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Review Article

Shoulder Dysfunction in Parkinson Disease: Review of Clinical, Imaging Findings and Contributing Factors

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Abstract

This study aimed to review shoulder clinical and imaging findings in Parkinson's disease (PD), focusing on the significance of timely diagnosis and management of shoulder dysfunction in PD for the prevention of shoulder-related complications. A bibliographical search was employed, using "Parkinson's" and "Shoulder Dysfunction" as keywords. A Magnetic Resonance Imaging, twenty clinical and three US studies were selected as relevant to shoulder dysfunction in PD. Shoulder pain, frozen shoulder and arm swing asymmetry are the most prevalent clinical findings that may antedate cardinal PD symptoms. Supraspinatus tendon thickening or tearing, adhesive capsulitis, acromioclavicular changes, bursa and joint effusion are common shoulder MRI or US-detected abnormalities in mild or severe PD stages. Fractures due to falls or osteoporosis are secondary shoulder pathologies. Higher ipsilateral Unified Parkinson's Disease Rated Scale (UPDRS) scores, rigidity, tremor, and bradykinesia are associated with frozen shoulder. Disease duration, rigidity, and falls are contributing factors for tendon tears, adhesive capsulitis, and fractures respectively. When common symptoms, such as pain and frozen shoulder are unaccounted for by orthopedic or other local primary pathology, they might indicate underlying early PD. Timely diagnosis and appropriate early management of PD may, in turn, help delay or prevent shoulder-related complications.

Keywords: Clinical Findings, Magnetic Resonance Imaging Findings, Musculoskeletal Ultrasonography, Parkinson's Disease, Shoulder Dysfunction

Introduction

Parkinson's disease (PD) is the second most frequent degenerative disorder of the central nervous system[1-2], affecting approximately 6.1 million individuals worldwide[3]. Depletion of dopaminergic connections in the basal ganglia is one of the main histopathologic characteristics, causing dysfunction of pathways that are involved in the control of movement and balance[1,3,4]. Although rigidity, rest tremor and bradykinesia are the three cardinal features of the disease[1,3], PD records a wide spectrum of motor and non-motor signs[1-2,4-14], such as musculoskeletal pain[5,8,9], articular (frozen shoulder, dystonia, arthritis)[4,6,10,11,13], postural (camptocormia, Pisa syndrome, kyphosis, scoliosis, dropped head syndrome)[3-6,13-14] and bone mineralization disorders (osteoporosis, osteopenia, low energy fractures)[4,7,10,12]. These non-motor disturbances often remain misdiagnosed and poorly treated[6,8,10,14].

Moreover, the bibliography which focuses on shoulder problems[19-55] leading to dysfunction[6,7,10,14] have been relatively sparse[26,31,36-37]. It is widely known that shoulder is a joint with

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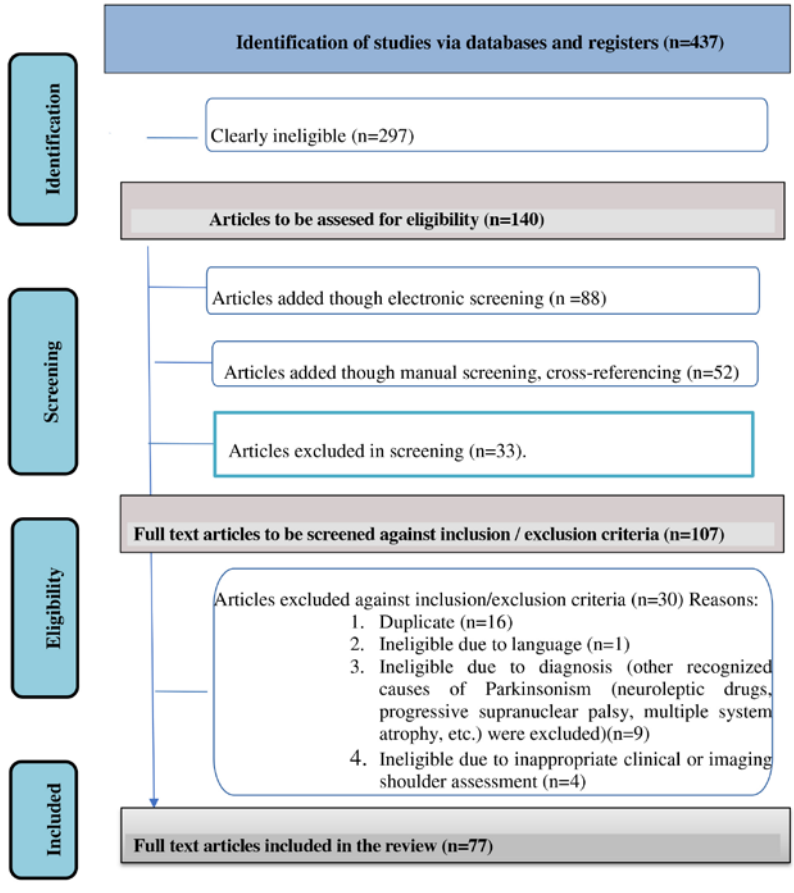

Figure 1. Study flowchart.

complex and precise function consisting of four articulations (glenohumeral, sternoclavicular, acromioclavicular, and scapulothoracic) and a supportive network of muscles, as well as articular and periarticular structures, providing a perfect compromise between stability and extreme mobility[15-18]. Shoulder dysfunction refers to abnormalities in function of one or more contractile or non-contractile components[15,19-21] and it is defined as an alteration in quality and quantity of shoulder in motion which might affect activities of daily living, even in the absence of shoulder pain or other readily recognized symptoms[16,19-20,22].

Two out of three of all adults experience shoulder dysfunction in the course of their lifetime, with shoulder pain being the third most common reason for referral for physiotherapy[16,17,20,22]. However, little is known about the way PD affects the shoulder[26,31,36-37].

The purposes of this literary review are threefold. The primary aim is to provide a critical overview of clinical findings of shoulder dysfunction in PD patients. Furthermore, in an attempt to understand the way that PD may affect shoulder function, the review is conducted beyond shoulder pathology in PD. Important insights into shoulder dysfunction may be gained by high-resolution imaging methods, primarily Magnetic Resonance Imaging (MRI)[37] and Musculoskeletal Ultrasonography (US)[28,31,36]. In conclusion, the major focus is provided on the significance of an accurate and early diagnosis of shoulder dysfunction in PD for the prevention of severe shoulder-related complications.

Materials and Methods

The methodology is depicted on the flowchart (Figure 1).

Search strategy

Comprehensive online literary research was conducted by the primary author (DP) in Pub Med, Google Scholar, Cochrane Collaboration, PLoS, Embase, Cinahl/EBSCO and PeDro bibliographic databases and registers, since May 2021 to gather relevant data on shoulder dysfunction in PD. A review of the literary sources was carried out from 1960 to 2022, while the final search was undertaken in May, 2022. MeSH-terms related to PD (Parkinson's disease (MeSH) OR Parkinson's) were explored and combined using the Boolean operator "OR" or "AND" "shoulder dysfunction (MeSH)", "diagnostic clinical findings (MeSH)" and "imaging findings (MeSH)".

Table 1. Common clinical and imaging findings and associations of shoulder dysfunction in Parkinson's Disease.

Shoulder Dysfunction (Clinical & Imaging Findings)	Authors (Year)	Methods		Prevalence	Associations	H&Y⁜ PD stages	Initial Symptom
		Assessment	Population (N)				
Clinical Findings (Decreased ROM⁜, Shoulder Pain, Frozen Shoulder)	Riley et al. (1989)[24]	Survey, UPDRS, H&Y, ADLS⁜	150 PD patients vs. 60 matched controls	History of Shoulder complaints: 43% in PD vs. 23% in controls, Frozen shoulder: 12.7% in PD vs. 1.7% in controls, Restricted ROM without pain : 2% -Pain without restriction of ROM: 8.6%	Akinesia 2 times more frequent than tremor in PD patients with frozen shoulder Upper limb cardinal PD symptoms ipsilateral to frozen shoulder	All H&Y PD stages	Frozen shoulder: 8%, 0-2 years prior to the onset of cardinal PD symptoms
Clinical Findings (Shoulder pain, Frozen shoulder)	Cleeves & Findley (1989)[25]	Interview	100 consecutive PD patients	12% Shoulder Pain, 8% Frozen Shoulder	Cardinal PD symptoms appeared on the same side as Shoulder pain.	-	Shoulder pain (12%) and Frozen shoulder (8%) 1 year prior cardinal PD symptoms
Clinical Findings (Shoulder pain)	Stamey et al. (2008)[27]	Interview	309 consecutive PD patients	Shoulder pain: 35 (11%)	Side of shoulder pain correlated with side of maximum severity of PD	All H&Y PD stages	Shoulder pain precedes onset of motor symptoms by several years.
Clinical Findings (Frozen shoulder)	Papalia et al. (2018)[4]	Preliminary online search	-	Hypothesis: postural alteration observed in PD could be the primum movens for shoulder pathology	Hypothesis: Camptocormia & decreased trunk mobility can yield a humeroacromial impingement and reduction of movement.	-	-
Clinical Findings (Frozen shoulder)	Alarcσn et al. (2020)[29]	MDS⁜, UPDRS III, video recordings	82 cases vs. 64 non-cases	Motor Dysfunction (frozen shoulder, action dystonia or postural/action/rest, tremor of a limb, anxiety, depression)	Frozen shoulder (OR 3.1; 95% CI 1.6-6.2).	0-I stages of H&Y	Motor dysfunction is clinical prodrome in PD
Clinical Findings (Shoulder Pain)	Madden & Hall (2010)[9]	Interview, Gelb criteria for PD diagnosis, H&Y⁜ to assess PD severity, Visual analog scale to assess pain severity	25 PD patients vs. 25 spouses as controls/	Shoulder pain: 80% of PD, Deep brain stimulation surgery improved shoulder pain in 40% of PD	Shoulder pain 21 times more likely in-PD patients vs. controls (adjusted for age, gender, and prior injury), Shoulder pain in PD related to underlying pathophysiology of PD rather than motor signs	2.2 H&Y stage	-
Clinical Findings (Frozen Shoulder and Pain)	Farnikova et al. (2012)[6]	Retrospective review of Hospital inpatient notes and outpatient clinic admission notes	82 PD patients	Musculoskeletal pain: a prodromal PD symptom in 27 (33%) cases initially diagnosed with osteoarthritis, degenerative spinal disease, and frozen shoulder	Improvement of musculoskeletal pain after the initiation of treatment in 23 (85%) cases.	All H&Y PD stages	Pain may be an early sing PD/ mean duration 6.6 years
Clinical Findings (Frozen Shoulder and Pain)	Kim et al. (2013)[14]	Interview, UPDRS I/II⁜	400 PD patients vs. 138 age- and sex-matched controls	Musculoskeletal problems: 66.3% in PD group vs. 45.7% in controls Commonly involved sites were low back, knee, and shoulder, Frozen shoulder: 2nd more common past diagnoses in the PD group	PD laterality coincided with musculoskeletal problems, Higher UPDRS in musculoskeletal group	All H&Y PD stages/ I Stage of H&Y	-
Clinical Findings (Shoulder Pain)	Teive et al. (2016)[34]	Interview, H&Y ⁜	15 early PD patients	Unusual motor and non-motor symptoms and signs, such as shoulder pain, related to the rigidity, akinetic syndrome in the early PD stage	-	Early H&Y PD stages	Shoulder pain in early stage of PD
Clinical Findings (Arm Swing Asymmetry)	Koh et al. (2019)[51]	3D motion Walking Analysis.	41 early PD and 23 controls	Shoulder ROM: -28o in PD group -33o in controls	Arm swing asymmetry at the wrist indicates PD involvement on the unilateral and distal upper limb in early stage.	I-II Stages of H&Y	Arm swing asymmetry in early stages.
Clinical Findings (Arm Swing Asymmetry)	Schneider et al. (2012)[32]	New battery focus on subtle motor features (asymmetric shoulder null position & delayed shoulder shrugs, reduced arm swing, subtle tremor, timed finger taps)	25 early PD patients & 57 controls (31 focal dystonia patients & 26 healthy individuals)	A total mean of 9.8 ± 4.9 (possible range: 0-94) in PD group	PD patients scored significantly higher than dystonia	Early H&Y PD Stages	Shoulder Asymmetry may be an early PD sign

Table 1. *(Cont. from previous page).*

Shoulder Dysfunction (Clinical & Imaging Findings)	Authors (Year)	Methods		Prevalence	Associations	H&Y⁜ PD stages	Initial Symptom
		Assessment	Population (N)				
Clinical Findings (Arm Swing Asymmetry)	Kwon et al. (2014)[33]	Visual inspections of video clips for asymmetric features of gait & posture (arm swing, leg swing, shoulder position, external foot rotation)	21 PD patients with rigidity, bradykinesia (concordance group) & 19 controls (discordance group) with a mismatch of pronounced symptoms	Side of more pronounced rigidity related with side of more decreased arm and leg swings	Reduction of arm and leg swings during gait in PD was associated with rigidity, but not with bradykinesia.	I Stage of H&Y	-
Clinical & EMG Findings (Arm Swing Asymmetry)	Buchthal & Fernandez-Ballesteros (1965)[23]	EMG ⁜ Action potentials were led-off from ten to thirteen shoulder muscles during walking	31 arms of 18 PD patients	Tremor of the shoulder muscles, difficult to assess clinically was quantitated EMG by the number of muscles with a pattern of rhythmical burst discharges during walking.	Direct relationship between proximal muscles with EMG tremor and degree of rigidity. The muscle primarily involved during walking was the posterior deltoid muscle	-	-
US ⁜ findings of shoulder dysfunction	Koh et al. (2008)[31]	Shoulder disability questionnaire, Musculoskeletal exam US⁜ shoulder examination	33 PD patients	22 PD patients had abnormal US findings. Tendon tearing = most common abnormal US finding, Supraspinatus tendon = the most common site (15/22).	Patients with tendon tearing had longer PD duration, Patients with adhesive capsulitis had a higher rigidity score	All H&Y PD stages	-
US findings of Shoulder dysfunction	Yucel & Kusbeci (2009)[36]	US evaluation H&Y PD stages	30 shoulders of patients with mild PD (I-II H&Y stages), and 37 shoulders of severe PD patients (III-IV stages of H&Y)	Effusion in the subacromial-subdeltoid bursa more often in severe (29.7%) vs. mild patients (16.7%), Full-thickness tears of supraspinatus tendon in 3 severe patients (8.1%) & in the infraspinatus tendon of 1 patient (2.7%).	Advanced shoulder pathologies are more frequently seen in severe patients with PD than the mild ones.	I-IV H&Y Stages	-
US findings in frozen shoulder	Chang et al. (2015)[28]	Clinical US Shoulder evaluation	60 shoulders of 30 PD patients	Frozen shoulder: in 14 of 30 PD patients Higher ipsilateral UPDRS scores and subscores associated with increased biceps effusion, increased subscapularis & supraspinatus tendon thickness	Positive correlation between frozen shoulder & US thickness bicipital effusion of subscapularis, supraspinatus tendon, mean UPDRSIII, tremor, rigidity& bradykinesia	All H&Y stages	-
MRI imaging of shoulder dysfunction	Yucel & Kusbeci (2010)[37]	MRI evaluation	28 PD patients (56 shoulders) and 13 age-matched (26 shoulders) controls	Full-thickness supraspinatus tears = higher UPDRS, tremor and rigidity, Mild PD = higher prevalence of resting tremor & subcoracoid effusion, Subcoracoid effusion in patients with higher UPDRS & rigidity, Higher frequency of full-thickness supraspinatus tendon tear in resting tremor	Longer PD duration in patients with full-thickness supraspinatus tear &acromioclavicular joint changes	All H&Y PD Stages	-
Postural, Bone, and Joint Disorders (Frozen Shoulder)	Rabin (2016)[35]	A Medline literature search	-	Posture (kyphoscoliosis, camptocormia, syndrome), Pisa syndrome, dropped head), bone (osteoporosis, bone fractures), and joint disorders (frozen shoulder, dystonia involving joints, joint pain) common in PD	Postural disorders, Bone mineralization disorders, Joint disorders are often related to PD	All H&Y PD Stages	-
Dysfunction Shoulder dysfunction (fractures)	Metz et al. (2001)[43]	Interview	A Case with PD	-	-	-	-
Shoulder Dysfunction (Dislocations)	Matsuzaki et al. (2009)[44]	Surgery, Interview, Radiography	A Case with PD	-Antero superior dislocation of the shoulder in a PD patient -Pain-free shoulder but reduced ROM after surgery	-	-	-
Shoulder Dysfunction (Rotator Cuff-Tear, Arthropathy & Dislocations)	Skedros et al. (2017)[45]	Surgery, Interview	A case with PD & shoulder dislocation	Reverse Total Shoulder Arthroplasty as Treatment for Rotator Cuff-Tear Arthropathy and Shoulder Dislocations in an Elderly Male with PD	-	H&Y IV Stages	-

Table 1. *(Cont. from previous page).*

Shoulder Dysfunction (Clinical & Imaging Findings)	Authors (Year)	Methods		Prevalence	Associations	H&Y⁜ PD stages	Initial Symptom
		Assessment	Population (N)				
Shoulder dysfunction (Fractures & Dislocations)	Burrus et al. (2015)[46]	Retrospective identification in a national database of total arthroplasty in PD patients and controls	3390 PD patients & 47034 controls who underwent arthroplasty;809 PD & 14262 controls who underwent; 2833PD & 38850 who had hemiarthroplasty	Shoulder Fractures after Total Arthroplasty: 1% in PD vs. 0.7% in controls; after Reverse arthroplasty Fractures: 1.4% in vs. 1% in controls; After Hemiarthroplasty 3.2% in PD vs. 2,2% in controls	PD associated with high rate of infection, fractures, dislocation, revised arthroplasty, systemic complications	-	-
Shoulder Dysfunction (Dislocations)	Sonnenblick et al. (1995)[47]	Surgery Interview	A PD case with recurrent bilateral dislocations	-	Recurrent bilateral shoulder dislocation resulting from dyskinesia associated with dopaminergic stimulation therapy	-	-
Shoulder Dysfunction (Fractures & Dislocations)	Dunn et al. (2011)[42]	Surgery, Interview, Radiography	3 Cases with PD	Reverse total shoulder arthroplasty in PD	-	-	-
Shoulder Dysfunction (Fractures & Dislocations)	Giannotti et al. (2015)[41]	Surgery, Radiography, CT	A Case with PD	Poor functional outcomes after Stemless humeral component in reverse shoulder prosthesis in PD		-	-
Shoulder Dysfunction (Fractures & Dislocations)	Borbas et al. (2021)[39]	Retrospective identification of institutional RTSA database	17 PD who underwent reverse total arthroplasty	Increased Complication Rate of Reverse Total Shoulder Arthroplasty in PD	-	-	-
Shoulder Dysfunction (Fractures & Dislocations)	Koch et al. (1997)[38]	Surgery, Interview H&Y score	15 PD patients	Pain relief Poor functional outcomes After Total shoulder arthroplasty in PD patients	-	All PD H&Y stages	-
Shoulder Dysfunction (Fractures & Dislocations)	Cusick et al. (2017) [48]	Range of motion, VAS, SST ASES function ⁜ scores	10 PD and 40 matched controls	Outcome of Reverse Shoulder Arthroplasty in PD Patients	-	-	-

⁜ PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; MDS: Movement Disorder Society Clinical Diagnostic Criteria for PD; H&Y: Hoehn and Yahr; US: Ultrasonography; MRI: Magnetic Resonance Imaging; EMG: Electromyography; VAS: Visual analog scale; SST: Simple Shoulder Test; ASES: American Shoulder and Elbow Society; ADLS: Activities of Daily Living

Inclusion Criteria

The inclusion criteria were: 1) articles written in English, French or German; 2) patients diagnosed with idiopathic PD based on standard diagnostic criteria (e.g. UK Brain Bank or MDS[56-57], The Unified Parkinson's Disease Rating Scale (UPDRS)[58,59], Hoehn and Yahr (H&Y) scale[60]); 3) relative or clinically assessed PD group with any shoulder symptom (e.g. pain, weakness) either defined as shoulder dysfunction or disorder (subacromial bursitis, adhesive capsulitis, rotator cuff disease, subacromial impingement syndrome, rotator cuff tendinosis or tendinitis, partial or full thickness tendon tear, calcific tendinopathy, proximal humeral head fractures, glenohumeral or acromioclavicular osteoarthritis, dislocation or shoulder instability, glenoid labrum pathologies, non-specific shoulder pain, which might affect the quality or quantity of shoulder motion[4,6,7,23-55]). Original studies using control group (healthy or PD patients without shoulder dysfunction)[6,7,23,61-71]; 4) clinical assessment of shoulder based on standardized criteria[61-71]; and 5) imaging assessment with high-resolution tools (e.g. MRI or US), following well-defined diagnostic criteria[31,36,37,72-73] were preferable.

Screening and Extraction

Records were primarily examined according to their title and abstract and those considered relevant to the purpose of the study were retrieved in full. The complete articles were imported to the same Mendeley Reference library and screened for duplicates. References from the included papers were also screened manually to find any further relevant publications (original articles, reviews, books, or other gray literature sources).

To conclude, any relative data to shoulder-related clinical and imaging (US and MRI) dysfunction in PD patients were selected (Figure 1).

Table 2. Clinical and Imaging Assessment of Shoulder Dysfunction in Parkinson's Disease.

Clinical Diagnostic Criteria for PD Diagnosis & PD Severity	Diagnostic Criteria for Frozen Shoulder in PD	Proposed clinical tests for Shoulder Dysfunction
PD diagnostic Criteria: United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria[58,59], Gelb criteria9, recent Movement Disorder Society Clinical Diagnostic Criteria for PD (MDS)[56,57]. **PD Severity Scales:** Unified Parkinson's Disease Rating Scale (UPDRS) III and Hoehn & Yahr staging (H&Y) or Modified H&Y scales[57-59].	Diagnostic criteria for adhesive capsulitis (1) insidious onset of pain associated with passive glenohumeral motion; (2) restricted range of glenohumeral motion both actively and passively, with external rotation <50% of the normal side; (3) normal radiography and a shoulder ultrasound demonstrating no significant	Measured Range of Active and Passive Motion; Special Clinical Tests 1) for rotator cuff (Jobe test, lift-off test drop arm test for tear); 2) for supraspinatus tendon tear); 3) for subscapularis tendon tear, belly press, Hawkin's test, for supraspinatus tendinitis, empty can test;4) for biceps (Speed's, Yergason's Bicipital groove tenderness); 5) for acromioclavicular joint (passive cross-chest adduction test); 6) tests for anterior instability (apprehension test); 7) Sulcius sign for inferior instability; 8) Neer's test for impingement syndrome; 9) Drawer test for anterior-posterior instability; 10) Palpation in trigger points;11) inspection for swelling or deformity; and 12) Apley scratch[53-60].
Magnetic Resonance Imaging (MRI) Protocols[37]	**Musculoskeletal Ultrasonography (US) Protocols for Shoulder in PD**	
Techniques • Oblique coronal and oblique sagittal proton density, weighted turbo spin echo with fat saturation, • Oblique coronal proton density weighted and axial T2 weighted gradient echo images[37]. **Structures Examined[37]** • Biceps, supraspinatus, infraspinatus and subscapularis muscles, • Acromiohumeral distance **Subacromial-subdeltoid and subcoracoid bursa[37]**	**Techniques** • Real-time equipment, Linear array transducer (11-MHz[30] - 12/5 MHz)[28] • Standardized protocols[31,36] • A stool in a comfortable position • Tendons evaluated in transverse and longitudinal planes in proper position[28,35] • Long head biceps: patient's hands on ipsilateral knee. • Supraspinatus tendon: full internal rotation, hyperextension, arm flexed at the elbow, palm of the hand placed over posterior iliac crest[28,36] • Subscapularis & biceps tendon grooves: arm in neutral position, elbow flexed to 90°, forearm supine on ipsilateral thigh, dynamic with internal and external rotation[28]. • Infraspinatus tendon: bent arm placed in front of chest, ipsilateral hand on contralateral arm[28]. **- The US criteria for Shoulder Pathology** * Complete tendon tears: tendon non visualization, anechoic or hypoechoic discontinuity, and deltoid herniation. * Partial tendon tears: focal heterogenous hypoechogenecity and an incomplete hypoechoic defect[28,31]. * Tendinosis: Increased tendon thickness and/or diffuse heterogeneous hypoechogenicity[36]. * Effusion in biceps tendon sheath: increased hypoechoic area (thickness >2 mm) around the long head of the biceps in the transverse view[28]. * Tendonitis: hypoechoic and swelling changes, difference in tendon thickness (>2 mm) compared to the healthy side[28]. * Dynamic US, adhesive capsulitis: difficulty adequate images of subscapularis due to reduced external rotation of subscapularis and increased fluid in dependent portion of the bicipital tendon sheath[30].	

The review is organized as follows: 1) Clinical findings of shoulder dysfunction in PD; Assessment protocols and symptoms; 2) Diagnostic US and MRI imaging protocols and findings of shoulder dysfunction in PD; 3) Classification of shoulder dysfunction in PD based on MRI and US-detected underneath pathology in PD; 4) Contributing factors to shoulder dysfunction in PD; 5) Early diagnosis of shoulder dysfunction for the prevention of severe shoulder-related complications and 6) Hypothesis for the pathophysiology of shoulder dysfunction in PD.

Results

A total of 459 records were screened by title and abstract (22 from registers and 437 from the Pub Med (n=137), Google Scholar (n=49), Cochrane Collaboration (n=67), PLoS (n=168) and PeDro (n=16) databases. From the electronic search, 297 were clearly ineligible and 140 were assessed for eligibility. Moreover, 88 papers from the electronic search and 55 records from manual screening (references after cross-referencing, original articles, reviews, books, or other gray literature) were further assessed. To sum up, 77 articles

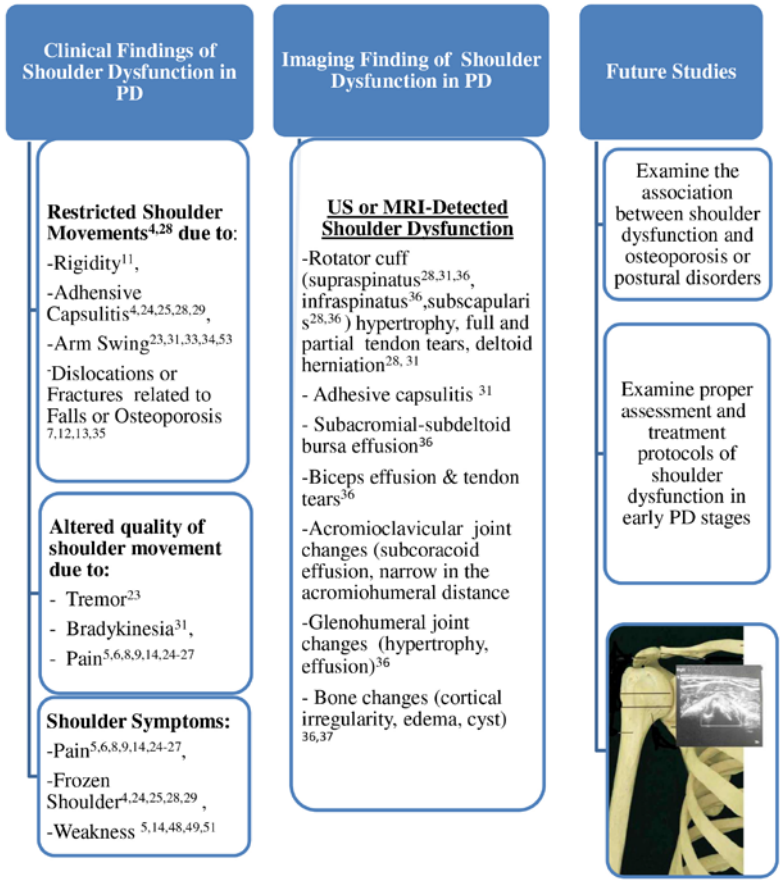

Figure 2. Clinical and imaging findings [based on Yucel & Kusbeci (2010)[37]; Madden & Hall (2010); Riley et al. (1989)[24]; Cleeves et al. (1989)[25]; Chang et al. (2015); Koh et al. (2008)[31]; Gundogdu et al. (2016); Koh et al. (2019)[53]; Stamey et al. (2008)[27]; Kwon et al. (2014)[33]; Metz et al. (2001)[43]; Matsuzaki et al. (2009)[44]; Yucel & Kusbeci (2009)[36]]. Timely diagnosis and proper management of shoulder dysfunction in early or prodromal stages are subjects of future research.

based on inclusion/exclusion criteria were incorporated (Figure 1).

Since 1965 when Buchthal and Fernandez-Ballest[23] published a study on alterations in electromyographic (EMG) activity of arm muscles, only nineteen papers were identified dealing with shoulder clinical symptoms[4,6,8-10,14,23-34], three with US-detected shoulder disorders[28,31,36] and one with MRI-detected shoulder disorders[37].

Out of these, only one retrospective and one prospective study examined the prevalence of musculoskeletal problems, focusing on the issue of frozen shoulder and pain, in the initial stages of PD[6,33]. It is essential to include eleven case studies in PD patients regarding secondary shoulder pathology, such as arthritis, fractures and dislocations due to falls[38-48]. However, no quantitative study was found to measure the range of restricted shoulder movements in PD, or the underlying shoulder pathology in early or prodromal stages of PD, before severe complications. Most pertinent studies on shoulder symptoms, and clinical and US-detected dysfunction in PD are summarized in Tables 1-2 and Supplementary Table.

Discussion

Clinical and imaging assessment and findings of shoulder dysfunction are presented in detail in the following sections and are summarized in Tables 1- 2 and Figures 2-4.

Clinical Assessment and Findings of Shoulder Dysfunction in PD

Clinical Features of Shoulder Dysfunction in PD

The shoulder is one of the body parts most commonly involved in the PD group[14,51]. The clinical characteristics of shoulder dysfunction in PD are: 1) Restricted movements due to shoulder rigidity, frozen shoulder, akinesia, arm swing loss, or muscle weakness[6,14,51]; and/or 2) altered quality of shoulder motion due to arm tremor, bradykinesia or pain. Shoulder pain and stiffness are the most frequent symptoms of shoulder dysfunction in PD (Tables 1-2).

Figure 3. Schematic Diagram shows contributing factors (green shapes) of shoulder symptoms and Ultrasonographic (US) and MRI (Magnetic Resonance Imaging) disorders related to shoulder dysfunction (blue shapes) in mild and severe stages of Parkinson's (PD). Unified Parkinson's Disease Rating Scale (UPDRS) PD severity scores, duration and rigidity are the most common contributing factors of tendon and joint shoulder dysfunction [based on Madden & Hall (2010)[9]; Riley et al. (1989)[24]; Cleeves et al. (1989)[25]; Chang et al. (2015); Kwon et al. (2014)[33]; Metz et al. (2001)[43]; Matsuzaki et al. (2009)[44]; Yucel & Kusbeci (2009)[36]; Yucel & Kusbeci (2010)[37]; Koh et al. (2008)[31]; Gundogdu et al. (2016)[52]; Koh et al. (2019)[53]; Stamey et al. (2008)[27]].

Prevalence of Shoulder Dysfunction in PD

Riley and colleagues (1989)[24] first found a significantly higher incidence of shoulder symptoms history (43% vs. 23%) in a group of 150 PD patients compared to 60 matched healthy controls[24]. Kim and colleagues (2013)[14] studied 400 PD patients and 138 age- and sex-matched controls and found that the shoulder was more affected in the PD group than in the control group (15.0% vs. 8.7%)[14].

Shoulder Dysfunction in the Early PD Stages

Literary search reveals that the main features of shoulder dysfunction, shoulder pain and frozen shoulder are well-recognized harbingers that may antedate PD by several months or even years[6,8,24,27,29,33,49,50]. Shoulder pain and mobility abnormalities may be present in early PD stages[3,7], or may antedate a diagnosis of cardinal PD symptoms by several months[6,8,24,27,29,33,49,50], yet they are only observed when more complex coordination is required[24,48].

Cardinal PD Symptoms Contributing Factors for Shoulder Dysfunction

Results from recent studies indicate that cardinal PD symptoms of rigidity[11], rest tremor[3,23] and bradykinesia[31] could alter shoulder function, as they are related to alterations in muscle activity[23,30,31,32], coordination[23] range of motion[4,28].

Concerning tremor, it is a cardinal PD symptom that is characterized by a frequency of 4 to 6-Hz in a relaxed limb, temporarily reducing or disappearing when the limb is held outstretched[3]. Buchthal and Fernandez-Ballesteros[23] (1965) managed to detect tremors using electromyography when it was not apparent in clinical examination. They concluded that rest tremor involves more distant than proximal shoulder muscles, whereas the number of involved proximal muscles had increased voluntary effort, both during walking and in slight effort. On the other hand, during voluntary effort the tremor rate was increased[23].

Rigidity is another cardinal PD symptom referring to increased muscle tone causing stiffness, as well as velocity-independent involuntary resistance to passive movement,

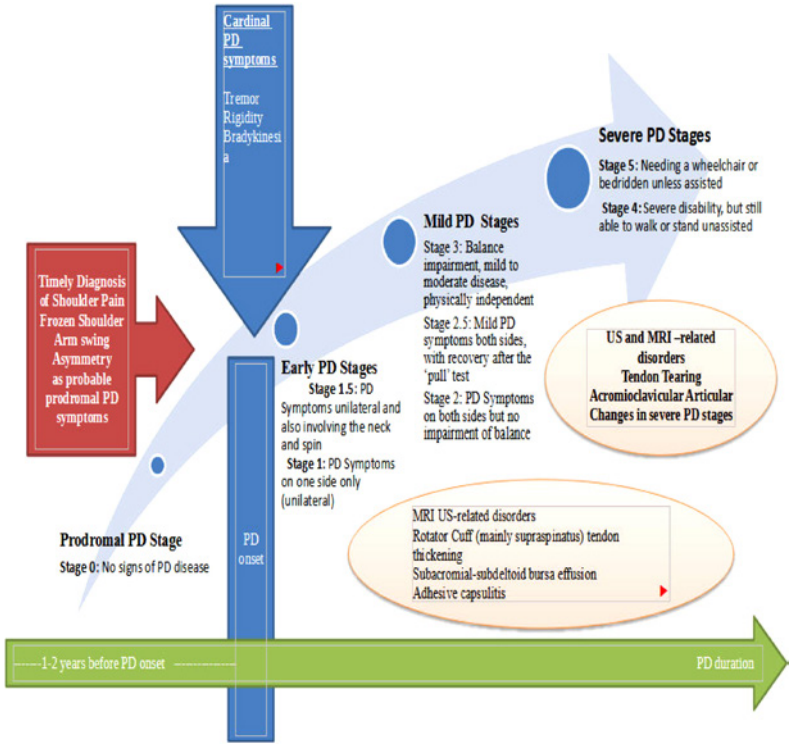

Figure 4. Schematic Diagram of Clinical and Imaging Findings of Shoulder Dysfunction in different modified Hoehn and Yahr stages of Parkinson's Disease (PD). Diagram highlights the necessity of timely diagnosis of shoulder pain, frozen shoulder and arm swing asymmetry as prodromal symptoms of PD. As PD progresses, more severe US and MRI disorders related to shoulder dysfunction [based on Kwon et al. (2014)[33]; Metz et al. (2001)[43]; Matsuzaki et al. (2009)[44]; Yucel & Kusbeci (2009)[36]; Yucel & Kusbeci (2010)[37]; Madden & Hall (2010)[9]; Riley et al. (1989)[24]; Cleeves et al. (1989)[25]; Chang et al. (2015)[28]; Koh et al. (2008)[31]; Gundogdu et al. (2016)[52]; Koh et al. (2019)[53]; Stamey et al. (2008)[27]].

with or without cogwheel phenomenon[11].

Furthermore, bradykinesia is a cardinal PD symptom referring to slowness of movement and progressively smaller movements in an individual's attempt to repeat a task multiple times[30].

Rigidity and bradykinesia are frequently associated with pain, muscle weakness[48] and reduction of arm swing[32] (Figure 2). Kwon and colleagues (2014)[32] studied two groups (a concordance group of twenty-one PD patients who had both rigidity and bradykinesia and a discordance group of nineteen PD patients, who had either bradykinesia or rigidity[32]. Two independent neurologists blindly analyzed video clips, accessed asymmetric characteristics of gait and posture, concluding that there was only a significant, but moderate association between the side of more dominant rigidity with the side of reduced arm and leg swing[32].

Rigidity and long PD duration have been identified as important contributing factors for the development of adhesive capsulitis and tendon tearing respectively[28,30,35]. Increased severity of PD and falls seem to lead to advanced shoulder pathologies, such as tendon tears, adhesive capsulitis[28,30,35] and fractures[42]. Higher UPDRS, tremor, rigidity and bradykinesia subscores are associated with increased effusion around biceps tendon, as well as with increased thickness of supraspinatus and subscapularis tendons in PD patients with frozen shoulder[28].

The relation of clinical and imaging findings of shoulder dysfunction with PD stages and duration are presented in Figure 3.

Shoulder Pain in PD

Cleeves and Findley first reported a total of twelve out of a hundred consecutive PD patients with shoulder pain as the first symptom[24]. Since then, there are six more papers regarding shoulder pain in PD. Prevalence of shoulder pain varies between 11% to 81% of PD patients[8,9,24-27,54].

De Mattos and colleagues (2019)[5] conducted a cross-sectional study in fifty-four PD patients, and found that pain was more common in the lower limbs (33.0%) and shoulders/cervical spine (31.0%). Musculoskeletal pain was more frequent (in 81.5% of subjects) than nocturnal (52.6%) or fluctuation-related pain (47.3%), involved in working and general activities in 55.3% of the subjects[5].

Tinazzi and colleagues (2006)[54] studied different types of pain in PD and revealed that musculoskeletal pain was the most predominant type, attributed to 41% of the total pain[54]. A cross-sectional and retrospective study by Madden and Hall (2010)[9] in 25 consecutively recruited PD subjects and their 25 normal controls, revealed that shoulder pain was characterized as dull and aching by most PD patients. 80% of the PD group and 20% of the control group mentioned bilateral shoulder pain. PD patients were six times more likely than controls to have shoulder pain. After adjusting for age, gender and prior injury, the odds increased to 21 times[9].

As previously mentioned, there is evidence that shoulder pain may antedate PD diagnosis for months or even years. Farnicova and colleagues (2012)[6] retrospectively studied the prevalence of musculoskeletal pain in the prodromal phase of PD. They searched the hospital inpatient and outpatient clinic admission notes of eighty-two PD patients. Musculoskeletal pain initially classified as osteoarthritis, degenerative spine disease, and frozen shoulder, was the presenting prodromal PD symptom in twenty-seven (33%) cases. Joint pain was present in nine cases and was usually diagnosed as "frozen shoulder" or arthritis. One out of three PD patients, who went on to develop motor features of PD, had musculoskeletal pain as an initial symptom. The mean time from initial symptom appearance to dopaminergic treatment was 6.6 years in the musculoskeletal pain group, compared to 2.3 years in the cardinal PD sign onset group[6]. An additional retrospective study of three-hundred and nine, which consecutively recruited PD patients, revealed that 20% of the sample reported that shoulder pain preceded the onset of cardinal PD symptoms within several years[27]. Finally, Teive et al. (2016)[34] conducted five years prospective study about the initial symptoms of 15 early PD patients at two tertiary movement disorders clinics. They concluded that PD patients may present with unusual symptoms, such as shoulder pain in an early stage. They urge specialists to be aware of these conditions as clues to an accurate diagnosis[34].

Regarding contributing factors, Gundogdu et al. (2016)[51] concluded that musculoskeletal pain is associated with female gender and older age, whereas it is independent of H&Y stage, PD disease duration, and medication[51] (Figure 3).

Frozen Shoulder in PD

In the general population, frozen shoulder or adhesive capsulitis is a common musculoskeletal problem that causes disabling pain, stiffness, severe mobility limitation and disability in activities of daily living[4,28]. The estimated cumulative incidence in the general population is 2.4 per 1000 people per year[54].

Recent studies[4,24,25,28,29] indicated that frozen shoulder could be a presenting symptom of PD[4,6,24,28] (Table 1, Figure 2). The frequency of frozen shoulder in PD patients was first assessed by Riley and colleagues (1989)[24]. PD patients had a significantly higher incidence of frozen shoulder (12.7% vs. 1.7%) compared to the controls, with an average duration of seven years, and a mean onset of two years before PD diagnosis. What is more, the onset of PD symptoms was ipsilateral to the frozen shoulder in sixteen out of nineteen PD patients[24]. In 2004, Gilbert[8] presented a case with frozen shoulder, severe pain and stiffness in bilateral lower biceps brachii for two years, before the PD onset responded promptly to the initiation of L-dopa therapy[8]. Kim and colleagues (2013)[14] also found that frozen shoulder (among other musculoskeletal problems) was significantly more prevalent in PD patients than in the control group[14]. Farnicova and colleagues (2012)[6] found that musculoskeletal pain was present as a prodromal PD symptom in 27 (33%) cases initially diagnosed with osteoarthritis, degenerative spinal disease, and frozen shoulder[6]. Joint pain was present in 9 cases and was usually diagnosed as "frozen shoulder" or arthrosis[6]. Alarcon and colleagues[29] (2020) evaluated 146 consecutively recruited PD patients, who did not have a progressive reduction in the speed and amplitude of finger tapping or other physical signs indicative of bradykinesia. MRI with 110 T2 FLAIR was performed at baseline. The clinical examination included videotaping, UPDRS, Part I-II-III, the Hamilton depression and anxiety scales, and the Mini-Mental State Examination (MMSE). Frozen shoulder (17% vs. 9%) showed no differences between groups at baseline. All patients were followed up every three months for a minimum of one year. T In the last follow-up visit, the probability of developing PD was higher when patients had a frozen shoulder (OR 3.1; 95%CI 1.6-6.2). They also found that frozen shoulder was one of the early signs of PD that may be related to bradykinesia[29].

Arm Swing Asymmetry in PD

Arm swing asymmetry is a common sign of early PD diagnosis[53] (Figure 2). In the literary search, four experimental electromyographic and kinematics studies were found relevant to the loss or asymmetry of arm swing during gait[23,31,33,53].

Buchthal and Fernandez-Ballesteros (1965)[23] first published a paper on arm swing reduction during walking in twenty-four out of twenty-four arms in eighteen PD patients. Abnormal electromyographic patterns, such as continuous rhythmical activity in both flexors were primarily observed in the muscles normally active during walking. These abnormal patterns were observed in the arms ipsilateral to the predominant PD signs. As the severity of the disease increased, muscles that were normally inactive during walking showed abnormal electromyographic patterns[23] as well.

Koh and colleagues (2019)[33] used 3D motion analysis in order to compare arm swing and gait parameters between forty-one early PD patients and thirty-three controls, walking at self-selected speed. They found that the reduction of arm and leg swings during gait in PD was associated with rigidity, but not with bradykinesia[33].

Shoulder Muscle Weakness in PD

Severe weakness in shoulder muscles is rare in PD[6,14,51]. Nevertheless, Buchthal and Fernandez-Ballesteros (1965) found that muscle force in the PD-affected shoulder was slightly reduced (graded as 4 and 4+) in 4/18 (22%) and moderately reduced (graded as 3) in 3/18 (16%) of patients (grading according to the definition of the Medical Research Council in 1942)[23]. According to King and Horak (2008)[49], muscle weakness, largely due to secondary to abnormal muscle activation associated with bradykinesia and rigidity, can be present at all stages of PD. Muscle weakness similar to other mobility abnormalities may be apparent in mild PD patients, but it is only observed when more complex coordination is required[48].

Clinical Assessment Protocols

Studies of shoulder dysfunction in PD rely on PD diagnostic criteria used when they were conducted. In studies conducted before 2015, PD was diagnosed using previous PD criteria, such as the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria[58,59], or Gelb criteria[9], and not the recent Movement Disorder Society Clinical Diagnostic Criteria for PD (MDS) that the International Parkinson and Movement Disorder Society[56,57] proposes. In the relevant studies, Unified Parkinson's Disease Rating Scale (UPDRS) III58 and/or Hoehn and Yahr staging (H&Y)[59,60] or modified H&Y scales were used to rate PD severity and progress respectively (Tables 1-2)[59,60].

Although the US and neurological exam protocols are well-defined in previous studies, thorough musculoskeletal exam protocols have not been reported. Data concerning shoulder pain and mobility problems or disability in PD patients were mostly retrieved from self-questionnaires[24,28,31,36] completed by enrolled patients and rarely from interviews[9]. Only Alwardata et al. (2018)[61] assessed disability and upper limb function with objective clinical tools, the Arm Shoulder and Hand (DASH) questionnaire, and Madden and Hall (2010)[9] assessed the severity of pain using a visual analog scale[9]. Pain could be also evaluated with the Brief Pain Inventory (BPI) or the King's Parkinson's Disease Pain Scale (KPPS). These scales were used by de Mattos and colleagues (2019)[5] to examine the relationship between pain characteristics and motor dysfunction in individuals with PD[5].

Imaging Assessment and Findings of Shoulder Dysfunction in PD

A literary search revealed an MRI[37] and three US studies[28,31,36] which evaluate shoulder pathology in PD patients (Tables 2-3). Moreover, radiography has been mainly used for the diagnosis of fractures, dislocations, arthritis or adhesive capsulitis[28,38-49].

Shoulder MRI Findings in PD

MRI is the primal tool in the detection of complex shoulder pathologies. A case-control study by Yucel and Kusbeci (2010)[37] is the only one evaluating MRI findings of the shoulder in PD patients. Twenty-eight PD patients (56 shoulders) and thirteen age-matched (26 shoulders) controls underwent MRI with a 1.5-T MR machine and a dedicated shoulder surface coil. The shoulder MR imaging protocol included: Oblique sagittal proton density-weighted turbo spin echo with fat saturation, oblique coronal proton density-weighted, and axial T2 weighted gradient-echo images[37]. The glenohumeral and acromioclavicular joints, the biceps, the rotator cuff muscles, the acromiohumeral distance, the subacromial-subdeltoid, and the subcoracoid bursa were examined[37].

Shoulder US Findings in PD

US is an effective imaging modality to detect shoulder disorders in real-time, as it is a low-cost imaging tool, easy to administrate. It is comprehensively used for the shoulder evaluation[36], as it neither utilizes ionizing radiation nor requires an invasive procedure. Moreover, it can be used in cases of tremor where MRI is difficult to perform, since it allows tendon imaging in a weight-bearing position, from different angles[28,71].

In the literary search, three studies[28,31,36] used US for the evaluation of shoulders in PD patients. In all sonographic studies, US was applied within real-time equipment, using a 11MHz[31] or 12/5 MHz[28] linear array transducer. Standard protocols and criteria for the US evaluation of the shoulder were also employed in PD patient's examination[28,31,36] (Table 2). The long head of the biceps as well as the supraspinatus, infraspinatus, and subscapularis tendons were examined in transverse and longitudinal planes in proper position[28,31,36].

Classification of Shoulder Dysfunction based on MRI and US-detected Underneath Pathology in PD

In the literary search, US and MRI findings of the shoulder were studied in mild and severe PD patients[30,35,36] and/or PD patients with frozen shoulder[28]. The most common US and MRI-detected abnormal findings leading to shoulder dysfunction, were partial or full-thickness tendon tear, tendinosis, bursa effusion, joint and bone changes[28,30,35,36]. MRI and US imaging tools enabled the classification of shoulder dysfunction according to the abnormalities detected in shoulder structures.

Dysfunction related to MRI or US-detected Rotator Cuff Disorders in PD

The most common shoulder disorders that cause rotator cuff dysfunction are tendon tear or thickness of supraspinatus[28,31,36], infraspinatus[36], biceps effusion and tendon thickness of subscapularis[28,36] (Figures 2 and 4).

Rotator Cuff Tendon Tears in PD

Complete tendon tears are detected as tendon non-visualization, anechoic or hypoechoic discontinuity, and

deltoid herniation[28,31]. Partial tears are defined as focal heterogenous hypoechogenicity and an incomplete hypoechoic defect[28,31]. Rotator cuff, mainly supraspinatus, and tendon tears were US-detected in 70% of the PD patients (22 out of 33) in the study of Koh and colleagues (2008)[31]. A significantly longer duration of disease was found in PD patients with tendon tearing than in patients without tearing[36] (Figure 3). Full-thickness supraspinatus tears were also observed in the MRI study conducted by Yucel and Kusbeci (2010)[36]. In this study, full-thickness tears of the supraspinatus were observed only in the mild and the severe PD groups, but not in the control group (Figure 3). Furthermore, significantly higher UPDRS total scores, tremor, and rigidity sub scores and a longer duration of PD were observed in PD patients with full-thickness tears[36].

Yucel and Kusbeci (2009)[36] sonographically evaluated the shoulders in PD, examining the difference between the mild and severe PD patients. Thirty-five PD patients (14 females, 53 males; mean age, 66.4±9.5 years) were divided into two groups according to H&Y scale. The first group included thirty shoulders of mild PD patients (H&Y stage I-II), and the second group examined thirty-seven shoulders of severe PD patients (H&Y stage III-IV). Three (8.1%) severe patients had full-thickness tears in the supraspinatus tendon and one patient (2.7%) had tear in the infraspinatus tendon. No significant difference was found in US findings between the patients with mild and severe PD[36].

Biceps Effusion and Tendon thickness of Subscapularis and Supraspinatus in PD Patients with Frozen Shoulder

On the contrary, abnormal effusion around the biceps tendon sheath was more common in mild patients (26.7%) than in severe (24.3%) ones, in the study of Yucel and Kusbeci (2009)[36]. In the prospective study of Chang et al. (2015)[28], increased effusion in the biceps tendon as well as increased tendon thickness of subscapularis and supraspinatus were associated with higher ipsilateral UPDRS and tremor, rigidity, and bradykinesia sub scores[28] (Table 1, Figure 3).

Dysfunction related to MRI or US-detected Adhesive Capsulitis in PD

Adhesive capsulitis is diagnosed as difficulty in US detection of subscapularis due to reduced external rotation of subscapularis and increased fluid in the dependent portion of the bicipital tendon sheath[31].

The MRI and US studies confirmed that adhesive capsulitis with frozen shoulder symptoms is common in PD. In 2008, Koh and colleagues[31] US evaluated the shoulders of 33 PD patients and they discovered concomitant adhesive capsulitis with symptoms of frozen shoulder in 9 patients and a significantly higher rigidity score in PD patients with adhesive capsulitis compared to controls[31].

In a prospective study, Chang and colleagues[28] (2015) evaluated clinically and sonographically sixty shoulders of 30 PD patients. Frozen shoulder syndrome was detected in nineteen shoulders of fourteen PD patients, including bilateral involvement in five and unilateral involvement in nine patients. Significant positive correlation was found between the mean ipsilateral UPDRS III and tremor, rigidity, and bradykinesia scores and US findings (i.e., the thickness of bicipital effusion, subscapularis and supraspinatus tendon thickness)[28].

In the study conducted by Yucel and Kusbeci (2010)[35], PD disease duration and clinical severity of rigidity were significantly correlated with US-diagnosed disorders[36] (Figure 3).

Dysfunction related to Effusion in Subacromial-subdeltoid Bursa in PD

Yucel and Kusbeci (2009)[36] found that abnormal effusion in the subacromial-subdeltoid bursa was more frequently detected in severe (29.7%) than in mild PD (16.7%) patients (Table 1, Figure 4). Nevertheless, there was no statistically important difference between the mild and the severe PD patients[36].

Dysfunction related to Articular Disorders in PD

Acromioclavicular and Subcoracoid Changes in PD

Abnormalities in the acromioclavicular joints, the subcoracoid effusion, and the narrow acromiohumeral distance were the most common MRI findings in PD patients[36] (Figures 2, 4). Severe PD patients with longer disease duration had a higher frequency of acromioclavicular joint changes, compared to the control group. Subcoracoid effusion was more common in patients with higher UPDRS and rigidity scores. Mild PD patients showed a higher frequency of resting tremor and subcoracoid effusion than severe ones[36]. An additional abnormal finding was that the acromiohumeral distance was notably reduced in PD patients compared to controls, but there was no statistically significant difference with respect to this parameter between mild and severe PD patients[36].

Dysfunction due to Myofascial Pain Syndrome in PD

Myofascial pain syndrome is characterized by pain on sustained compression over the tender point within a taut band of the muscle, a referred pain, or a local twitch response within the band[30]. Koh and colleagues (2008)[31] studied the association between myofascial syndrome and PD severity, bradykinesia, tremor and shoulder disability and found no significant difference between PD patients with and without myofascial syndrome[31].

Dysfunction related to Bone Disorders in PD

The results of the MRI and other imaging studies unveiled bone abnormalities, such as cortical irregularity, fractures, edema and cyst formation in PD patients[36]. Shoulder arthritis is also associated with bone dysfunction[45-48].

Shoulder Fractures and Dislocation in PD-Secondary Pathology due to Falls or Osteoporosis

Eleven case studies were found relevant to secondary shoulder bone pathology[38-48], due to falls or osteoporosis. Osteoporosis contributes to low-energy shoulder fractures[45-46]. Falls commonly cause fractures in the humeral bone or glenohumeral dislocations[38-48].

These bone disorders were diagnosed with MRI or X-ray radiography and treated with surgical procedures[38,45,46]. Numerous studies suggest poor outcomes in the recovery of function and a higher postoperative complication rate after shoulder arthroplasty for fractures and dislocations in patients with PD[41,44,45].

Timely Diagnosis for Prevention of Shoulder-Related Complications in PD

Based on the above data, although musculoskeletal pain and frozen shoulder could adversely affect the quality of life, they are often misdiagnosed, under-evaluated, and/or under-treated[10,27]. Early clinical and imaging diagnosis of these disabling syndromes is crucial for the quality of life among high-risk population[4,28] as it may prevent or delay severe shoulder-related complications. Musculoskeletal shoulder complaints should be evaluated attentively in PD patients on clinical basis[51], in order to provide them with targeted and comprehensive management of dysfunction.

Arm swing asymmetry may prove a useful clinical symptom for early PD diagnosis[52]. Frozen shoulder, restricted movements, pain and other clinical features of shoulder dysfunction might be clues to an accurate PD diagnosis and should ideally be objectively examined among the PD population, a procedure that is seldom performed in studies so far. In published clinical studies, mobility limitations are usually based on subjective variables and not on objective measurements.

An evidence-based approach that stems from focused, validated physical exam maneuvers and objective measurements of shoulder dysfunction through imaging modalities would be crucial for contemporary research, especially in early stages of PD, to promote timely, accurate diagnosis and target rehabilitation regarding dysfunctional structures.

Proposed Assessment Protocols for Shoulder Dysfunction in PD

Based on other studies among the majority of population, a detailed examination of shoulder function and kinematics could include goniometry and special tests for rotator cuff (e.g. Jobe test, Hawkin's test, drop arm test for rotator cuff tear)[61-66], tests for biceps (e.g. Speed's test)[68], Neer's test for impingement syndrome[66-68] and Apley scratch test for shoulder flexibility[61,69,70] (Table 2).

Hypothesis for Pathophysiology of Rotator Cuff Dysfunction in PD

The supraspinatus tendon is the most commonly affected tendon and it is prone to degeneration and tears, probably due to the location and poor vascularity of the "critical area", an anatomical landmark demarcator, situated approximately 10 mm close to the insertion of the supraspinatus tendon with complex vascular pattern[36,71]. The developing process of rotator cuff degeneration and tear should be taken into consideration in order to explain the high frequency of tendinosis of the long head and the biceps tendon in mild PD patients[36,72]. In the beginning, a thickening of the tendon (tendinosis) is observed, followed by its decline, which appears as micro-tears and atrophy[36,72]. The correlation between tendon tear with longer PD duration, leads us to the assumption that the earlier the PD diagnosis and treatment, the better the delay of tendon rupture process.

Hypothesis for Pathophysiology of Shoulder Pain in PD

The differential diagnosis and pathophysiology of shoulder pain is a complex process due to the anatomical and biomechanical complexity in the function of articular and periarticular shoulder structures. So far, there is no sufficient evidence to explain the pathophysiology of shoulder pain, especially before the clinical manifestation of PD[25]. Madden and Hall (2010)[9] tested the hypothesis that prior injury is related to shoulder pain in PD, but none of the PD subjects reported previous shoulder injury compared to 70% of the controls. The increased prevalence of shoulder pain may be related to the rigidity observed in PD. Nevertheless, in that study, the majority of PD subjects suffered from bilateral shoulder pain, despite the asymmetry of rigidity during the exam[9]. Another study concludes that PD patients have a lower heat pain threshold compared to controls, with the authors hypothesizing that basal ganglia abnormalities may alter pain coding[74]. Additionally, Positron Emission Tomography (PET) scans have shown that striatal D2 receptors are involved in central pain pathways and that a decrease in D2 receptors increases pain perception[75]. Valkovic et al. (2015)[76] attest that different types of pain were reported in a sample of 100 PD patients, such as musculoskeletal, dystonic, central neuropathic, radicular and other pains. These findings suggest that pain in PD may be related to the underlying pathophysiology of PD rather than motor signs[76].

Hypothesis for Pathophysiology of Frozen Shoulder in PD

Regarding the pathophysiology of frozen shoulder, inflammation plays a leading role in the primary disease process, yet the way it begins is not clear[77]. Causes of inflammation in adhesive capsulitis include tendon inflammation, trauma, subacromial impingement, and bursitis[4]. From a pathogenic point of view, a three-phase pathogenesis that advocates spontaneous recovery has been

proposed[77]. The first phase is characterized by increasing pain during movement, without significant loss of motion. In phase two, the shoulder range of motion becomes progressively limited and pain occurs at the end of the range[4].

Hypothesis for the Involvement of Other Musculoskeletal Disorders in Shoulder Dysfunction

Future studies may examine more thoroughly the involvement of other common musculoskeletal disorders[34], such as postural disorders of the spine (camptocormia) and low bone mineralization (osteoporosis, low energy fractures) in shoulder pathology in PD patients (Figure 1). All in all, special consideration should be given to the disturbances of neuromuscular coordination, muscle synergy, articular and periarticular shoulder dysfunction in different stages of PD.

Conclusion

In conclusion, shoulder dysfunction in PD is characterized by pain and mobility limitation due to rigidity, frozen shoulder, arm swing loss or weakness. Dysfunction is related to the underlying pathology of rotator cuff tendons, capsule and other articular or periarticular structures of glenohumeral and sternoclavicular joints which should be early diagnosed using high-resolution imaging tools, such as US or MRI.

The US constitutes an effective imaging modality to detect shoulder dysfunction in real-time, especially in cases of tremor where MRI is difficult to be applied. US and MRI examination of shoulder reveals that the most commonly detected abnormalities in mild and severe PD patients, are partial or full-thickness supraspinatus tendon tear, tendinosis, bursa effusion, joint and bone changes.

Frozen shoulder and pain are well-recognized harbingers that may antedate PD diagnosis. Therefore, the diagnosis of PD needs to be suspected along with the presence of otherwise unexplained shoulder symptoms. Long duration, tremor, rigidity, increased severity of PD, and falls seem to predispose experts to advanced shoulder pathologies, such as tendon tears, adhesive capsulitis, and fractures. Therefore, it is essential not only to address local shoulder symptomatology but also to appropriately diagnose and manage the motor symptoms of PD as, among other reasons, the symptoms themselves bespeak the above shoulder-related complications.

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Supplementary Table. Summary of included studies.

Author (Year)	Clinical Parameters of Shoulder Dysfunction	Study Design	Population	Results
Riley et al. (1989)[24]	Frozen shoulder and other shoulder disturbances	Cross-sectional study	150 PD patients vs. 60 matched control subjects	Shoulder complaints: 43% in PD patients vs. 23% in controls, Frozen shoulder pain: 12.7% in PD vs. 1.7% in controls, Initial symptom of akinesia 2 times more prevalent in PD patients with frozen shoulder.
Cleeves & Findley (1989)[25]	Frozen shoulder and other shoulder disturbances	Cross-sectional study	100 consecutive PD patients	Shoulder pain as initial symptom in 12% of PD patients.
Madden & Hall (2010)[9]	Shoulder Pain	Case-control study	25 PD patients vs. 25 controls	Shoulder pain 21 times more prevalent in PD patients than controls (adjusted for age, gender, and prior injury)
Stamey et al. (2008)[27]	Shoulder pain	Retrospective study	309 consecutive PD patients Shoulder pain: 35 (11%)	Side of shoulder pain correlated with side of maximum severity of PD.
Papalia et al. (2018)[4]	Frozen Shoulder	Review	Hypothesis: postural alteration observed in PD could be the primum movens for shoulder pathology	Hypothesis: Camptocormia & decreased trunk mobility can yield a humeroacromial impingement and reduction of movement.
Teive et al. (2016)[34]	Shoulder Pain	Prospective	15 early PD patients	Unusual motor and non-motor symptoms and signs, such as shoulder pain, related to the rigidity, akinetic syndrome in the early PD stage, Shoulder pain in early stage of PD.
Rabin et al. (2016)[35]	Postural, Bone, and Joint Disorders in Parkinson's Disease	Review	-	Joint disorders (frozen shoulder, dystonia involving joints, joint pain) are often seen in association with PD, Treatment options for these conditions are varied and may include medications, physical therapy, or surgical interventions.
Kwon et al. (2014)[33]	Arm Swing	Case-control study	21 PD patients with rigidity, bradykinesia (concordance group) & 19 controls (discordance group) with a mismatch of pronounced symptoms	Reduction of arm and leg swings during gait in PD was associated with rigidity, but not with bradykinesia.
Metz et al. (2001)[43]	Fractures	Case study	A Case with PD& fractures	Post-surgery Complications.
Matsuzaki et al. (2009)[44]	Anterosuperior dislocation	Case study	A case with dislocation	Post-surgery Complications.
Skedros et al. (2017)[45]	Rotator Cuff-Tear, Arthropathy and Shoulder Dislocations	Case study	Case series with PD Rotator Cuff-Tear, Arthropathy and Shoulder Dislocations in an Elderly Male with PD	Reverse Total Shoulder Arthroplasty as Treatment: Pain relief, poor outcomes in function, Complications.
Burrus et al. (2015)[46]	Fractures & Dislocations	Case series	3390 PD patients & 47034 controls who underwent arthroplasty; 809 PD & 14262 controls who underwent; 2833PD & 38850 who had hemiarthroplasty	Shoulder Fractures after Total Arthroplasty: 1% in PD vs. 0.7% in controls; Reverse Arthroplasty Fractures: 1.4% in vs. 1% in controls; After Hemiarthroplasty 3.2 % in PD vs. 2.2% in controls.
Sonnenblick et al. (1995)[47]	Dislocations	Case study	A PD case with recurrent bilateral dislocations	Recurrent bilateral shoulder dislocation resulting from dyskinesia associated with dopaminergic stimulation therapy.
Giannotti et al. (2015)[41]	Fractures & Dislocations	Case study	A Case with PD	Poor functional outcomes after Stemless humeral component in reverse shoulder prosthesis in PD.
Koch et al. (1997)[38]	Fractures & Dislocations	Case study	15 PD patients	Pain relief but Poor functional outcomes After Total shoulder arthroplasty in PD patients.
Dunn et al. (2011)[42]	Fractures & Dislocations	Case series	3 Cases with PD	Reverse total shoulder arthroplasty in PD.
Borbas et al. (2021)[39]	Fractures & Dislocations	Case study	17 PD who underwent reverse total arthroplasty	Increased Complication Rate of Reverse Total Shoulder Arthroplasty in PD.
Cusick et al. (2017)[48]	Fractures & Dislocations	Case study	10 PD and 40 matched controls	Outcome of Reverse Shoulder Arthroplasty in PD Patients.
Koh et al (2019)[30]	Arm Swing	Case-control study	41 early PD and 23 controls, 3D motion analysis used, Arm swing at the wrist and shoulder and elbow range of motion obtained	Arm swing asymmetry at wrist represents involvement of PD effect on unilateral and distal upper limb in PD stages.
Schneider et al. (2012)[31]	Arm Swing	Case-control study	25 early PD patients. Controls: Focal dyston ia patients (31) and healthy individuals (26)	Reduced arm swing and tremor of individual fingers best distinguished PD from the other groups, The battery was sensitive to detect subtle motor features missed by the UPDRS.
Buchthal & Ballesteros (1965)[23]	Arm Swing	Electromyographic study	Elucidate mechanism of arm swing loss during walking and the relationship to tremor and rigidity.	Swinging movements were absent during walking in 24 arms. due to wrongly timed activation of the flexors or of the extensors or both.

Supplementary Table. *(Cont. from previous page).*

Author (Year)	Clinical Parameters of Shoulder Dysfunction	Study Design	Population	Results
Farnikova et al. (2012)[6]	Musculoskeletal Problems (Frozen Shoulder and Pain) as initial manifestation in PD	Retrospective Study	Hospital inpatient notes and outpatient clinic admission notes of 82 PD patients were retrospectively reviewed.	Musculoskeletal pain: a prodromal PD symptom in 27 (33%) cases initially diagnosed with frozen shoulder, Osteoarthritis, spinal disease, Mean duration: 6.6 years before the initiation of dopaminergic treatment, Pain Improvement after treatment initiationin 23 (85%) cases.
Kim et al. (2013)[10]	Musculoskeletal pain may be a feature in earlier PD stages: neglected issues	Cross-sectional Case-Control Study	400 PD patients & 138 age-, sex-matched controls interviewed by physicians.	Musculoskeletal problems: 66.3% in PD vs. 45.7% in controls, Commonly involved sites low back, knee, shoulder. Among frozen shoulder was more common past diagnoses in PD group.
Alarcón et al. (2020)[29]	Frozen Shoulder & Motor Dysfunction as a Prodrome of PD	Prospective Case-Control Study	46 consequently recruited patients, with symptom s suggestive of PD and video recordings. Cases: patients 'converted' evaluated with MDS-UPDRS III to PD Non-cases: those who did not meet PD criteria.	Motor dysfunction: clinical prodrome in PD; Frozen shoulder (OR 3.1; 95% CI 1.6-6.2).