

# Review

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Systematic review of biochemical biomarkers for neck and upper-extremity musculoskeletal disorders <sup>1</sup>

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1            Supplementary material

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<b>Table S1.</b> Questions used in the primary screen for exclusion of articles. An answer “yes” to one or more questions led to exclusion.	
Exclusion questions	
Case study?	Yes
Gray literature?	Yes
Review article?	Yes
Cadaver study?	Yes
Lower extremity MSD?	Yes
Widespread pain?	Yes
Traumatic onset?	Yes
Participants with known disc problems?	Yes
In vitro study/findings involving stimulated cell cultures?	Yes
Histological study examining cell or tissue morphology or their microanatomical components?	Yes
Experiment which induce pain in healthy subjects or those with MSDs by injecting substances into the body?	Yes

*Note: two independent reviewers had to agree on these items in order to exclude a study.*

**Table S2.** Search terms for musculoskeletal disorders (MSDs) and biochemical markers.

MSD		
	MESH terms	Upper extremity/pathology, upper extremity/physiopathology, hand-arm vibration syndrome, rotator cuff, Dupuytren's contracture, neck muscles, musculoskeletal pain, thoracic outlet syndrome, shoulder impingement syndrome, shoulder pain, cumulative trauma disorders, tennis elbow, neck pain, musculoskeletal diseases tendinopathy, myofascial pain syndromes, arm injuries
	Keywords	Secondary Raynaud's, hand-arm vibration syndrome, vibration white finger, rotator cuff , Dupuytren's contracture, musculoskeletal pain, thoracic outlet syndrome, shoulder impingement syndrome, frozen shoulder, adhesive capsulitis, shoulder pain, musculoskeletal disorder, MSD, muscle pain, neck pain, trapezius myalgia, neck-shoulder pain, musculoskeletal diseases, tendinopathy, tendonitis, tendinitis, tendinosis, tenosynovitis, carpal

		tunnel syndrome, arm pain, forearm pain, diffuse forearm pain, elbow pain, wrist pain, hand pain, ganglion cyst
Biochemical marker		
	MESH terms	Biological markers, "antibodies, antineutrophil cytoplasmic", "antigens, differentiation", "antigens, CD", "antigens, CD29", "antigens, differentiation, B-lymphocyte", "antigens, differentiation, myelomonocytic", "antigens, differentiation, T-lymphocyte", "antigens, Ly", "antigens, Thy-1", fibrinopeptide A, "antigens, CD30", "proliferating cell nuclear antigen", synaptophysin, microdialysis, saliva, "blood circulation", "regional blood flow", "neovascularization, physiologic"
	Keywords	Biological marker, biomarker, microdialysis, physiologic, saliva, serum, blood, urine, synovial fluid, blood circulation, blood flow, microcirculation

*Note: the search was restricted to include peer-reviewed articles between 1988/06/04 - 2013/06/04, English language, humans, and adults. Terms within each broad category (MSD, Biochemical marker) are combined with OR and between categories with AND.*

<b>Table S3.</b> Questions used in the secondary screen for quality assessment.	
1.	Was the hypothesis/aim/objective clearly stated?
2.	Was the biomarker described in sufficient detail to permit its replication?
3.	Was the MSD definition or diagnostic criteria clearly described?
4.	Was the MSD symptom severity clearly described?
5.	Was there a comparison group?
6.	Were the selection criteria (inclusion/exclusion) clearly described?
7.	Was the participation/response rate to the initial invitation 65% or greater?
8.	Was loss to follow up less than 35%?
9.	Was an attempt made to blind those analyzing the biomarker to case condition?
10.	Was the time period between assessment of case condition and biomarker assessment short enough to be reasonably sure that the case condition did not change?
11.	Was there any control for confounding either through restriction of subjects or through adjustment in the analysis?
12.	Was the distribution of principal confounders in each group of subjects clearly described?
13.	Was there a power analysis to find an adequate sample size?
14.	Were the statistical models used to assess the main outcomes adequately described?
15.	Was the statistical analysis appropriate?
16.	Were estimates of the random variability in the main effect reported?
17.	Were the main findings clearly described?

*Note: Possible responses were “yes”, “unknown/not applicable” or “no”.*



Castagna (51)	1	1	1	1	1	1	0	0	0
Flodgren (67)	1	1	1	1	1	1	0	0	1
Rechardt (42)	1	1	1	1	1	1	0	0	0
Rechardt (41)	1	1	1	1	1	1	0	0	0
Riva (104)	1	1	1	1	1	1	0	0	0
Rosendal (72)	1	1	1	0	1	1	0	0	1
Sjörs (105)	1	1	1	1	1	1	0	0	0
Xu (54)	1	1	1	1	1	1	0	0	1
Xu (55)	1	1	1	1	1	1	0	0	1
Akesson (38)	1	1	1	0	1	1	1	0	0
Andersson (32)	1	1	1	1	1	1	1	0	0
Bovenzi (39)	1	1	1	0	1	1	1	0	1
Carp (40)	1	1	1	1	1	1	0	0	0
Flodgren (61)	1	1	1	1	0	1	0	0	1
Gumina (33)	0	1	1	1	0	1	1	1	0







Insufficient quality (below median)									
Demirkol (107)	1	1	0	0	1	1	0	0	0
Ghafouri (108)	1	1	1	1	1	1	0	0	0
Hallgren (109)	1	1	1	1	1	1	0	0	0
Han (110)	1	1	1	1	1	1	0	0	0
Hasselhorn (111)	1	1	0	1	0	1	0	1	0
Hindocha (112)	1	1	1	1	1	1	0	0	0
Hirata (113)	1	0	1	1	1	1	0	0	0
Hirata (114)	1	1	1	1	1	1	0	0	0
Kim (115)	1	1	1	1	1	1	0	0	0
Lau (116)	0	1	1	1	1	1	0	0	0
Nakama (117)	1	1	1	1	0	0	0	0	0
Nilsson (118)	1	1	0	1	1	1	0	0	0

Nowak (119)	1	1	1	0	1	0	0	0	0
Sanderson (120)	1	1	1	1	1	1	0	0	0
Tajana (121)	1	1	1	1	1	1	0	0	0
Zeisig (122)	1	1	1	1	1	1	0	0	0
Bergenudd (123)	1	1	1	0	1	0	0	0	0
Hyvönen (124)	1	1	1	1	1	0	0	0	0
Keniston (125)	1	1	1	1	1	1	0	0	0
Laskar (126)	1	1	1	0	1	1	0	0	0
Okumus (127)	1	0	1	1	1	1	0	0	0
Olausson (128)	1	1	1	1	1	0	0	0	0
Ratajczak-Wielgomas (129)	1	1	1	1	1	0	0	0	0
Toesca (130)	1	1	1	1	1	0	0	0	0

Kang (131)	1	1	1	0	1	1	0	0	0
Kent (132)	0	1	1	0	1	0	0	0	0
Meek (133)	1	1	0	0	1	0	0	0	0
Riondino (134)	1	1	0	0	1	1	0	0	0
Chambler (135)	1	1	0	0	0	1	0	0	0
Greenstein (136)	1	1	1	0	1	0	0	0	0
Ljung (137)	1	1	1	0	0	1	0	0	0
Osawa (138)	0	1	1	0	1	0	0	0	0
Tucci (139)	1	1	1	0	1	1	0	0	0
Gudmundsson (140)	1	1	0	0	1	0	0	0	0
Harada (141)	0	1	0	1	1	1	0	0	0
Ohlsson (36)	1	1	0	0	0	0	1	0	0
Ljung (142)	0	1	1	1	1	0	0	0	0

Yoshihara (143)	0	1	0	1	0	0	0	0	0
Donato (144)	0	1	0	0	0	0	0	0	0
Kohout (145)	0	1	0	0	0	0	0	0	0
Santavirta (146)	0	0	0	1	0	0	0	0	0
Percentage of "yes" scores	86	94	84	69	86	70	11	3	15

<b>Table S4. (cont.)</b>									
Criteria (see table S3), Author	Time-period short enough	Control for confounding	Principal confounders described	Power analyses	Statistical methods described	Statistical Analyses Appropriate	Estimates of variability	Findings clearly described	<b>Total score</b>
Sufficient quality (above median)									
Kaergaard (37)	1	1	1	0	1	1	1	1	15
Gerdle (74)	1	1	1	0	1	1	1	1	14
Larsson (71)	1	1	1	0	1	1	1	1	14
Moreno-Torres (66)	1	1	1	0	1	1	1	1	14
Rosendal (75)	1	1	1	0	1	1	1	1	14
Sjøgaard (31)	1	1	1	0	1	1	1	1	14
Castagna et al. (51)	1	1	1	0	1	1	1	1	13

Flodgren (67)	0	1	0	1	1	1	1	1	13
Rechardt (42)	1	1	1	0	1	1	1	1	13
Rechardt (41)	1	1	1	0	1	1	1	1	13
Riva (104)	1	1	1	0	1	1	1	1	13
Rosendal (72)	1	1	1	0	1	1	1	1	13
Sjörs (105)	1	1	1	0	1	1	1	1	13
Xu (54)	1	0	1	0	1	1	1	1	13
Xu (55)	1	0	1	0	1	1	1	1	13
Akesson (38)	0	1	1	0	1	1	1	1	12
Andersson (32)	0	1	1	0	1	0	1	1	12
Bovenzi (39)	0	1	1	0	1	1	1	0	12
Carp (40)	0	1	1	0	1	1	1	1	12
Flodgren (61)	1	1	0	0	1	1	1	1	12
Gumina (33)	1	0	1	0	1	1	1	1	12
Hnanicek (48)	1	1	1	0	1	1	1	1	12

Lakemeier (45)	1	1	1	0	1	1	1	0	12
Lau (63)	0	1	1	0	1	1	1	1	12
Longo (46)	1	1	1	0	1	1	1	1	12
Nilsen (68)	0	1	1	0	1	1	1	1	12
Ozgocmen (77)	1	1	1	0	1	1	1	1	12
Papalia (52)	0	1	1	0	1	1	1	1	12
Rechardt (34)	0	1	1	0	1	1	0	1	12
Tsujii (58)	1	0	1	0	1	1	0	1	12
Abboud (43)	1	1	1	0	0	1	1	1	11
Augoff (73)	1	0	1	0	1	1	1	1	11
Bunker (35)	0	1	0	0	0	1	1	1	11
Freeland (70)	1	0	0	1	1	1	1	1	11
Ghafouri (64)	0	1	0	0	1	1	1	1	11
Ghafouri (76)	0	1	1	0	1	1	1	1	11
Hadrevi (62)	0	1	1	0	1	1	0	1	11

Iqbal (47)	1	0	1	0	1	1	1	1	11
Kennedy (59)	0	1	1	0	1	1	1	1	11
Lakemeier (45)	1	0	1	0	1	1	1	1	11
Lubis (56)	1	0	1	0	1	1	0	1	11
Nakamura (60)	0	1	1	0	1	1	1	1	11
Sjøgaard (106)	0	1	1	0	1	0	1	1	11
Teodorczyk-Injeyan (69)	0	0	1	0	1	1	1	1	11
Ulrich (49)	1	0	0	0	1	1	1	1	11
Ulrich (50)	1	0	1	0	1	1	1	1	11
Insufficient quality (below median)									
Demirkol (107)	0	1	1	0	1	1	1	1	10



Ghafouri (108)	1	1	1	0	0	0	0	1	10
Hallgren (109)	0	1	0	0	1	0	1	1	10
Han (110)	1	0	1	0	1	0	0	1	10
Hasselhorn (111)	0	1	1	0	1	1	1	0	10
Hindocha (112)	1	0	1	0	0	0	1	1	10
Hirata (113)	1	0	0	0	1	1	1	1	10
Hirata (114)	1	0	0	0	0	1	1	1	10
Kim (115)	1	0	0	0	1	0	1	1	10
Lau (116)	0	1	1	0	1	0	1	1	10
Nakama (117)	1	0	1	0	1	1	1	1	10
Nilsson (118)	1	0	1	0	1	0	1	1	10
Nowak (119)	0	1	1	0	1	1	1	1	10
Sanderson (120)	0	1	0	0	0	1	1	1	10
Tajana (121)	1	0	1	0	0	0	1	1	10

Zeisig (122)	1	0	1	0	0	1	0	1	10
Bergenudd (123)	1	1	1	0	0	0	1	1	9
Hyvönen (124)	1	0	1	0	1	0	0	1	9
Keniston (125)	0	1	1	0	1	0	0	0	9
Laskar (126)	0	0	1	0	1	0	1	1	9
Okumus (127)	0	0	1	0	1	1	0	1	9
Olausson (128)	1	1	1	0	0	0	0	1	9
Ratajczak-Wielgomas (129)	1	0	1	0	0	1	1	0	9
Toesca (130)	1	0	1	0	0	1	0	1	9
Kang (131)	0	1	1	0	0	0	1	0	8
Kent (132)	0	0	1	0	1	1	1	1	8
Meek (133)	1	0	1	0	0	1	1	1	8

Riondino (134)	0	1	1	1	0	0	1	0	8
Chambler (135)	1	0	0	0	0	1	1	1	7
Greenstein (136)	0	0	1	0	0	0	1	1	7
Ljung (137)	1	0	1	0	0	0	0	1	7
Osawa (138)	1	0	1	0	0	0	1	1	7
Tucci (139)	1	0	0	0	0	1	0	0	7
Gudmundsson (140)	0	0	0	0	1	0	1	1	6
Harada (141)	0	1	1	0	0	0	0	0	6
Ohlsson (36)	0	0	0	0	1	0	1	1	6
Ljung (142)	0	0	0	0	0	0	0	0	4
Yoshihara (143)	1	0	0	0	1	0	0	0	4
Donato (144)	1	0	0	0	0	0	0	0	2
Kohout (145)	0	0	1	0	0	0	0	0	2

Santavirta (146)	1	0	0	0	0	0	0	0	2
Percentage of "yes" scores	59	53	77	3	70	68	76	83	

**Table S5.** Overview with descriptive information of included studies, by anatomical region of the disorder

<b>MSD Classificati on or diagnosis Author</b>	<b>Biomark er</b>	<b>Medium &amp; anatomical location</b>	<b>Study population<sup>a</sup>; Sample size (N)</b>	<b>Mean age in years  (range if available)</b>	<b>Gend er</b>	<b>Study design</b>	<b>Experimental condition</b>
<b>NECK DISORDERS &amp; SYMPTOMS</b>							
Chronic & recurring neck pain  Teodorczyk- Injeyan et al. (69)	TNF- $\alpha$ , CCL2/M CP- 1,CCL3/ MIP-1 $\alpha$ , NO <sub>2</sub> <sup>-</sup>	Serum and whole blood (used for cultures),  Systemic	Cases (N=27) & controls (N=13): patients from chiropractic outpatient clinic.	Cases: 40.2 (23-65);  Controls: 34.7 (24-54)	M/F	Control	At rest
<b>SHOULDER DISORDERS &amp; SYMPTOMS</b>							
Rotator cuff tear	Cholester ol, triglycerid e, LDL, HDL	Serum,  Systemic	Cases (N=74) & controls (N=73): surgical patients from outpatient tertiary care clinic for shoulder pain.	Cases: 66.1;  Controls: 67.2	M/F	Control	At rest

Abboud et al. (43)			Cases: full-thickness rotator cuff tear.				
			Controls: non-tendon shoulder complaints.				
Rotator cuff tear	MMP-1,2,3,8,9,10,13; TIMP-1,2	Tendon - 3 sampled areas: L – lateral edge supraspinatus tear;  M – arthroscopically intact middle portion tendon;  S – macroscopically intact superior 1/3 of subscapularis tendon as control.  Local.	Cases (N=13): patients undergoing surgery for rotator cuff tendon tears.	Cases: 55 (40-65)	M/F	During surgery	
Castagna et al. (51)							
Rotator cuff tear	VEGF	Tendon,  Long head biceps	Cases (N=108 <sup>a</sup> ): rotator cuff tear patients needing arthroscopic surgery. <sup>a</sup> Partial	Cases:	M/F	Control	During surgery

Lakemeier et al. (45)			tear (N=48) [cuff arthropathy patients not included, N=8]	Partial thickness tears: 61 (39-78);			
			Controls (N=8): trauma patients with humeral head fractures.	Full thickness tears: 67 (55-80);			
				Controls: 56 (37-69)			
Rotator cuff tear	MMP-1,3,9	Tendon, Rotator cuff tear margin	Cases (N=33): patients undergoing surgery for full-thickness rotator cuff tears.	Patte grade I: 61 (55-68);	M/F	Control	During surgery
Lakemeier et al. (44)				Patte grade II: 65 (55-75);			
			Controls (N=6): patients undergoing surgery for traumatic humeral head fractures.	Patte grade III: 69 (51-79);			
				Controls: 56 (47-69)			
Rotator cuff tear	Cholesterol, triglyceride	Blood, Systemic	Cases: arthroscopic repair patients (N=120) for rotator cuff tear.	Cases: 64.9 (40-83);	M/F	Control	At rest

Longo et al. (46)			Controls (N=120): patients for meniscal tear repair with no evidence of shoulder pathology.	Controls: 63.9 (38-78)			
Rotator cuff tear	NPN, creatinine	Plasma, Systemic	Cases: arthroscopic repair patients (N=200) for rotator cuff tear.	Cases: 56.8 (23-81)  Controls: 53.9 (20-81)	M/F	Control	At rest
Papalia et al. (52)			Controls (N=200): knee arthroscopy for a meniscal tear.				
Rotator cuff tear	PGP9.5, GAP43	Tendon, Localized edges of torn supraspinatus from cases, macroscopically normal subscapularis from cases, and	Patients undergoing surgery:  Cases (N=26): rotator cuff tear.  Controls (N=10): shoulder instability.	Cases: 56 (30-73)  Controls: 33 (17-59)	M/F	Control	During surgery
Xu (54)							



		subscapularis from controls					
Rotator cuff tendinitis	CRP	Serum, Systemic	Population aged >30 years in Finland contacted via Health 2000 survey. Current sample obtained through systematic sampling from health center districts. <sup>b</sup>	Males: 50.8 (95% CI: 50.2- 51.3)  Females: 52.9 (95% CI: 52.4- 53.4)	M/F	Populat ion based; Control	At rest
Rechardt et al. (34)			Males: N=2850,  w. rotator cuff tendinitis: N=80;  Females: N=3387,  w. rotator cuff tendinitis: N=95				
Frozen shoulder (Adhesive capsulitis)	Cholesterol, triglyceride	Serum, Systemic	Orthopedic hospital patients:  Cases (N=43): presenting with shoulder pain.	Cases:  males: 59,  females: 56   Controls:	M/F	Control	At rest

Bunker et al. (35)			Controls (N=43): admitted for arthroscopic surgery to knee or foot.	males: 57.3 females: 55.8			
Frozen shoulder (Adhesive capsulitis)	MMP-1,2, TIMP-1,2, TGF-β1, MMP/TIM P ratio	Serum, Systemic	Cases (N=50): patients with frozen shoulder.  Controls (N=50): persons with no shoulder disorder, of unclear origin.	Cases: 49.5 (37-77)  Controls: 53.5 (32-56)	M/F	Control	At rest
Lubis et al. (56)							
Frozen Shoulder (Adhesive capsulitis)	CD34, GAP43, PGP9.5, P75	Sectioned capsular tissue shoulder capsule just above subscapularis tendon, immediately adjacent to glenoid labrum.  Local, Symptom region	Cases (N=8): patients undergoing surgery for arthroscopic shoulder capsular release.  Controls (N=10): patients undergoing surgery for rotator cuff repair.	Cases: 58 (55-64 )  Controls: 51 (29-79)	M/F	Control	During surgery
Xu et al. (55)							

Frozen Shoulder (Adhesive capsulitis)	CRP, glucose, total cholesterol, LDL, HDL, rheumatoid factor	Serum, Systemic	Consecutive patients with shoulder adhesive capsulitis (N=56)	56 (39-68)	M/F	Longit (treatment), only baseline results used in review	At rest
Gumina et al. (33)							
Shoulder pain (unilateral & bilateral)	CRP	Serum, Systemic	Population aged >30 years in Finland contacted via Health 2000 survey. Current sample obtained through systematic sampling from health center districts. <sup>b</sup>	Males: 50.8 (95% CI: 50.2-51.3)  Females: 52.9 (95% CI: 52.4-53.4)	M/F	Population based  Control	At rest
Rechardt et al. (34)			Males: N=2850:  257 w. unilateral shoulder pain & 171 w. bilateral shoulder pain  Females: N=3387				

			339 w. unilateral shoulder pain &				
			237 w. bilateral shoulder pain				
NECK/SHOULDER DISORDERS & SYMPTOMS							
Trapezius myalgia	Glutamate, , lactate, PGE2, pyruvate	Muscle interstitium  Trapezius,  Local: Glutamate, lactate, PGE2, pyruvate  Blood, systemic: lactate	Cases (N=14): recruited through contacts with local industries and through advertisement on university hospital intranet.	40 (SD = 8)	F		Expt protocol:  Rest - after inserting MDy probe (90 min),  Rest – baseline (30 min),  Repetitive, physical work (30 min),  Recovery (60 min)
Trapezius myalgia	Bradykinin, kallidin	Muscle interstitium  Trapezius,  Local	Cases (N=19): female out-patients referred to the Pain and Rehabilitation Centre.  Controls (N=20): newspaper advertisements.	Cases: 41 (21-61)  Controls: 36 (26-56)	F	Control	Expt protocol:  Rest - after inserting MDy probe (120 min),  Rest - baseline (20 min),
Gerdle et al. (74)							

							Repetitive, low force exercise (20 min),
							Recovery (120 min)
Trapezius myalgia	Serotonin (5-HT)	Muscle interstitium	Cases (N=18): former outpatients from the Pain and Rehabilitation Centre.	Cases: 40 (28-48)	F	Control	Expt protocol:
		Trapezius,		Controls: 40 (26-50)			Rest - after inserting MDy probe (120 min),
Ghafouri et al. (64)		Local	Controls (N=30): newspaper advertisements.				Rest - baseline (20 min),
							Repetitive, physical work (100 min) ,
							Mental stress task (TSST) (20 min),
							Recovery (20 min)
Trapezius myalgia	Multiple proteins (proteomics study):	Muscle trapezius, Local	Cleaners: Cases (N=12) and controls (N=12)	Cases: 42 (SD = 8)	F	Control	During biopsy
	See table 1			Controls: 41 (SD = 8)			



	kinase, LDH	Plasma, systemic: creatine kinase, LDH	newspaper advertisements.				force work (20 min),  Recovery (120 min)
Trapezius myalgia  Rosendal et al. (72)	IL-6, K+, LDH, PINP/ICTP ratio	Muscle interstitium trapezius,  Local	Cases (N=19): former out-patients from Pain and Rehabilitation Centre.  Controls (N=20): newspaper advertisements.	Cases: 41 (21-61)  Controls: 36 (26-56)	F	Control	Expt protocol:  Rest – after inserting MDy probe (120 min), Sample for interstitial muscle collagen , Repetitive, low-force work (peg board) (20 min),  Recovery (120 min)
Trapezius myalgia  Sjogaard et al. (31)	Lactate, pyruvate, glucose, potassium (K+)	Muscle interstitium  Trapezius,  Local	Cases (N=43) & controls (N=19): from 7 workplaces (blue + white collar), or via advertisements in local newspapers.	Cases: 44 (SD = 9.8)  Controls: 44 (SD = 9.1)	F	Control	Expt protocol:  Rest after inserting MDy probe (120 min),  Rest – baseline (40 min),

								Repetitive, low force task (pegboard) (120 min),  Rest – intermediate (10 min),  Mental stress task (Stroop) (30 min), Recovery (30 min)
Trapezius myalgia	Cortisol	Saliva,  Systemic	Cases (N=18): former female out-patients from Pain and Rehabilitation Center.	Cases: 40 (28-48)  Controls: 40 (26-50)	F	Control	Expt protocol:	Rest - after inserting MDy probe (120 min),  Rest - baseline (20 min),  Repetitive physical work tasks – simulated assembly and pegboard (100 min),
Sjörs et al. (65)			Controls (N=30): newspaper advertisements.					



							Combined physical (pegboard) and mental task (20 min),  Recovery (80 min)  Additional saliva samples for cortisol awakening response, after lunch and evening
Myofascial pain syndrome (esp. in periscapular region)  Ozgocmen et al. (77)	Cholesterol, triglyceride, HDL, LDL, VLDL	Blood, Systemic	Housewives $\pm$ myofascial pain.  Cases: (N=32) Controls: (N=31)	Cases: 38.5 (17-60)  Controls: 35.5 (23-57)	F	Control	At rest
Chronic neck/shoulder pain	Glutamate, PGE2	Muscle interstitium	Cases (N=9): recruited when consulting a chiropractor.	Cases: 42.2 (35-53)	F	Control	At rest

		Trapezius,		Controls: 44.1 (35-52)			4 h rest after inserting MDy probe	
Flodgren et al. (67)		Local	Controls (N=9): healthy persons from university hospital and university.					
Chronic neck/shoulder pain	PEA, SEA	Muscle interstitium	Advertisements in the local daily paper.	Cases: 45 (29-60)	F	Control	Expt protocol:	
Ghafouri et al. (76)		Trapezius,	Cases (N=34) and Controls (N=24)	Controls: median=44 (27-56)			Rest – after inserting MDy probe (120 min),	
		Local					Rest - baseline (20 min),	
							Repetitive low-force exercise (pegboard) (20 min),	
Shoulder & neck pain	Noradrenaline PPP, noradrenaline PRP,	Plasma, serum (cortisol)	Cases (NSP, N=29): patients from primary care centers and physiotherapists.	Cases: 48.3 (32-63)	F	Control	Recovery - post-exercise (20 min)	
								Expt protocol:
								Baseline (10 min),
				Controls: 41.1 (19-59)			Mental stress (60 min),	

Nilsen et al. (68)	adrenaline PPP, cortisol		Controls (N=35): from public institutions and private companies				Recovery (30 min)
Shoulder & neck pain	Cortisol	Saliva, Systemic	Cases (N=18): staff at a university and secondary school.	Cases: 44.3 (23-59)  Controls: 51.9 (37-64)	F	Control	At rest
Riva et al. (57)			Controls (N=27): donors to a hospital blood bank.				
Neck & shoulder disorders (see paper for complete list)	Testostero ne	Plasma, Systemic	Cases &controls: female employees from 4 industrial factories.  Baseline: 32 Cases and 112 Controls  Follow-up: 16 Cases and 57 Controls	40.4 (SD = 9.1)	F	Control  longitud inal: subject s tested at baselin e; subgro up tested at 1 year	At rest
Kaergaard et al. (37)							

							follow-up
<b>HAND/WRIST DISORDERS &amp; SYMPTOMS</b>							
Carpal tunnel syndrome	PGE2, IL-1, IL-6, MDA	Serum, Systemic	Cases (N=41): consecutive patients with “idiopathic” carpal tunnel syndrome who underwent carpal tunnel release during an 18-month period.	Cases: 46.7  Controls: not stated	M/F	Control	At rest
Freeland et al. (70)			Controls (N=21): unclear origin.				
Carpal tunnel syndrome	Tenascin -C	Flexor tenosynovium in carpal tunnel, Local	Patients surgically treated for idiopathic CTS.	53.2 yrs (31-79 yrs)	M/F		During surgery
Tsujii et al. (58)			Gp A (<4 mo symptom onset until surgery [SOS]): N=8;  Gp B (4-6 mo SOS): N=12;  Gp C (7-12 mo SOS): N=8;  Gp D (>12 mo SOS): N=12				

Hand-arm vibration syndrome (HAVS)	Endothelin (ET <sub>1-21</sub> )	Saliva, Systemic	Cases (N=6): all male forestry workers with HAVS operating chain and brush saws in a public company	Cases: 43.0 (SD = 5.1)	M	Control	Expt protocol: Rest (20 min), Local cooling test (one finger was cooled in cold water (10°C) (5 min))
Bovenzi et al. (39)			Controls: workers from the same company unexposed to hand-transmitted vibration.  Gp 1 (forestry workers without HAVS, N=48) & Gp 2 (N=52)	Controls Gp 1: 44.7 (SD = 6.1)  Controls Gp 2: 41.7 (SD = 6.7)			
HAVS	sICAM-1, IL-8	Blood, Systemic	Subject origin not stated.  Cases: (N=8)  Controls: (N=8)	Cases: 59.5 (29-76)  Controls: 59.0 (29-71)	M	Control	At rest
Kennedy et al. (59)							
HAVS	PMN, MDA	Blood, Systemic	Cases (N=22): Raynaud's clinic patients warranting hospital referral.	Cases: median=44 (19-71)  Controls: median=46 (21-71)	M/F	Control	At rest
Lau et al. (63)							

			Controls (N=56): general surgical ward patients for minor elective operations.				
HAWS	Endotheli n-1	Plasma, Systemic	Chain-saw workers that had a special annual exam due to their use of vibrating hand tools.	Cases: 58.1 (SD = 4.7)	M	Control	experimental protocol:
Nakamura et al. (60)			Cases: (N=7)	Controls: 57.9 (SD = 6.7)			rest (30 min)
			Controls: (N=7)				cold water-immersion test (immersing hands 10°C) (10 min)
							recovery - immediately after immersion
Dupuytren's contracture	MMP-2	Fascia, Palm; Local	Surgical patients: Cases (N=71): for Dupuytren's contracture.	(33-72) (no mean given)	M/F	Control	During surgery

Augoff et al. (73)			Iselin's classification of disease: degree I (N=13), degree II (N=20), degree III (N=22), degree IV (N=16).  Controls (N=16): for carpal tunnel syndrome.				
Dupuytren's contracture	MSC markers: CD73, CD90, CD105; Hematopoietic marker: CD34	Fascia, skin, & fat; Palm, Local	Surgical patients  Cases (N=27): for Dupuytren's contracture.  Controls (N=14): for carpal tunnel syndrome.	Cases: 65 (47-80)  Controls: 59 (44-80)	M/F	Control	During surgery
Iqbal et al. (47)							
Dupuytren's contracture	Ferritin, iron, total iron binding capacity, transferrin	Serum,  Systemic  Fascia, palm	Cases (N=90): patients undergoing surgery for Dupuytren's.	Cases: 60.6 (29-81)  Controls: 56 (26-89)	M/F	Control	Serum - at rest  Fascia - during surgery
Hnanicek et al. (48)							

	saturation, total cholesterol	Local	Controls (N=33): from general population.				
Dupuytren's contracture	MMP-1,2,9; TIMP-1,2; MMP/TIMP ratio	Serum, Systemic	Surgical patients: Cases (N=22): for Dupuytren's regional or radical fasciectomy.	Cases: 67 (SD = 11) Controls: 60 (SD = 15)	M/F	Control	At rest
Ulrich et al. (49)			Controls (N=20): for carpal tunnel syndrome				
Dupuytren's contracture	MMP-2,9; TIMP-1,2	Fascia, palm Local	Surgical patients: Cases (N=30): for Dupuytren's disease. Included 14 with proliferative active disease (proliferative and early involutional phase), and 8 with late involutional and residual phase.	Cases: 61.3 (SD = 9.5) Controls: 63 (SD = 11)	M/F	Control	Curing surgery
Ulrich et al. (50)							



Controls (N=30): for carpal tunnel syndrome.							
Non-specific pain in finger extensor musculature	Pi, Pi/PCr	Biochemical spectral peaks ID with P-MRS (phosphorous magnetic resonance spectroscopy) in hand extrinsic extensor muscles (dorsal forearm)	Volunteer instrumentalists: Cases: (N=11) Controls: (N=8)	Cases: 23.2 (SD = 5.0) Controls: 22.6 (SD = 3.2)	M/F	Control	Expt protocol: Rest (unspecified time, brief MRI scans),  Finger extensor exercise (until pain/exhaustion or 1000 sec)
Moreno-Torres et al. (66)							
Muscle, Local							
<b>UPPER EXTREMITY DISORDERS &amp; SYMPTOMS WITHOUT SPECIFIED LOCATION</b>							
Musculoskeletal symptoms	Selenium, mercury	Se - plasma  Hg – whole blood, plasma, urine	Exposed (N=268): 1) All dental personnel from public dental health services, and 2) dental hygienists.	not stated	M/F	Population based study	at rest
Akesson et al. (38)			Unexposed (N=111): 1) 30 medical nurses from hospital				

		Systemic	blood centers and occupational health service centers, and 2) a stratified matched sample of N=81 from general population.	Control (unexposed)			
Musculoskeletal disorders (MSDs) due to overuse (see paper for complete list)	IL-1 $\beta$ , TNF- $\alpha$ , IL-6, CRP	Serum, Systemic	Cases (N=22): from outpatient physical therapy clinic, recruited using stratified non-random sampling procedure based on UBMA scores.  Controls (N=9): not stated.	45.2 (19-74)	M/F	Control	At rest
Carp et al. (40)							
Specific & non-specific MSDs, mainly lateral epicondylitis & rotator cuff	CRP, IL-1 $\alpha$ , IL-1 $\beta$ , IL-1 Ra, IL-6, IL-18, IL-33, sST2, sIL-1RII, TNF- $\alpha$	Blood, Systemic	Cases (N=163): patients from 3 occupational health units seeking medical advice for MSDs.	Cases: 45.0 (SD = 9.8)  Controls: 43.9 (SD = 9.2)	M/F	Control	At rest

tendinitis (see paper for complete list)			Controls (N=42): employees from Finnish Institute of Occupational Health.				
Rechardt et al. (42)							
MSDs (see paper for complete list)	cholesterol, triglyceride, HDL, LDL, glucose, CRP, leptin, andipone ctin, resistin, visfatin	Serum, Systemic	Cases (N=163): patients from 3 occupational healthcare units seeking medical advice for incipient upper extremity pain:  36% shoulder disorders, 31% epicondylitis, 13% wrist tendinitis or carpal tunnel syndrome, and 20% non- specific	45.0 (SD =9.8)	M/F	Population based study	At rest
Rechardt et al. (41)							

<sup>a</sup> - healthy controls unless otherwise indicated.

<sup>b</sup> - unknown number of referents since the overlap between shoulder pain and rotator cuff tendinitis patients is unknown.

## Appendix 1. PubMed search string.

("Upper Extremity/pathology"[Mesh] OR "Upper Extremity/physiopathology"[Mesh] OR "Hand-Arm Vibration Syndrome"[Mesh] OR "secondary raynaud's"[Title/Abstract] OR "hand-arm vibration syndrome"[Title/Abstract] OR "vibration white finger"[Title/Abstract] OR "Rotator Cuff"[Mesh] OR "rotator cuff"[Title/Abstract] OR "Dupuytren Contracture"[Mesh] OR "dupuytren's contracture"[Title/Abstract] OR "Neck Muscles"[Mesh] OR "Musculoskeletal Pain"[Mesh:noexp] OR "musculoskeletal pain"[Title/Abstract] OR "Thoracic Outlet Syndrome"[Mesh:noexp] OR "thoracic outlet syndrome"[Title/Abstract] OR "Shoulder Impingement Syndrome"[Mesh] OR "shoulder impingement syndrome"[Title/Abstract] OR "frozen shoulder"[Title/Abstract] OR "adhesive capsulitis"[Title/Abstract] OR "Shoulder Pain"[Mesh] OR "shoulder pain"[Title/Abstract] OR "Cumulative trauma disorders"[Mesh] OR "musculoskeletal disorder"[Title/Abstract] OR "MSD"[Title/Abstract] OR "muscle pain"[Title/Abstract] OR "Tennis Elbow"[Mesh] OR "Neck pain"[Mesh] OR "neck pain"[Title/Abstract] OR "trapezius myalgia"[Title/Abstract] OR "neck-shoulder pain"[Title/Abstract] OR "Musculoskeletal Diseases"[Mesh:noexp] OR "musculoskeletal diseases"[Title/Abstract] OR "Tendinopathy"[Mesh] OR "tendinopathy"[Title/Abstract] OR "tendonitis"[Title/Abstract] OR "tendinitis"[Title/Abstract] OR "tendinosis"[Title/Abstract] OR "tenosynovitis"[Title/Abstract] OR "carpal tunnel syndrome"[Title/Abstract] OR "Myofascial Pain Syndromes"[Mesh] OR "Arm Injuries"[Mesh] OR "arm pain"[Title/Abstract] OR "forearm pain"[Title/Abstract] OR "diffuse forearm pain"[Title/Abstract] OR "elbow pain"[Title/Abstract] OR "wrist pain"[Title/Abstract] OR "hand pain"[Title/Abstract] OR "ganglion cyst"[Title/Abstract]) AND ("Biological Markers"[Mesh:noexp] OR "Biological marker"[Title/Abstract] OR "Biomarker"[Title/Abstract] OR "Antibodies, Antineutrophil Cytoplasmic"[Mesh] OR "Antigens, Differentiation"[Mesh:noexp] OR "Antigens, CD"[Mesh] OR "Antigens, CD29"[Mesh] OR "Antigens, Differentiation, B-Lymphocyte"[Mesh] OR "Antigens, Differentiation, Myelomonocytic"[Mesh] OR "Antigens, Differentiation, T-Lymphocyte"[Mesh] OR "Antigens, Ly"[Mesh] OR "Antigens, Thy-1"[Mesh] OR "Fibrinopeptide A"[Mesh] OR "Antigens, CD30"[Mesh] OR "Proliferating Cell Nuclear Antigen"[Mesh] OR "Synaptophysin"[Mesh] OR "Microdialysis"[Mesh] OR "Microdialysis"[Title/Abstract] OR "Saliva"[Mesh] OR "Saliva"[Title/Abstract] OR "Serum"[Title/Abstract] OR "Blood"[Title/Abstract] OR "Urine"[Title/Abstract] OR "Synovial fluid"[Title/Abstract]) AND (("1988/06/04"[PDAT] : "2013/06/04"[PDAT]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])

**Appendix 2.** Data extraction items.

1. What is the hypothesis/aim/objective of the study?
2. What is the biomarker(s) of interest?
  - 2a. Where was it extracted from (blood, urine, synovial fluid, etc.)?
  - 2b. What is the location of the body tissue from which it was extracted?
  - 2c. Is the biomarker systemic or localized?
3. Describe any experimental challenge during which biomarkers and/or MSD severity was assessed.
4. What is the MSD/pain outcome(s) of interest?
  - 4a. How is symptom/case severity described? State the average severity and severity range, if given.
  - 4b. What is the duration of symptoms/MSD? State the average duration and duration range, if given.
5. Is there a control group in the study?
  - 5a. Is the study longitudinal?
6. What is the study population from which potential participants were selected from? Specify for cases and controls.
  - 6a. What inclusion and/or exclusion criteria were used?
  - 6b. What was the size of the study population – specify for cases and comparison group (if there is one)?
  - 6c. What is the mean age and range (or SD) of cases and controls?

6d. Which genders are study participants?

6e. What was the participation/response rate?

7. State results in terms of effect sizes and precision (ex., OR = 3.2 [95% CI: 2.2-4.6]), if possible.

7a. Is there at least one statistically significant association between MSD(s) and biomarker(s) in the study?

Definition and descriptions of abbreviations and biomarker analytes.

<b>Abbreviation/Analyte</b>	<b>Full Name</b>	<b>Description</b>
5-HT	Serotonin	A monoamine neurotransmitter; biochemically derived from tryptophan; a key mediator in the physiology of mood, vascular function and gastrointestinal motility.
Adiponectin	Adiponectin	An adipokine produced by white adipose tissue; decreased serum levels are associated with higher incidence of diabetes; a reliable marker of insulin resistance.
Adrenaline	Also known as epinephrine, adrenalin, or $\beta$ ,3,4-trihydroxy-N-methylphenethylamine)	A hormone and neurotransmitter produced in high-stress situations.
ANOVA	Analysis of Variance	A statistical term.
Assoc.	Association	--
BMI	Body mass index	A measure of body fat based on height and weight.
Bonf	Bonferroni	The Bonferroni correction is a conservative statistical method used to counteract the problem of multiple comparisons.
Bradykinin	Bradykinin	An endogenous vasodilator nonapeptide kinin; a very powerful vasodilator; increases capillary permeability; also stimulates pain receptors. Bradykinin, along with kallidin, is a kinin

		produced by the kallikrein-mediated enzymatic cleavage of kininogen.
CCL2/MCP-1	Macrophage Chemotactic Factor-1	Inflammatory chemoattractant protein; regulates migration and infiltration of monocytes and macrophages.
CCL3/MIP-1 $\alpha$	Macrophage inflammatory protein-1 $\alpha$	Inflammatory chemokine that is chemoattractant for a variety of cells including monocytes, T cells, B cells and eosinophils.
CD	Cluster of Differentiation Molecule	Cluster of designation of cell surface molecules.
CD34	Cluster of Differentiation Molecule 34	A glycosylated transmembrane protein; a well-known marker for primitive blood- and bone marrow-derived progenitor cells, especially hematopoietic and endothelial stem cells. Biological functions are largely unknown; recent data suggest it is involved in maintenance of progenitor cells in a phenotypically undifferentiated state.
CD73	Cluster of Differentiation Molecule 73; also called ecto-5'-nucleotidase	A membrane-bound enzyme that catalyzes the conversion adenosine monophosphate to bioactive adenosine at neutral pH. Present on subsets of T and B lymphocytes, follicular dendritic cells, endothelial cells, and mesenchymal stem cells (MSCs). Implicated in epithelial ion and fluid transport, tissue injury, platelet function, hypoxia, vascular leak and more.



CD90	Cluster of Differentiation Molecule 90	A conserved cell surface protein, first identified in the thymus as a T-cell maturation and differentiation. Also expressed in primitive hematopoietic progenitor cells and fibroblasts.
CD105	Cluster of Differentiation Molecule 105; also known as endoglin	An endothelial homodimeric membrane glycoprotein found on endothelial cells, activated macrophages, fibroblasts, and smooth muscle cells. Part of the TGF-beta1 receptor complex. Plays a crucial role in angiogenesis: of interest in the study of monocyte differentiation into macrophages.
CI	Confidence interval	A statistical term.
Cortisol	Hydrocortisone/Compound F	A major glucocorticoid hormone produced in the adrenal cortex; actively involved in the regulation of calcium absorption, blood pressure maintenance, anti-inflammatory function, gluconeogenesis, gastric acid and pepsin secretion, and immune function.
Creatinine	Creatinine	A break down product of creatine phosphate in muscles. Depending on muscle mass, creatinine is produced daily at a constant rate. Blood carries creatinine into kidneys, where is removed from the blood by filtration into the urine. Blood and urine creatinine levels are important indicators of kidney function.
Creatine kinase	The enzyme creatine kinase (EC). Also known as creatine	An enzyme expressed by various tissues and cell types. Catalyzes the formation of phosphocreatine from ATP and creatine (and the reverse reaction). Creatine kinase is assayed in blood tests as a marker of myocardial infarction,

	phosphokinase, and phosphocreatine kinase.	severe muscle breakdown, muscular dystrophy, and in acute renal failure.
CRP	C-reactive protein	A nonspecific inflammatory marker.
CTS	Carpal tunnel syndrome	--
DPF	Distal Palmar Fat	The palmar fat pad of the hand; a reliable anatomic landmark during carpal tunnel release.
Dunn	Dunnett's	A multiple comparison statistical procedure.
Endothelin-1	Endothelin-1	The most potent vasoconstrictor agent currently identified; has pathophysiological roles in pulmonary arterial hypertension, heart failure, systemic hypertension, and female malignancies, with emphasis on ovarian cancer.
ET <sub>1-21</sub>	Endothelin <sub>1-21</sub>	The mature form of endothelin; a 21 amino acid vasoconstrictor <i>peptide</i> able to induce cardiac hypertrophy.
Expt	Experiment	--
Ferritin	Ferritin	A protein in the body that binds to iron; most iron stored in the body is bound to ferritin. Found in the liver, spleen, skeletal muscles, and bone marrow. Only a small amount is found in blood. Amount in blood indicates how much iron is stored in your body.

f-u	Follow-up	Follow-up time period.
GAP43	Growth associated protein 43	High levels in neuronal growth cones during axonal regeneration; a crucial component of an effective regenerative response in the nervous system.
Glucose	Glucose	The most important simple sugar in human metabolism.
Glutamate	Glutamate	An excitatory neurotransmitter, and a key metabolite in cellular metabolism.
GM-CSF	Granulocyte macrophage-colony stimulating factor	A growth and differentiation factor for cells in the granulocyte, macrophage and eosinophil lineage.
HAWS	Hand-arm vibration syndrome	Medical term for symptoms in <i>hand</i> , <i>arm</i> , and fingers caused by <i>vibration exposure</i> .
HDL	High-density lipoprotein	A plasma lipoprotein that helps to remove cholesterol from extracellular fluids, including the blood stream.
Hg	Mercury	A neurotoxic compound found in dental amalgam, an intermetallic compound that contains approximately 50% elemental metallic mercury.
ICTP	Cross-linked carboxyterminal telopeptide of type I collagen	Collagen degradation marker indicative of increased pathological degradation of type I collagen, often in association with arthritis.

IFN-gamma	Interferon gamma	An anti-fibrogenic cytokine that also increases lysosomal activity of macrophages.
IL	Interleukins	A group of proteins that are made primarily in immune system cells. Each subtype has a specific function.
IL-1RA	Interleukin 1 receptor antagonist	A member of the IL-1 cytokine family; expressed by monocytes, neutrophils, macrophages, epithelial cells and fibroblasts; inhibits activity of both IL-1 $\alpha$ and IL-1 $\beta$ .
IL-1 $\alpha$	Interleukin-1 alpha	A pro-inflammatory cytokine because it stimulates the activity of genes involved in inflammation and immunity. Produced mainly by activated macrophages, neutrophils, epithelial cells, and endothelial cells. Listed as IL-1 typically in older studies that did not differentiate between IL-1 subtypes.
IL-1 $\beta$	Interleukin-1 beta/catabolin	A pro-inflammatory cytokine expressed by many cells including macrophage, monocytes, and neutrophils; induces PGE2 production and release of collagenases (e.g. MMPs); causes increased pain sensitivity, vasodilation and hypotension.
IL-2	Interleukin 2	A cytokine that regulates the activities of white blood cells (lymphocytes) responsible for immunity.
IL-4	Interleukin 4	A pleiotrophic cytokine; an immune-response protein derived from T lymphocytes that is a growth factor for activated B cells, resting T cells, and mast cells.

IL-5	Interleukin 5	A cytokine derived from T lymphocytes that causes activation of B lymphocytes and differentiation and activation and enhanced survival of eosinophils.
IL-6	Interleukin 6	A pleiotropic cytokine that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine secreted by T cells and macrophages.
IL-8	Interleukin 8/CXCL8	A chemotactic factor that attracts neutrophils, basophils, and T-cells, but not monocytes; released in response to an inflammatory stimulus.
IL-10	Interleukin 10; originally known as the cytokine synthesis inhibiting factor (CSIF)	A potent anti-inflammatory cytokine that functions as an important immunoregulator protein, suppressing the production of pro-inflammatory cytokines by macrophages, for example.
IL-18	Interleukin 18	Also known as interferon-gamma inducing factor; belongs to the IL-1 superfamily and is produced by macrophages and other cells.
IL-33	Interleukin 33	A pro-inflammatory cytokine structurally related to IL-1. Binding of IL-33 to the soluble receptor IL1RL-1 (IL1 receptor-like-1;ST2) induces expression of IL-4, IL-5, IL-13 by helper T cells, mast cells, eosinophils and basophils.
Iron	Iron	Levels in blood indicates amount of iron in body. Higher-than-normal iron levels in blood may indicate liver inflammation, too much iron in the body (hematochromatosis), etc. Lower-than-

		normal iron levels in blood may indicate heavy menstrual bleeding, not enough dietary iron, etc.
K+	Potassium	Concurrent accumulation of K+ <i>in muscle interstitium</i> may be one cause of fatigue during intense exercise.
Kallidin	Kallidin	A decapeptide vasodilator consisting of bradykinin with a lysyl group attached to the amino terminus. Kallidin, along with bradykinin, is a kinin produced by the kallikrein-mediated enzymatic cleavage of kininogen.
L	Large	--
Lactate	Lactate	A product of metabolism that builds up in muscles and blood during vigorous exercise. Lactic acidosis due to exercise leads to temporary muscle ache and fatigue.
LDH	lactate dehydrogenase	An enzyme; a general indicator of tissue and cellular damage when present in the blood stream.
LDL	Low density lipoprotein	A plasma lipoprotein that poses a cardiovascular risk; the main source of cholesterol buildup and blockage in the arteries.
Leptin	Leptin	A metabolic hormone produced mainly by adipocytes; has a wide range of functions, e.g. decreasing appetite, regulating body fat, stimulating and maintaining energy expenditure; increased levels are a reliable marker for obesity and insulin resistance. May act as a pro-inflammatory agent.

M	Medium	--
MSC	Mesenchymal stem cells/marrow stromal cells.	Multipotent stem cells that can differentiate into a variety of cell types, including adipocytes, cartilage, bone, tendons, muscle, and skin; adult stem cells can be isolated from bone marrow, peripheral blood, and fallopian tubes.
MD	Muscle dialysate	Extracellular fluid samples from muscle as obtained through muscle microdialysis.
MDA	Malodialdehyde	A stable end product of free radicals induced by lipid peroxidation; a marker of free radical induced damage to tissues; a marker in reperfusion of cell distress and damage that may be used to assess the severity of the disease process; consequences of elevated MDA includes leakiness of cell membranes, inactivation of membrane bound enzymes, and involvement of oxidized LDL leading to atherosclerosis.
MDy	Muscle microdialysis	A minimally-invasive sampling technique used for continuous measurement of free, unbound analyte concentrations in the extracellular fluid of virtually any tissue.
MMP	Matrix metalloproteinase	MMPs are proteases involved in breakdown of extracellular matrix in normal physiological processes, including tissue remodeling; play central roles in cell proliferation, migration, differentiation, angiogenesis, apoptosis and host defenses. These enzymes are detectable after injury or inflammatory

		stimulation. MMP1 = an interstitial and fibroblast collagenase. MMP-2= a type IV collagenase (gelatinase A).
MRI	Magnetic Resonance Imaging	Uses a magnetic field and pulses of radio waves to make pictures of organs and structures inside the body.
Noradrenaline	Also called norepinephrine or 4,5- $\beta$ -tihydroxy phenethylamine	A neurotransmitter and a catecholamine-type hormone that is manufactured as a drug and produced naturally in the human body.
NO	Nitric oxide	A free radial; also known as “endothelium-derived relaxing factor”; an important cellular signaling molecule functioning in vasodilation and neurotransmission.
NO <sub>2</sub> <sup>-</sup>	Nitrate	A stable end product of NO oxidation.
NPN	Nonprotein nitrogen plasma	End products of all nitrogen constituents of blood except protein, includes: urea, amino acids, uric acid, creatine and creatinine. Traditionally used to monitor renal function; increases with renal impairment.
NS	Not significant	A statistical term.
OR	odds ratio	A statistical term.
P-MRS	Phosphorus magnetic resonance spectroscopy	A method that monitors muscle energy metabolism by recording the ratio of phosphocreatine (PCr) to inorganic phosphate (Pi).



P75	Nerve growth factor receptor P75	Promotes growth cone and neurite formation, elongation, and arborization in regenerating nerve axons.
PCr	Phosphocreatine	A phosphorylated creatine molecule that, in its chemical partnership with adenosine triphosphate, serves as a rapidly mobilizable reserve of high-energy phosphates in skeletal muscle.
PEA	N-palmitoylethanolamine	A member of N-acylethanolamines family; binds to a receptor in the cell-nucleus and mediates several biological functions related to chronic pain and inflammation.
PGE2	Prostaglandin E2	Generated from arachidonic acid by cyclo-oxygenases and prostaglandin E synthase; affects both macrophage and T cell activation and inhibits CCL3 (MIP-1 $\alpha$ ) and CCL4 (MIP-1 $\beta$ ), thus, exerting a general anti-inflammatory effect; believed to cause vasodilation, edema, and enhancement of cytokines that induce synoviocyte proliferation; also shown to sensitize nociceptors.
PGP9.5	Protein gene product 9.5	A pan (general) neuronal marker.
Pi	Inorganic phosphate/ orthophosphate	A byproduct of adenosine 5'-triphosphate (ATP) hydrolysis; released during muscle contraction crossbridge cycle; Pi accumulation during exercise leads to a reversal of its release step, causing a decrement in force production capability (and therefore fatigue).

PINP	Procollagen I intact N-terminal propeptide	An indicator of type I collagen metabolism; a sensitive marker of bone formation, although collagen type I propeptides may also arise from skin, vessels, fibrocartilage and tendons.
PMN	Polymorphonuclear cells	Also known as <i>polymorphonuclear leukocytes</i> (PMLs); white blood cells containing a segmented lobular nucleus, including eosinophils, basophils, and neutrophils.
PNF	Perinodular fat	Subcutaneous fat surrounding the nodular fibromatosis observed with Dupuytren's Disease.
PPP	Platelet poor plasma	Blood plasma with very low number of platelets ( $< 10 \times 10^3/\mu\text{L}$ ).
PRP	Platelet rich plasma	Blood plasma that has been enriched with platelets and, thereby, the concentration of growth factors — can be 5 to 10 times greater (or richer).
Pyruvate	Pyruvate	A muscle metabolism protein; the end produce of glycolysis; also produced by the liver.
Resistin	Resistin	An adipocytokine considered to have an important role in energy metabolism; secreted from adipocytes and macrophages; antagonizes insulin effect and causes insulin resistance especially in obese patients; also plays a role in inflammation; a potential biomarker of cardiovascular disease.

Rheumatoid factor	Rheumatoid factor	An antibody in the blood present in many people with rheumatoid arthritis.
S	Small	--
SD	Standard deviation	--
Se	Selenium	An essential mineral found in small amounts in the body; works as an antioxidant, especially when combined with vitamin E; plays roles in thyroid and immune functions.
SEA	Stearoylethanolamide	Part of the family of N-acylethanolamines; increased in inflammatory and neuropathic conditions.
sICAM-1	Soluble intercellular adhesion molecule-1	A soluble and circulating form of ICAM-1 present on endothelial cells; helps facilitate leukocyte adhesion and migration across endothelium; a biomarker of inflammatory processes involving activation or damage to platelets and endothelial cells.
Sig.	Significant	A statistical term.
sIL-1RII	Soluble interleukin-1 receptor II; also known as IL-R2	This protein binds interleukin alpha, interleukin beta, and interleukin 1 receptor, type I. Acts as a decoy receptor that inhibits the activity of its ligands.
SNP	Shoulder-neck pain	--

SON	Skin overlying nodule	Skin overlying the nodular fibromatosis observed with Dupuytren's Disease.
SOS	Symptom Onset until Surgery	--
sST2	Soluble form of suppression of tumorigenicity 2	Interleukin-1-like receptor 1 (IL-1RL1) commonly known as sST2 or soluble IL-33 receptor; may act as a decoy receptor by binding IL-33 (an inflammatory cytokine), thereby inhibiting signaling by ST2; can serve as an anti-inflammatory mediator.
TC	Total cholesterol	Lipid substance; an unsaturated alcohol of the steroid family; a measure of total amount of fats in the blood, including including LDL, HDL, and VLDL cholesterol.
Tenascin-C	Tenascin-C	An extracellular matrix glycoprotein; contains domains homologous to epidermal growth factor, fibronectin and fibrinogen; thought to play a role in organizing growth of the extracellular matrix, e.g. in wound healing; expression correlates with inflammation.
TGF- $\beta$ 1	Transforming growth factor beta 1	A matrix regulatory protein (cytokine) that is an established and potent stimulator of connective tissue formation in skeletal muscle and tendon healing after injury.
TIMP	Tissue inhibitor of matrix metalloproteinase	Specific inhibitors of matrixins that participate in controlling the local activities of MMPs in tissues. Individual TIMPS (e.g., 1 or

		2) target specific MMPs (e.g., MMP1 and MMP2, respectively).
Transferrin Saturation	Transferrin Saturation, TSAT	A medical laboratory value of the ratio of serum iron and total iron-binding capacity, multiplied by 100. Indicative of iron-binding capacity. Transferrin saturations of less than 20% indicate iron deficiency, while transferrin saturations of more than 50% suggest iron overload.
TNF- $\alpha$	Tumor necrosis factor alpha	A key pro-inflammatory cytokine.
Triglycerides	Triglycerides	A plasma lipoprotein; can raise the risk of heart disease; increased triglyceride plasma concentration reflects a shift of metabolism towards lipolysis.
TSST	Trier Social Stress Test	A laboratory procedure used to reliably induce psychological stress in human research participants.
UBMA	Upper-Body Musculoskeletal Assessment	A clinical assessment tool developed to quantify MSD severity irrespective of specific diagnosis.
VAS	Visual Analogue Scale	A validated 10-point pain scale.
VEGF	Vascular endothelial growth factor	A chemical signal produced by cells that stimulates proliferation, migration, and proteolytic activity of endothelial cells (i.e., angiogenesis); enhances MMP production.

VIP	Variable Influence on Projection	A statistical term.
Visfatin	Visfatin	An adipocytokine produced predominantly by human visceral adipose tissue; plasma levels are related to adiposity; exerts insulin-mimetic actions through insulin receptors.
VLDL	Very-low-density lipoprotein	A plasma lipoprotein; molecules made up of mostly triglycerides, cholesterol and proteins; also known as the "very bad" cholesterol; serves as a precursor to LDLs.