearman's correlation was used for the correlation analysis. Correlation coefficient abbreviated as "r" had a range of -1 to +1. Strong correlations were denoted by -1 and +1, respectively, whereas no correlation is denoted by 0 and -1. $P \leq 0.05$ was regarded as significant.

RESULTS

Forty diabetic patients, 28 females (70%) and 12 males (30%) (F:M 2.3:1) with mean age of 49.8 ± 13.7 years, their disease duration ranged between 1 year and 22 years with mean of 10.01±7.7 years.

Table (1): Demographic and laboratory parameters among the studied diabetic patients

Variable	Mean ± SD
Age	49.8±13.7
Hb (g/dl)	9.66± 2.3
WBCs (cells/mm³)	8040 ± 208.6
Platelets (cells/mm³)	56440 ± 4152.1
FBG (mg/dl)	143.6 ± 15.5
2hour post prandial (mg/dl)	236.3 ± 44.9
HbA1c (%)	9.44 ± 2.7
Serum creatinine (mg/dl)	0.93 ± 0.14
Blood urea (mg/dl)	30.2 ± 7.32
Serum uric acid (mg/dl)	3.97 ± 0.97

HB: Hemoglobin, WBC: white blood cells, FBS: Fasting blood suger, HA1c: Hemoglobin A1c

Twenty-five age and sex matched apparently healthy subjects were also included as a control group. 21 females (84%) and 4 males 16% (F:M 5.2:1) with mean age of 54.5±10.5 years. Demographic and laboratory data were listed in table (1). Clinical characteristics were summarized in table (2).

Table (2): Clinical characteristics of the study groups

		Group I (n=40)		Group II (n=25)		Test of sig.	p-value
		No.	%	No.	%		
Point tenderness	**Negative**	30	75%	22	88.0%	7.6	**0.001***
	Positive	10	25%	3	12.0%		
Thompson test	**Negative**	40	100%	25	100%	_	_
	Positive	0	0%	0	0%	-	-
Empty can test	**Negative**	34	85%	24	96%	0.9	0.2
	Positive	6	15%	1	4%		
Drop arm test	**Negative**	36	90%	25	100%	0.2	0.5
	Positive	4	10%	0	0%		
Rent test	**Negative**	40	100%	25	100%	1.2	0.3
	Positive	0	0%	0	0%		
Yergason test	**Negative**	36	90.0%	25	100.0%	1.2	0.2
	Positive	4	10.0%	0	0.0%		
Speed sign	**Negative**	38	95.0%	25	100.0%	0.2	0.5
	Positive	2	5.0%	0	0.0%		

There was highly statistically significant difference between diabetic patients and healthy individuals as regards tendons thickness alterations seen via musculoskeletal ultrasound examination of both upper and lower limb tendons (biceps, supraspinatus, Achilles tendon) ($p < 0.001$, 0.01 & 0.05 respectively) (Tables 3, 4 & 5).

Table (3): Comparison between the studied groups ultrasonographic findings of Supraspinatus tendon

		Group I (n=40)		Group II (n=25)		Test of sig.	p-value
		No.	%	No.	%		
Supraspinatous tendon thickness	**Mean SD**	Mean 0.54	SD 0.19	Mean 0.45	SD 0.09	2.3	**0.01**
Calcification	**Negative**	38	95.0%	25	100.0%	0.2	0.5
	Positive	2	5.0%	0	0.0%		
Fiber degeneration	**Negative**	32	80.0%	18	72.0%	0.5	0.5
	Positive	8	20.0%	7	28.0%		
Impingement test	**Negative**	38	95.0%	25	100.0%	0.2	0.5
	Positive	2	5.0%	0	0.0%		
Partial Tear	**Negative**	36	90.0%	25	100.0%	1.2	0.3
	Positive	4	10.0%	0	0.0%		

Table (4): Comparison between the studied groups regarding MSUS findings of Biceps tendon.

		Group I (n=40)		Group II (n=25)		Test of sig.	p-value
		No.	%	No.	%		
Biceps tendon thickness	**Mean SD**	Mean .36	SD .09	Mean .27	SD 0.06	4.7	**<0.001**
Irregular shape	**Negative**	32	80.0%	25	100.0%	3.9	**0.02***
	Positive	8	20.0%	0	0.0%		
Transposition	**Negative**	38	95.0%	22	88.0%	0.3	0.5
	Positive	2	5.0%	3	12.0%		
Tenditis / Effusion	**Negative**	36	90.0%	25	100.0%	1.2	0.2
	Positive	4	10.0%	0	0.0%		
Calcification	**Negative**	36	90.0%	25	100.0%	1.2	0.2
	Positive	4	10.0%	0	0.0%		
Tear	**Negative**	38	95.0%	25	100.0%	0.2	0.5
	Positive	2	5.0%	0	0.0%		
Fiber degeneration	**Negative**	28	70.0%	21	84.0%	1.6	0.2
	Positive	12	30.0%	4	16.0%		

Table (5): Comparison between the studied groups regarding MSUS findings of Tendon Achilles tendon

		Group I (n=40)		Group II (n=25)		Test of sig.	p-value
		No.	%	No.	%		
Tendon Achilles thickness	**Mean SD**	Mean 0.48	SD 0.09	Mean 0.42	SD .07	1.8	**0.05**
Tendon degeneration	**Negative**	36	90.0%	23	92.0%	0.6	0.3
	Positive	4	10.0%	2	8.0%		
Calcification	**Negative**	38	95.0%	24	96.0%	0.01	0.9
	Positive	2	5.0%	1	4.0%		
Retrocalcaneal bursa	**Negative**	34	85.0%	24	96.0%	0.9	0.2
	Positive	6	15.0%	1	4.0%		

MSUS detected pathological changes, represented in form of lamellar fibers degenerative changes and thickness increment were detected to be significantly connected to disease chronicity and HA1c (p= .019, 0.03, 0.008, r=0.218,0.18.0.42, p=0.016,0,05, <0.001 r=0.323 ,0.07, 0.71) respectively, while other detected pathologies showed insignificant correlations to these variables (Table 6, figs. 4, 5 & 6).

Table (6): Correlation between different tendons thickness and different variables

	Biceps tendon thickness		Supraspinatus thickness		Tendo Achilles thickness	
	r	p-value	r	p-value	r	p-value
Biceps tendon thickness	---	---	0.28	0.01*	0.14	**0.02***
Supraspinatus thickness	0.28	0.02*	---	---	0.37	**0.003***
Tendo Achilles thickness	0.14	0.03*	0.37	0.003*	---	---
Age	0.302	0.01*	0.08	0.52	0.18	0.14
DM duration/y	0.218	0.019*	0.18	0.03*	0.42	**0.008***
HbA1c	0.323	0.016*	0.07	0.05*	0.71	**<0.001***

*Spearman' correlation coefficient (rho). Bold values are significant at p<0.05

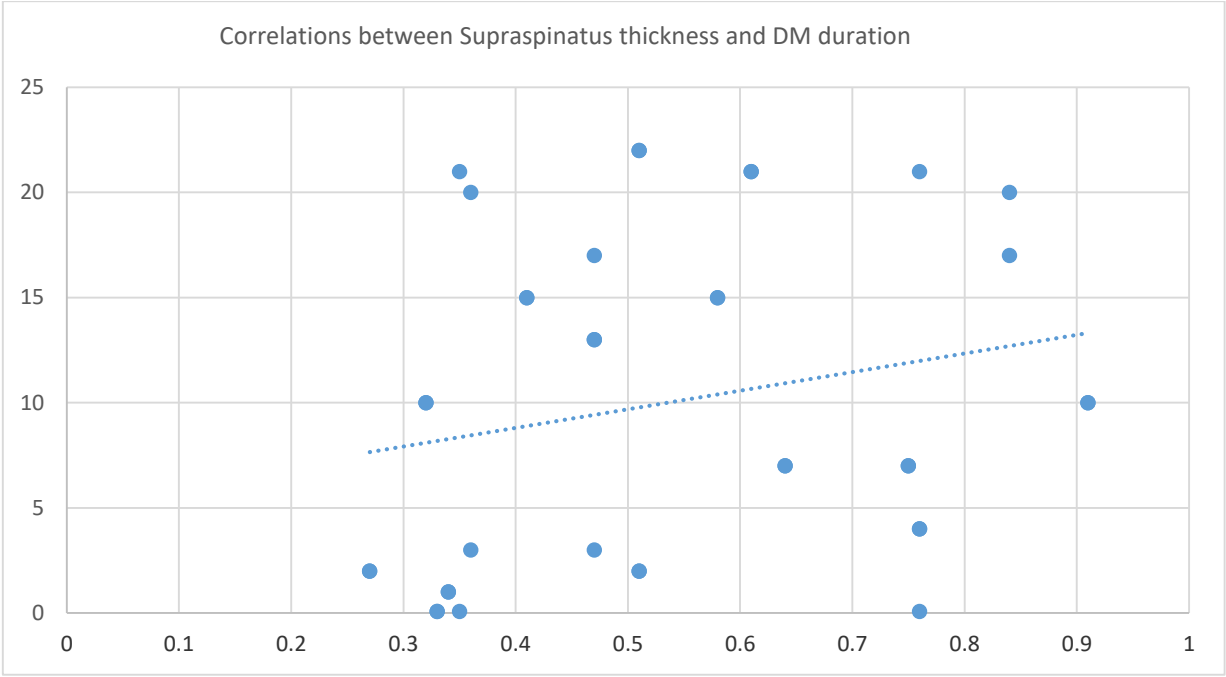

Fig. (4): Showed correlation between supraspinatus thickness and DM duration/Y (p=0.03).

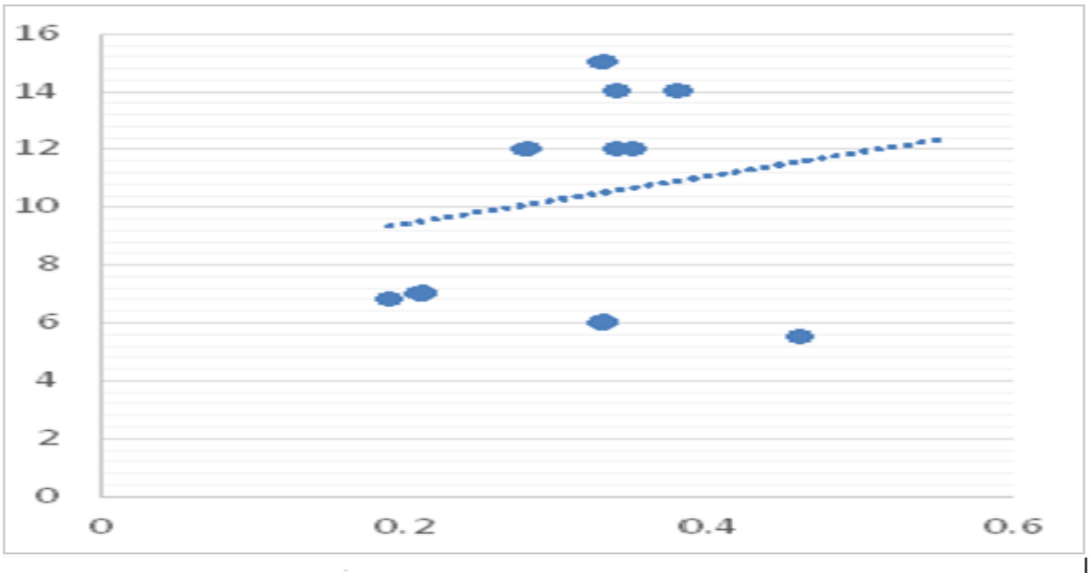

Fig. (5): Showed correlation between biceps tendon thickness and HbA1c (p=0.016).

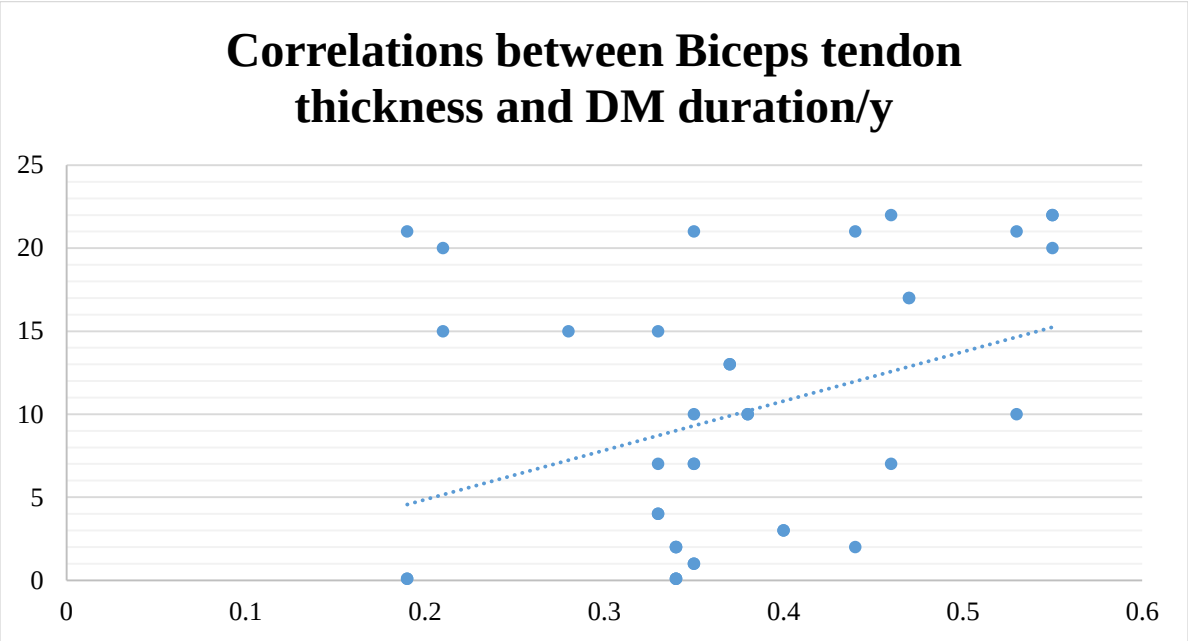

Fig. (6): Showed correlation between biceps tendon thickness and DM/Y duration (p=0.019).

DISCUSSION

Since the effects of diabetes on tendon structure and homeostasis sometimes go unnoticed until major problems or acute injuries manifest, tendinopathy is a common musculoskeletal comorbidity of DM [(13)]. It is debatable if this causes bad biomechanics. The biomechanical characteristics of the rotator cuff are unaffected by hyperglycemia on its own, although it does cause a persistent inflammatory response [(5)].

In the present work, among DM patients, tendon degeneration was detected in 8 supraspinatus tendons (20%), 6 subscapularis tendons (15%) and 12 biceps tendons (30%)), with statistically insignificant differences compared to healthy controls (p>0.05). Although **Abate *et al.*** [(14)] study showed that diabetics were more likely to have degenerative characteristics in the rotator cuff and biceps (Supraspinatus Tendon: 42.7% vs. 20.3%, p 0.003 & Biceps Tendon: 27% vs. 7.8%, p 0.002). It's interesting to note that **Abate *et al.*** [(14)] also showed that T2DM patients with AT pathology who did not exhibit any symptoms had a higher prevalence of ultrasonography abnormalities (T2DM: 25.7% vs. 11.7% of non-diabetics).

In the current study, statistically significant difference (p<0.05) was reported regarding tendon thickness of biceps, supraspinatus and Achilles tendons between DM patients and healthy controls on contrary to insignificant difference detected according to tendon calcifications (p=0.2, p=0.5, p=0.9) respectively. Effusion was detected among 4 (10%) biceps tendons of the studied cases although none of the examined healthy controls had bicipital tendinitis on examination but with statistically insignificant differences (p>0.05). On contrary, **Çağlar and Çiftçi** [(15)] found that there was a substantial difference in the frequency of calcific tendinitis between the examined groups (p<0.05). In agreement to work achieved by **Liu *et al.*** [(16)], that while type 2 diabetes (T2DM) causes pathological changes in many different tendons, there is some evidence that not all tendons are equally susceptible to diabetic tendinopathy, and that the incidence of tendinopathy is significantly higher in patients with type 2 diabetes compared to non-diabetic patients. Similar to our results **Afolabi *et al.*** [(17)], revealed that type 2 diabetes participants had considerably more degenerative alterations (disorganised fibres and/or hypoechoic foci) than controls in both the right and left side (55.0 vs. 18.8%, p0.001) (52.5% vs. 18.8%, p0.001).

Given the significant incidence of T2DM in society and the elevated risk of rotator cuff pathology and adhesive capsulitis in persons with T2DM, shoulder US is frequently done on T2DM patients [[18]]. With the use of ultrasonography, **Batista *et al.*** [(19)] discovered a nearly nine-fold rise in the organisation of the Achilles tendon as well as a notable rise in the prevalence of tendon fibre disorganisation (89% of T2DM vs. 10% of non-diabetic controls). On contrary to **Kuo *et al.*** [[20]], who found that lower thickness of Achilles tendon among DM patients compared to healthy controls with statistically insignificant difference (p=0.98).

In the current work, partial tendon tear was detected more frequently among supraspinatus tendons (10%) than biceps tendons (5%). Similar to results of **Abate *et al.*** [(14)] study where there were higher percentages of tears in both the SST and BT with associated higher percentages of effusion in the BT sheet [[14]]. In **Çağlar and Çiftçi** [(15)] study, in 4 diabetes patients (8.7%) and 1 control patient (1.9%), partial tears in the supraspinatus tendon were found.

Anomalies in the structure, such as thickening or loss of collagen organisation, as well as calcification, can all raise the risk of tendon rupture. It is challenging to determine the exact prevalence of diabetic

tendinopathy, and studies showed significant variations in the relative prevalence [21].

In the present work, significant positive correlations were reported between tendon thickness with disease duration and HbA1c [r=0.323,0.07,0.71, p=<0.05, r=.218,0.18,0.42, p<0.05 consecutively]. Whereas, biceps tendon thickness was positively correlated with patients' age (p=0.01, r=0.302). **Vance *et al.*** [22] reported that increased blood haemoglobin A1c (HbA1c) levels have been linked to the development of tendinopathy, according to research. More precisely, an independent risk factor for tendinopathy has been established as HbA1c >7%.

The length of the diabetes disease and musculoskeletal (MSK) symptoms were shown to be significantly correlated in 2019, with individuals who had the condition for longer than 10 years being more likely to experience these manifestations [23]. Insignificant association between the outcomes and the length of diabetes was found in contrast to **Abate *et al.*** [14] the inability to pinpoint the age of diabetes development may be the cause of the lack of connection.

Chronic Achilles tendinopathy, which includes hypoechogenicity, entheseal thickening, and enthesophytes, is more prevalent in long-term diabetics [24].

Uchendu *et al.* [25] reported positive correlations between diabetes duration, age and dominant limb tendon thickness with (r =0.48, p=0.000, r = 0.5, p = 0.000) for supraspinatus thickness and (r=0.317, p=0.01, r=0.51, p= 0.000)) for biceps tendon thickness respectively. Thus they concluded increased prevalence of shoulder pathology with the duration of diabetes [25].

LIMITATIONS

The study's limited sample size, patient demographics, and the particular tendon under examination. The full extent of diabetes-related tendon pathology was only partially represented due to the large community of diabetic individuals with degenerative tendon alterations who have not yet reached the threshold for symptoms. Additionally, this study did not examine how widely given medications could influence individuals with diabetes mellitus' altered collagen structure and tendon structure.

CONCLUSION

Earlier sonographic detection of this comorbidity is crucial as early sign for prediction of other multiple serious end-organ complications (end-stage renal disease and non-traumatic limb amputations. Through this opportunistic screening strategy, earlier diagnosis, lifestyle changes, and treatment of this condition may help relieve some of the massive financial strain on healthcare while also preventing or reducing the recognised catastrophic consequences of DM. While, more research needs to be done to identify the precise pathways/mechanisms that hyperglycemia uses as well as its short- and long-term impacts.

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- **Conflicts of interest:** no conflicts of interest.

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