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Research Article

Clinical Predictors of Shoulders Tendon Pathology in Patients with Early Parkinson's Disease: Sonographic and Clinical Associations

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Abstract

Introduction: Shoulder pathology is under-diagnosed in Parkinson's disease (PD).

Objectives: To examine clinical and Ultrasonographic (US) associations of rotator cuff (RC) tendinopathies in early Parkinson's disease (PD) patients.

Methods: Clinical and US examination were performed in 200 shoulders of 100 consecutively recruited early PD patients. Modified Hoehn and Yahr (H&Y) scale and goniometer were used to assess PD stages and shoulder dysfunction respectively. Multiple logistic regression analysis was performed.

Results: Hypomobility in active movements (67.7%, n=109/161) and rigidity (52.2%, n=84/161) were common clinical findings in early PD. US abnormalities were detected in 80.5% (n=161/200) symptomatic and in 15% (n=30/200) asymptomatic shoulders. The most frequent US-detected abnormalities were calcification (42.9%, n=69/161), tendinosis (38.5%, n=62/161), partial tears (32.3%, n=52/161), and atrophy (28%, n=45/161). Rigidity was significant predictor of partial tear (OR: 3.48) and tendinosis (OR: 2.96). Bradykinesia was predictor of impingement (OR: 8.61) and hypomobility was predictor of tendon calcification (OR: 5.68), tendinosis (OR: 11.67), atrophy (OR 15.77) and partial tears (OR 22.2) ($p<0.05$).

Conclusion: Tendon calcification and degeneration were the most common RC abnormalities in early PD stages. US enables the detection of RC pathology even before the establishment of clinical symptoms. Frozen shoulder and rigidity are clinical predictors of RC tendinopathies.

Keywords: Calcific tendinopathy; Musculoskeletal static and dynamic ultrasonography; Parkinson's disease; Rotator cuff tendinopathies; Shoulders dysfunction

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Introduction

PD is the second most common neurodegenerative disease that mainly affects the motor system and can also cause musculoskeletal problems, such as shoulder disorders. To date, tendon pathology and other shoulder disorders have been understudied in PD, although their prevalence is higher in patients with PD than in healthy individuals. Pathology of the rotator cuff (RC) is considered to be the main cause of shoulder pain and disability and the third most common musculoskeletal complaint in the general population with poor long-term outcomes. RC pathology includes a wide spectrum of disorders, such as RC tendinosis due to improper tendon healing processes, tears, tendinitis and impingement. The prevalence of RC disorders, specifically RC tendon tears, has been shown to exceed 50% by the age of 60 years. RC pathology significantly impact upon the most basic activities of daily living, including eating, dressing, sleep, personal hygiene and work and persist in more than a third of patients, regardless of conservative or surgical treatment [1-11].

Few studies have focused on shoulder pathology in PD and none, to our knowledge, has specifically studied RC tendinopathies in the initial stages of the disease. Shoulder musculoskeletal disorders are common and could be early manifestation of PD. Their prevalence was estimated between 11% and 15%. Recent sonographic studies evaluating patients in different PD stages, showed that tendon pathology (increased tendon thickness and tear) was one of the most common shoulder disorders and were associated with disease duration [12-17].

The aim of this study was to clarify RC disorders in early PD patients using physical and real-time sonographic. US is a noninvasive, inexpensive diagnostic method, with high resolution, increased sensitivity and specificity for the diagnosis of shoulder disorders. Dynamic US also enables real-time visualization of internal shoulder structures during movement.

Materials and Methods

Patient Selection

This study was conducted at Health Care center of Peristeri, Athens. Ethics' Committee of the 2nd Regional Health Administration of Piraeus approved the study protocol and written informed consent was obtained from all participants. A total of 100 consecutively recruited PD patients to department of physical therapy underwent clinical and US examination, over a two-year period. All subjects fulfilled the

clinical diagnosis for PD, based on MDS clinical diagnostic criteria and belong to early PD stages (1-2 modified H&Y scale stages [18]. Patients with a medical history of pre-existing causes of shoulder (e.g. shoulder trauma, dislocation, fracture, surgery, rheumatoid arthritis, cancer, stroke, cervical spine disease) or advanced PD pathology (e.g. cognitive impairment, dementia) were excluded.

Clinical Assessment

A questionnaire with information pertaining to demographics, neurological (rigidity, bradykinesia and tremor) and musculoskeletal symptoms (pain, hypomobility, frozen shoulder, fatigue, weakness, arm swing loss) of all enrolled PD patients was completed.

Physical evaluation of shoulder dysfunction involved: 1) measurements of passive and active glenohumeral and scapular joint movements with a digital goniometer; 2) test impingement syndrome (Neer and Hawkins's clinical tests); 3) Yergason's test; 4) Speed's test; 5) a bicipital groove tenderness test for diagnosis of tendinitis of the long head of the biceps; palpation of tender points within shoulder muscles; 6) a tender point within a taut band of the muscle, as a characteristic referred pain on sustained compression over the tender point, or a local twitch response within the band [19-20].

Musculoskeletal Ultrasonographic Technique

Real-time static and dynamic ultrasonography (US) was applied by DP, an experienced US physiotherapist, to evaluate both shoulders, using a 12-15 MHz linear-array transducer (Phillips, iU 22 equipment). Standard protocols and criteria for the US shoulder evaluation were also employed in this study. During the exam, participants were seated on a stable stool in a slightly lower level than the examiner. Long head of the biceps tendon, supraspinatus, and subscapularis and infraspinatus tendons were examined in transverse and longitudinal plane. The tendon thickness, homogeneity of the fibrillar pattern, margins regularity and identification of calcifications were assessed [21-26].

Tendinosis, calcific tendinopathy, partial and full-thickness tears, bicipital tenosynovitis and impingement were recorded as US-detected shoulder abnormalities. Diffuse hypoechogenicity within a fibrillar pattern, a >2mm difference in tendon thickness compared to the healthy side, swelling changes and/or irregularity of tendon margins were interpreted as tendinosis. Partial tendon tear was identified as focal heterogeneous hypoechogenecity within the fibrillar pattern and hypoechoic defect limited to a part of tendon thickness. Full-thickness tear was confirmed in cases of non-visualization, anechoic or hypoechoic fiber discontinuity of tendon. Bicipital tenosynovitis was identified as a thickened hypoechoic area around the biceps tendon with increased power Doppler flow [27]. Calcium deposit detected on tendons confirmed calcific tendinopathy. Impingement syndrome was assessed with the transducer placed above the acromion during lateral passive elevation of the arm. Normally, the supraspinatus tendon slides smoothly inferior to the acromion. Finally, adhesive capsulitis was defined as a difficulty in obtaining adequate images of the subscapularis tendon in dynamic US external rotation and increased fluid in the dependent portion of the bicipital tendon sheath.

Statistical Analysis

All analyses were carried out using SPSS vr 21.00 (IBM Corporation, Somers, NY, USA). Data were expressed as percentages for qualitative variables and as mean ± S.D for quantitative variables. The Kolmogorov-Smirnov test was utilized for normality analysis of the quantitative variables. Bivariate analyses were made by using the Independent samples t-test or Mann-Whitney test in case of violation of normality. Chi-square test, Fisher's exact test were used to analyze the relation between the US markers and the quantitative or qualitative clinical variables respectively. Multivariable logistic regression models were used to identify independent clinical predictors of the US-detected tendinopathies. All tests were two-sided, a p-value of <0.05 was used to denote statistical significance.

Results

Demographics and Shoulder Pathologic Findings

Demographic and clinical variables are summarized in Table 1. The 64% of PD patients had unilateral (32% right and 32% left) and 36 (36%) had bilateral PD involvement. The median PD duration was 3 (0-20) years and the median duration of shoulder dysfunction was 1.0 (0-18) year. 55 out of 100 subjects (55%) were at 1 stage at modified H&Y scale.

Rigidity was the most common PD cardinal symptom (42%, n=84/200). Tremor and bradykinesia were also assessed in 69/200 (34.5%) and 36/200 (18%) shoulders, respectively. Arm swing loss (71/200, 35.5%); disability in activities of daily living (dressing, eating etc.) (81/200, 40.5%); pain (67/200, 33.5%); "*frozen shoulder*" (48/200, 24%); fatigue (16/200, 9.9%) and weakness (12/200, 6%) were other clinical findings. Shoulder hypomobility was detected as decreased range (<90º) of shoulder movements in 109 out of 200 (54.5%) examined shoulders of early PD patients (Figure 1).

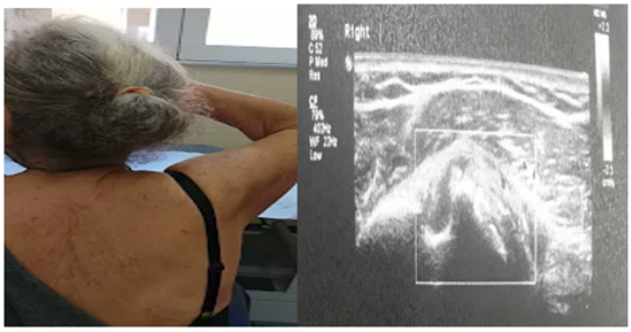

Figure 1: Shoulder hypomobility and sonographically detected abnormality in patients with early Parkinson's disease.

Demographics & Shoulder Clinical Findings		n (%)
Demographics (n=100) †	Age (y); mean± SD (min-max)	64.85±10.61 (31-86)
	Gender; male/female, n (%)	59(59%)/41(41%)
	Dominant hand; right / left, n (%)	97(97%)/3(3%)
	PD involvement; right/left/bilateral, n (%)	32(32%)/32(32%)/36(36%)
	PD duration (y); median (min-max)	3.0 (0.1-20)
	PD stages (modified H&Y scale); 1/1.5/2, n (%)	55(55%)/9(9%)/36(36%)

PD cardinal symptoms (n=200 shoulders)	Arm Tremor; n (%)	69(34.5%)
	Arm Rigidity; n (%)	84(42%)
	Arm Bradykinesia; n (%)	36(18%)
Other Clinical Features (n=200 shoulders)	Frozen shoulder; n (%)	48 (24%)
	Arm swing loss; n (%)	71(35.5%)
	Pain; n (%)	67(33.5%)
	Weakness; n (%)	12 (6%)
	Fatigue; n (%)	16 (9.9%)
	Shoulder disability in activities of daily living; n (%)	81(40.5%)
	Measured hypomobility; n (%)	109(54.5%)
	Shoulder dysfunction duration; median (min-max)	1.0 (0-18)
Data are summarized as n, percentage (%) of qualitative variables and mean± S.D, range of quantitative variables, in a sample of 200 shoulders of 100 patients with early Parkinson's disease. † y: years, PD: Parkinson's disease, modified H&Y scale: modified Hoehn and Yahr scale rating Parkinson's severity.		

Table 1: Clinical and US pathologic Shoulder findings (n=200) and demographics of patients with early Parkinson's disease (n=100).

US Findings

RC tendinopathies were US detected in 103 (64%) out of 161 shoulders with PD symptoms. The most frequent US tendon abnormalities were tendon calcification (42.9%, n=69/161), tendinosis (38.5%, n=62/161), atrophy (28%, n=45/161), hypertrophy (5.6%, n=9/161), impingement (26.1%, n=42/161), partial (32.3%, n=52/161), and full tendon tears (8.7%, n=14/161). Acute tendon inflammation was extremely rare (0.006%, n=1/161) (Table 2).

RC Tendon US Abnormalities in PD symptomatic shoulders (n=161) †	**n (%)**
Clinical & US pathologic findings in symptomatic shoulders; n (%)	161 (80.5%)
RC Tendon US abnormalities; n (%)	103 (64%)
Calcification; n (%)	69 (42.9 %)
Tendinosis; n (%)	62 (38.5%)
Partial tears; n (%)	52 (32.3%)
Atrophy; n (%)	45 (28%)
Impingement; n (%)	42 (26,1%)
Full tears; n (%)	14 (8.7%)
Hypertrophy; n (%)	9 (5.6%)
Tendinitis; n (%)	1 (0.006%)
Subclinical soft tissue involvement (US abnormal findings or shoulder dysfunction in asymptomatic shoulders); n (%)	30/200 (15%)

Table 2: Rotator Cuff (RC) Tendon Sonographic (US) findings in shoulders of early PD patients (n=).

†Data are summarized as n, percentage of the presence (p) of US abnormal findings in 161 pathologic shoulders of 100 patients with early Parkinson's disease, RC: rotator cuff, PD: Parkinson's disease, US: ultrasonography.

Abnormal US findings or shoulder dysfunction were detected in 30/200 asymptomatic shoulders (15%), revealing subclinical involvement. In total, US pathologic signs were detected in 161/200 (80.5%) PD symptomatic shoulders. Normal clinical and US finding were observed in 39/200 (19.5%) shoulders.

Correlation between Clinical and Sonographic Findings

Correlation between clinical predictors and tendon impingement were summarized in Table 3. In multiple logistic regression analysis using the enter method, the independent variables were accounting for 42.7% of the variance in tendon impingement [Nagelkerke R2=0.427]. The results shown that statistically significant independent predictors of tendon impingement were bradykinesia (OR 7.57, 95% CI 2.20-26.04; p=0.001) and dysfunction duration (OR 1.33, 95% CI 1.05-1.68; p=0.017). The results in analysis using the forward LR method (R2=0.339) shown that both bradykinesia (OR 8.61, 95% CI 2.81-26.38; p<0.0005) and dysfunction duration (OR 1.32, 95% CI 1.07-1.61; p=0.008) were the most significant independent predictors of tendon impingement. Patients with bradykinesia have 8.61 times higher probability of tendon impingement compared with those without. One year increase of shoulder dysfunction increases the likelihood of tendon impingement by 1.32%.

			Reference category	**OR**	**95% CI**		**p-value†**
Tendon Impingement	Enter method R2=0.427.	Shoulder dysfunction (Hypomobility)	No	4.5	0.33	60.89	0.258
		Shoulder pain	No	0.87	0.25	3.07	0.828
		Shoulder tremor	No	0.65	0.21	2.03	0.456
		Shoulder rigidity	No	1.73	0.49	6.13	0.398
		Shoulder bradykinesia	No	7.57	2.2	26.04	0.001
		Age	-	0.98	0.93	1.04	0.552
		Gender	Male	1.49	0.47	4.71	0.495
		Parkinson duration	-	0.89	0.74	1.07	0.21
		Shoulder dysfunction duration	-	1.33	1.05	1.68	0.017
		Parkinson stages (modified H&Y)	1 or 1.5	0.26	0.01	10.11	0.472
		Parkinson side	-	-	-	-	0.648
		Left	right	1.39	0.35	5.43	0.639
		Bilateral		5.25	0.13	209.41	0.378
	Forward LR R2=0.339.	Shoulder bradykinesia	no	8.61	2.81	26.38	<0.0005
		Shoulder dysfunction duration	-	1.32	1.07	1.61	0.008

Table 3: Correlations between clinical predictors and US-detected tendon impingement in shoulders (n=200) of early PD patients (n=100).

†Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multiple logistic regression analysis using Enter and forward LP (Nagelkerke R2); PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD stages

Concerning tendon thickness, the correlations between clinical and US-detected RC atrophy are reported in Table 4. The independent variables were accounting for 26.9% of the variance in tendon atrophy using Enter method in regression analysis [Nagelkerke R2=0.269]. Significant independent predictor of tendon atrophy was the shoulder dysfunction (OR 9.45, 95% CI 0.80-111.46; p=0.074).Multivariable regression analysis using the forward LR method (R2=0.173) shown that the shoulder dysfunction (OR 15.77, 95% CI 2.0-125.11; p=0.009) was the most statistically significant independent predictor of tendon atrophy. Shoulder pain was significant independent predictor in case of shoulder dysfunction exclusion (OR 3.64, 95% CI 1.54-8.6; p=0.003). PD Patients with shoulder dysfunction have 15.77 times higher probability of tendon atrophy compared with those without. Patients with shoulder pain have 3.64 times higher probability of tendon atrophy compared with those without, if shoulder dysfunction was excluded.

			Reference Category	OR	95% CI		p-value†
Tendon Atrophy	Enter method R2=0.269	Shoulder dysfunction (Hypomobility)	No	9.45	0.8	111.5	0.074
		Shoulder pain	No	1.61	0.6	4.62	0.379
		Shoulder tremor	No	1.83	0.7	4.92	0.228
		Shoulder rigidity	No	1.49	0.5	4.27	0.462
		Shoulder bradykinesia	No	0.95	0.3	2.82	0.933
		Age	-	0.97	0.9	1.01	0.166
		Gender	Male	1.27	0.5	3.4	0.628
		Parkinson duration	-	0.99	0.9	1.12	0.877
		Shoulder dysfunction duration	-	0.93	0.8	1.08	0.37
		Parkinson stages (modified H&Y)	1 or 1.5	0.47	0	17.89	0.687
		Parkinson side	-				0.81
		left	Right	0.87	0.3	2.85	0.823
		bilateral		2.84	0.1	108	0.574
	Forward LR R2=0.173	Shoulder dysfunction	No	15.8	2	125.1	0.009
	Shoulder dysfunction excluded	Shoulder pain	No	3.64	1.5	8.6	0.003

Table 4: Correlations between clinical variables in relation to US detected RC atrophy in shoulders (n=200) of early PD patients (n=100).

†Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multifactorial logistic regression analysis using Enter and forward LP (Nagelkerke R2), PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity

The correlations between clinical predictors and RC hypertrophy are summarized in Table 5. In analysis using the enter method, the independent variables were accounting for 37.6% of the variance in tendon hypertrophy [Nagelkerke R2=0.376]. Significant independent predictor of tendon hypertrophy was the shoulder dysfunction duration (OR 1.44, 95% CI 1.04-2.01; p=0.028). Forward LP method (R2=0.147) also showed that shoulder dysfunction duration was the statistically significant independent predictor of tendon hypertrophy (OR 1.26, 95% CI 1.06-1.52; p=0.011). One year increase of shoulder duration increases the likelihood of tendon hypertrophy by 1.26%.

			Reference category	OR	95% CI		p-value†
Tendon Hypertrophy	Enter method R2=0.376	Shoulder dysfunction (Hypomobility)	No	0.18	0.001	13.87	0.444
		Shoulder pain	No	4.91	0.59	41.03	0.142
		Shoulder tremor	No	0.18	0.02	1.59	0.122
		Shoulder rigidity	No	6.7	0.41	110.83	0.184
		Shoulder bradykinesia	No	0.73	0.08	6.71	0.785
		Age	-	1	0.9	1.11	0.983
		Gender	male	0.15	0.02	1.41	0.097
		Parkinson duration	-	1.17	0.93	1.48	0.19
		Shoulder Dysfunction duration	-	1.44	1.04	2.01	0.028
		Parkinson stages (modified H&Y)	1 or 1.5	0.046	0.001	1.85	0.103
		Parkinson side					0.492
		left	right	3.65	0.32	42.1	0.299
		bilateral		6.37	0.16	251.96	0.324
	Forward LR R2=0.147 Shoulder dysfunction excluded.	Shoulder dysfunction duration	No	1.26	1.06	1.52	0.011

Table 5: Correlations relation between clinical predictors and US-detected RC hypertrophy in shoulders of early PD patients.

† Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multifactorial logistic regression analysis using Enter and forward LP (Nagelkerke R2). PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity

RC partial tears were other US-detected RC abnormalities in early PD patients. In Enter method, the independent variables were accounting for 35.1% of the variance in tendon partial tear [Nagelkerke R2=0.351]. Independent predictors of tendon partial tear were the shoulder dysfunction (OR 27.74, 95% CI 2.25-341.36; p=0.009) and the gender (male) (OR 4.08, 95% CI 1.3-11.97; p=0.010). Forward LR method (R2=0.270) also showed that the most significant

predictors of tendon partial tear were shoulder dysfunction (OR 22.2, 95% CI 2.70-181.50; p=0.004) and gender (male) (OR 2.86, 95% CI 1.10-7.20; p=0.025). Patients with shoulder dysfunction have 22.2 times higher probability of tendon partial tear compared with those without. Males have a higher likelihood of partial tear by 2.86%. compared with females. If shoulder dysfunction was excluded, shoulder rigidity (OR 3.48, 95% CI 1.44-8.42; p=0.006) and gender (male) (OR 2.48, 95% CI 1.04-5.93; p=0.042) were the most significant independent predictors of tendon partial tear (Table 6).

			Reference category	OR	95% CI		p-value†
Tendon Partial Tear	Enter method R2=0.351	Shoulder dysfunction (Hypomobility)	no	27.74	2.25	341.36	0.009
		Shoulder pain	no	0.67	0.23	2	0.477
		Shoulder tremor	no	1.7	0.61	4.75	0.311
		Shoulder rigidity	no	1.45	0.48	4.33	0.508
		Shoulder bradykinesia	no	198	0.61	6.46	0.259
		Age	-	0.99	0.95	1.04	0.724
		Gender	male	4.08	1.39	11.97	0.01
		Parkinson duration	-	0.92	0.8	1.05	0.209
		Dysfunction duration	-	0.89	0.75	1.04	0.146
		Parkinson stages (modified H&Y)	1 or 1.5	0.31	0.01	17.84	0.57
		Parkinson side	-	-	-	-	0.806
		left	right	0.96	0.28	3.3	0.953
		bilateral		3.74	0.06	218.57	0.525
	Forward LR R2=0.270	Shoulder dysfunction	no	22.2	2.7	181.5	0.004
		Gender	male	2.86	1.1	7.2	0.025
	Shoulder dysfunction excluded	Shoulder rigidity	no	3.48	1.44	8.42	0.006
		Gender	male	2.48	1.04	5.93	0.042

Table 6: Correlations between clinical predictors and US-detected RC Partial Tear in shoulders of early PD patients.

† Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multifactorial logistic regression analysis using Enter and forward LP (Nagelkerke R2). PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity.

In the Enter method, the independent variables were accounting for 27.2% of the variance in RC degeneration [Nagelkerke R2=0.272, Table 7]. Significant independent predictor of tendon degeneration was shoulder dysfunction (OR 11.89, 95% CI 1.62-87.21; p=0.015). The forward LR method (R2=0.187) showed that the most significant independent predictor of tendon degeneration was the shoulder dysfunction (OR 11.67, 95% CI 2.48-54.93; p=0.002). If shoulder dysfunction was excluded, shoulder rigidity was the most significant independent predictor of tendon degeneration (OR 2.96, 95% CI 1.27-6.88; p=0.012).

			Reference category	OR	95% CI		p-value†
Tendinosis (Tendon Degeneration)	Enter method R2=0.272	Shoulder dysfunction	No	11.9	1.6	87.21	0.015
		Shoulder pain	No	0.73	0.3	2.14	0.562
		Shoulder tremor	No	1.51	0.6	4.14	0.422
		Shoulder rigidity	No	1.07	0.4	3.18	0.897
		Shoulder bradykinesia	No	1.96	0.6	6.29	0.257
		Age	-	0.97	0.9	1.02	0.191
		Gender	Male	1.91	0.7	5.17	0.203
		Parkinson duration	-	0.93	0.8	1.06	0.253
		Shoulder dysfunction duration	-	1.05	0.9	1.24	0.526
		Parkinson stages (modified H&Y)	1 or 1.5	0.72	0	24.64	0.858
		Parkinson side					0.859
		Left	Right	1.28	0.4	4.22	0.683
		Bilateral		2.21	0.1	76.72	0.66
	Forward LR R2=0.187	Shoulder dysfunction	No	11.7	2.5	54.93	0.002
	Shoulder dysfunction excluded	Shoulder rigidity	No	2.96	1.3	6.88	0.012

Table 7: Correlations between clinical predictors and US-detected RC degeneration in shoulders of early PD patients.'

† Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multifactorial logistic regression analysis using Enter and forward LP, (Nagelkerke R2). PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity.

Concerning the detection of calcium crystal deposits in RC tendons, the enter method, showed that the independent variables were accounting for 29.4% of the variance in RC calcification [Nagelkerke R2=0.294]. Independent predictors of tendon calcification were shoulder dysfunction (OR 5.68, 95% CI 0.91-35.43; p<0.006) and PD duration (OR 0.86, 95% CI 0.75-0.98; p=0.029). One year increase of PD duration decreases the likelihood of tendon calcification by 0.86%. The forward LR method (R2=.111) showed that the most statistically significant independent predictor of tendon calcifications was shoulder dysfunction (OR 5.28, 95% CI 1.56-17.87; p=0.008) (Table 8).

			Reference category	OR	95% CI		p-value†
Tendon Calcification	Enter method R2=0.294	Shoulder dysfunction (Hypomobility)	no	5.68	0.9	35.43	0.006
		Shoulder pain	no	1.66	0.6	5.05	0.371
		Shoulder tremor	no	1.89	0.7	5.21	0.216
		Shoulder rigidity	no	0.6	0.2	1.93	0.396
		Shoulder bradykinesia	no	1.16	0.4	3.7	0.807
		Age	-	1.04	1	1.09	0.1
		Gender	male	1.71	0.6	4.81	0.311
		Parkinson duration	-	0.86	0.8	0.98	0.029
		Shoulder dysfunction duration	-	1	0.9	1.17	0.974
		Parkinson stages (modified H&Y)	1 or 1.5	0.35	0	7.83	0.51
		Parkinson side					0.323
		left	right	1.28	0.4	4.11	0.682
		bilateral		11.2	0.5	259.2	0.133
	Forward LR R2=0.111	Shoulder dysfunction	no	5.28	1.6	17.87	0.008

Table 8: Correlations between clinical predictors and US-detected RC Calcification in shoulders of early PD patients.

† Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multifactorial logistic regression analysis using Enter and forward LP (Nagelkerke R2). PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity.

			Reference category	OR	95% CI		p-value†
RC Tendon Abnormalities	Enter method R2=0.684	Shoulder dysfunction (Hypomobility)	no	651.26	18.36	23091.6	0.0005
		Shoulder pain	no	0.24	0.018	3.35	0.291
		Shoulder tremor	no	4.78	0.69	32.84	0.111
		Shoulder rigidity	no	0.38	0.02	4.19	0.323
		Shoulder bradykinesia	no	4.67	0.3	71.42	0.267
		Age	-	0.97	0.89	1.07	0.618
		Gender	male	6.77	0.81	56.12	0.076
		Parkinson duration	-	0.9	0.7	1.15	0.414
		Shoulder dysfunction duration	-	1	0.73	1.38	0.965
		Parkinson stages (modified H&Y)	1 or 1.5	1.97	0.07	55.37	0.69
		Parkinson side	-	1.01	0.18	5.56	0.995
	Forward LR R2=0.608	Shoulder dysfunction	-	92.16	18.58	457.05	0.005

Table 9: Correlations between clinical predictors and all US-detected RC abnormalities in shoulders of early PD patients.

† Odds Ratio (OR), 95% CI, sig. p-value<0.05 were calculated in multiple logistic regression analysis using Enter and forward LP (Nagelkerke R2). PD: Parkinson's disease, modified H&Y: modified Hoehn and Yahr scale rating PD severity.

Correlations between clinical predictors and RC tendon pathology are summarized in Table 9. The enter method showed that the independent variables were accounting for 60.8% of the variance in all RC tendon disorders [Nagelkerke R2=0.608]. Significant predictor of RC tendinopathies was shoulder dysfunction (OR 651.26, 95% CI 18.36-23091.60; p<0.005). Forward LR method [R2=0.608] also confirmed that the most significant independent predictor of RC tendon disorders was shoulder dysfunction (OR 92.16, 95% CI 18.58-457.05; p=0.0005).

Discussion

RC pathology is a common musculoskeletal disorder that can cause severe pain and disability in the general population especially in middle age. To date, few studies have been focus on shoulder disorders in PD patients and none, to our knowledge, has specifically studied RC tendinopathies in the initial stages of the disease. Therefore, we conducted this study to identify and accurately assess RC pathology and clinical symptomatology in early PD patients. In our sample, the prevalence of US pathologic findings was higher than the prevalence of the perceived shoulder symptoms, indicating that there was a subclinical involvement. Shoulder hypomobility, rigidity and tremor were the most common clinical findings.

US is an imaging tool with high resolution and enables the visualization of RC tendons without utilizing ionizing radiation, in a weight-bearing position. It is used even in cases of tremor, where it is difficult to perform MRI due to movement artifacts. In our study, US enabled the detection of RC tendon abnormalities in 64% of the shoulders with clinical symptoms. The most frequent US tendon abnormalities were tendon calcification, degeneration, partial tears and atrophy. Hypertrophy, full tendon tears and tendinitis were rarely detected.

The most significant independent predictor of RC tendinopathies in early PD patients was shoulder dysfunction in terms of decreased

			Reference Category	OR	95% CI		p-value†
RC Tendon Abnormalities	Enter method R^2= 0.684	Shoulder dysfunction	No	651.3	18.4	23092	0.0005
	Forward LR R^2= 0.608	Shoulder dysfunction	-	92.16	18.6	457.05	0.005
Tendon Calcification	Enter method R^2=0.294	Shoulder dysfunction	No	5.68	0.91	35.43	0.006
		Parkinson duration	-	0.86	0.75	0.98	0.029
	Forward LR R^2= 0.111	Shoulder dysfunction	-	5.28	1.6	17.87	0.008
Tendinosis	Enter method R^2=0.272	Shoulder dysfunction	No	11.89	1.62	87.21	0.015
	Forward LR R^2=0.187	Shoulder dysfunction	No	11.67	2.48	54.93	0.002
	Shoulder dysfunction excluded	Shoulder rigidity	No	2.96	1.27	6.88	0.012
Tendon Partial Tear	Enter method R^2=0.351	Shoulder dysfunction	No	27.74	2.25	341.36	0.009
		Gender	Male	4.08	1.39	11.97	0.01
	Forward LR R^2=0.270	Shoulder dysfunction	No	22.2	2.7	181.5	0.004
		Gender	Male	2.86	1.1	7.2	0.025
	Shoulder dysfunction excluded	Shoulder rigidity	No	3.48	1.44	8.42	0.006
Tendon Atrophy	Enter method R^2=0.269	Shoulder dysfunction	No	9.45	0.8	111.46	0.074
	Forward LR R^2=0.173	Shoulder dysfunction	No	15.77	2	125.11	0.009
	Shoulder dysfunction excluded	Shoulder pain	No	3.64	1.54	8.6	0.003
Tendon Hypertrophy	Enter method R^2=0.376	Shoulder dysfunction duration	-	1.44	1.04	2.01	0.028
	Forward LR R^2=0.147	Shoulder dysfunction duration	No	1.26	1.06	1.52	0.011
Tendon Impingement	Enter method R^2=0.427	Shoulder bradykinesia	No	7.57	2.2	26.04	0.001
		Shoulder dysfunction duration	-	1.33	1.05	1.68	0.017
	Forward LR R2=0.339	Shoulder bradykinesia	No	8.61	2.81	26.38	<0.0005
		Shoulder dysfunction duration	-	1.32	1.07	1.61	0.008

Table 10: Correlations relation between clinical predictors and US-detected tendon abnormalities in shoulders of early PD patients.

range of active flexion. In early PD stages, patients with shoulder dysfunction had higher probability of tendon partial tear, tendon atrophy and degeneration compared with those without. If shoulder dysfunction was excluded, shoulder rigidity was other significant independent predictor of tendon partial tear and degeneration. What-is-more, PD patients with shoulder pain had higher probability of tendon atrophy compared with those without, in case of shoulder dysfunction exclusion.

Arm bradykinesia seems to increase the probability of impingement. One year increase of PD duration may also decrease the likelihood of tendon calcification. One year increase of shoulder dysfunction duration may increase the likelihood of tendon hypertrophy and of impingement. Males had greater likelihood of tendon partial tear compared with females.

Other sonographic studies, that enrolled patients in different stages of PD, also reported tendon problems. Increased tendon thickness were the most common US findings in PD patients with frozen shoulder, and was associated with rigidity. In this study, atrophy was more frequent than hypertrophy. Rigidity was a significant clinical predictor of RC degeneration and partial tear.

Evidence indicates that the etiology of RC tendinopathy is multi-factorial. Extrinsic, intrinsic or a combination of both mechanisms play a role. Extrinsic factors, such as alterations in scapular and glenohumeral kinematics that could cause compression of the RC tendons, contributing to external impingement. Our findings suggest that arm bradykinesia may increase the probability of external impingement. Biomechanical factors that can lead to extrinsic mechanical RC tendon compression include shoulder dysfunction due to abnormal scapular and humeral kinematics, postural abnormalities, RC and scapular muscle performance deficits and decreased extensibility of pectoralis minor or posterior shoulder tissues. Scapular and humeral kinematic abnormalities can cause dynamic narrowing of the sub acromial space leading to RC tendon compression secondary to superior translation of the humeral head or abnormal scapular motion that causes the acromion to move inferiorly [28]. Shoulder dysfunction detected in early PD patients, may follow similar extrinsic mechanisms of RC pathology.

Soft tissue tightness is other external factor that can directly influence scapular and humeral kinematics. Rigidity could be another mechanism leading to RC degeneration and partial tears in early PD patients, as it related to inflexibility of muscles and inability to relax. Reduced dopamine levels in PD are thought to disrupt the coordination between the muscles which extend and relax for each movement. In PD patients, rigidity may decrease extensibility of pectoralis and posterior shoulder muscles alter humeral and scapular kinematics and cause an abnormal load increase on the RC tendons during movements.

Prominent osteophytes to the inferior aspect of the acromio-clavicular joint or coraco-acromial ligament, as far as other anatomical factors (such as variations in shape of the acromion [29], orientation of the slope/angle of the acromion and postural abnormalities) may excessively narrow the sub acromial space and outlet to the RC tendon pathology.

Calcification was a common US tendon abnormality in our study. We can hypothesize that the process of calcification in PD patients follows similar processes with other degenerative diseases, triggered by the calcium paradox and other mechanisms. Repetitive trauma, degenerative, tenocyte necrosis, reactive and endochondral ossification are some factors proposed to interfere in the process of calcific formation [30-32].

In our study, degeneration of RC tendon was another frequent US abnormality detected in shoulders of early PD patients. Intrinsic mechanisms, such as RC tendon mechanical properties, composition, and vascularity, are those that associated with degeneration of the RC tendons contribute to internal impingement and appear to be particularly significant factors of RC tendinopathy in the general population. Intrinsic mechanisms of RC tendinopathy influence tendon morphology. Intrinsic factors of RC tendinopathy result in tendon degradation due to the process of aging, poor vascularity, and altered biology, and inferior mechanical properties resulting in damage with tensile or shear loads. Proposed intrinsic mechanism of RC tendinopathy is related to the response of the tendons to tensile load, or mechanical properties of the supraspinatus tendon. Lower ultimate strain and greater tissue stiffness to longitudinal loading have been found on the articular side of the supraspinatus tendon than to the bursal side. In our study, shoulder dysfunction, rigidity, bradykinesia may alter the response of RC tendon to the tensile or shear loads and increase the likelihood of degeneration.

What-is-more partial tear were more common than full tendon tears. A deficient in vascular supply of the human RC tendons has been implicated in the pathogenesis of RC degenerative changes and tears. Research suggests an increased vascular response, or neovascularization, in regions of degenerative changes and partial tendon tears such as with chronic RC tendinopathy that is theorized to be a healing response to tissue micro trauma. In contrast, tendinopathies that progress to complete tendon tears have been shown to be avascular. Repetitive micro trauma is considered a more relevant factor than acute trauma to rotator cuff tear and could predispose tendinosis of the long head of the biceps tendon in mild PD patients.

Formations of cross-links stabilize the collagens within the RC tendon matrix. Within RC tendons of elderly, such as of our sample, the distribution of collagen types has been shown to vary with greater proportion of type II and III collagen near the insertional fibrocartilagenous region, that has been proposed to weaken the tendon and precede full-thickness tear. Tear and pain are common, when the loads placed on the tendon cells exceeds the ability to effectively repair structural deficits.

This study has some limitations. First, US is an imaging tool with high resolution but in a complex anatomic site as the shoulder, which includes several superficial and deeper structures, different acoustic windows are required for an adequate shoulder assessment. The patient's body size can largely influence the US visualization of the shoulder structures. We should ideally have performed reference standard techniques (shoulder MRI, MR arthrography, arthroscopy, or open surgery) for diagnostic confirmation. However, MRI was actually difficult to perform in PD patients because of the limitation of tremor, which was frequent in our subjects. In order to get a broader insight into RC pathology across the range of severity of the diseases, inclusion of PD patients with more advanced disease may be warranted in future studies.

Despite the limitations, our results strongly suggest that RC tendinopathies are common findings in early PD patients. Calcification, degeneration, atrophy and partial tears of RC tendons can be objectively assessed by US. Shoulder hypomobility, rigidity, bradykinesia and shoulder duration could be clinical predictors of RC pathology.

Conclusion

Rotator cuff tendinopathies are common in patients with early Parkinson's disease. Hypomobility of active movements and rigidity are the most common clinical should findings in early PD stages. Calcification, degeneration and partial tear were the most common RC abnormalities detected with US. US may also detect tendon abnormalities before the establishment of clinical symptoms. Frozen shoulder and rigidity are clinical predictors of RC tendon pathology.

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