Work-Related Musculoskeletal Disorders of the Hand and Wrist: Epidemiology, Pathophysiology, and Sensorimotor Changes

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The purpose of this commentary is to present recent epidemiological findings regarding work-related musculoskeletal disorders (WMSDs) of the hand and wrist, and to summarize experimental evidence of underlying tissue pathophysiology and sensorimotor changes in WMSDs. Sixty-five percent of the 333 800 newly reported cases of occupational illness in 2001 were attributed to repeated trauma. WMSDs of the hand and wrist are associated with the longest absences from work and are, therefore, associated with greater lost productivity and wages than those of other anatomical regions. Selected epidemiological studies of hand/wrist WMSDs published since 1998 are reviewed and summarized. Results from selected animal studies concerning underlying tissue pathophysiology in response to repetitive movement or tissue loading are reviewed and summarized. To the extent possible, corroborating evidence in human studies for various tissue pathomechanisms suggested in animal models is presented. Repetitive, hand-intensive movements, alone or in combination with other physical, nonphysical, and nonoccupational risk factors, contribute to the development of hand/wrist WMSDs. Possible pathophysiological mechanisms of tissue injury include inflammation followed by repair and/or fibrotic scarring, peripheral nerve injury, and central nervous system reorganization. Clinicians should consider all of these pathomechanisms when examining and treating patients with hand/wrist WMSDs. *J Orthop Sports Phys Ther 2004;34:610-627.*

Key Words: *carpal tunnel syndrome, hand/wrist tendinitis, inflammation, neuroplasticity, repetitive-motion injury*

The US Department of Labor[20] defines work-related musculoskeletal disorders (WMSDs) as injuries or disorders of the muscles, nerves, tendons, joints, cartilage, and spinal discs associated with exposure to risk factors in the workplace. WMSDs do not include disorders caused by slips, trips, falls, motor vehicle accidents, or similar accidents.[20] Sixty-five percent of the 333 800 newly reported cases of occupational illness in 2001 were attributed to repeated trauma.[21] WMSDs account for approximately one third of all lost workday illnesses.[20] WMSDs of the hand and wrist are associated with the longest absences from work[20] and are, therefore, associated with greater lost productivity and wages than those of other anatomical regions.

Epidemiological research associates the onset and severity of hand and wrist WMSDs with the performance of repetitive and forceful hand-intensive tasks.[17,81,116] These disorders are worsened by the performance of such tasks in the presence of awkward or extreme wrist and forearm postures, cold temperatures, and vibration.[17,81] Workplace psychosocial factors as well as nonwork exposures also contribute to these disorders.[81] Dose-response relationships between work task demands and upper extremity (UE) WMSDs are not clearly defined. For this reason, attempts to regulate workplace exposures are surrounded by controversy. Lack of clarity concerning the underlying pathophysiological mechanisms of WMSDs results in rehabilitation programs that are not focused, which makes their efficacy difficult to evaluate.

Physical therapists are among those health care providers who not only treat WMSDs, but also advise patients and their employers on safe work practices. It is imperative that such recommendations be based on the best evidence available concerning work-

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place and nonworkplace risk factors, as well as tissue effects and the behavioral indicators of underlying pathophysiology. The purpose of this commentary is to present recent epidemiological findings regarding WMSDs of the hand and wrist and to summarize experimental evidence of underlying tissue pathophysiology and sensorimotor changes in WMSDs.

EPIDEMIOLOGY OF HAND AND WRIST WMSDs

In 2001, service industries reported the highest proportion of WMSDs (25.8% of WMSD cases), followed by manufacturing industries (22.9% of WMSD cases). Data from the US Department of Labor, Bureau of Labor Statistics[20] show that newly reported illnesses due to repeated trauma have represented about 4% of all injuries and illnesses since their peak number in 1993. Among the top 10 industries reporting WMSDs,[20] half (ie, assemblers, construction laborers, supervisors in sales, carpenters, and cashiers) are prone to develop UE WMSDs through the use of hand tools or the performance of hand-intensive tasks. Illnesses due to repetitive motion resulted in the longest absences from work in 2001—a median of 18 days.[20] Carpal tunnel syndrome (CTS), caused by compression of the median nerve in the carpal tunnel with subsequent loss of sensorimotor function along the median nerve distribution, was associated with the highest median days away from work (25 days), and injuries to the wrist in general resulted in a median of 13 days away from work.[20]

Of the 355 344 cases of injury or illness of the UE in 2001, 33 431 were sprains or strains of the hand, wrist, or fingers.[20] There were 26 794 cases of CTS, the most frequently reported occupational neuritis. Tendinitis cases of the hand and wrist (eg, DeQuervain's tenosynovitis) or fingers (eg, trigger finger) numbered 4 896 in 2001.[20] WMSDs of the hand and wrist represent a substantial burden to the US workplace.

Two comprehensive reviews of the literature concerning WMSDs have been completed since 1997 with the purpose of determining causality and identifying gaps in epidemiological, experimental, and clinical research. A review undertaken by the National Institute for Occupational Safety and Health included over 600 epidemiological studies concerning WMSDs of the neck, UE, and low back dating from the 1970s to the mid-1990s.[17] The summary of this review states that there was strong evidence for a relationship between exposure to combinations of force and repetition, or force and posture, and development of CTS. This review also provides evidence for a relationship between exposure to combinations of force and repetition, and development of hand/wrist tendinitis. There was evidence for a relationship between cumulative exposure to force, repetition or hand/wrist vibration, and CTS; and to force, repetition, or awkward postures, and hand/wrist tendinitis. There was insufficient evidence to determine the role of awkward postures in the development of CTS.

Amid concerns that the National Institute for Occupational Safety and Health (NIOSH) review may have been biased in light of efforts at the time to regulate WMSDs through an Occupational Safety and Health Administration (OSHA) work rule, NIOSH charged the National Research Council (NRC) and the Institute of Medicine to conduct a second, more comprehensive review of the literature. The NRC review includes studies from the late 1970s to the late 1990s that examined tissue pathophysiology, mechanical, organizational, and psychosocial risk factors, and clinical interventions for WMSDs of the UE and low back.[81] The overall conclusions from the NRC review were essentially the same as those of the NIOSH review: evidence supports associations between workplace physical and psychosocial exposures and UE WMSDs. Detailed summaries of the studies reviewed by NIOSH and the NRC will not be repeated here. The interested reader is encouraged to consult these documents and their extensive bibliographies.

Both the NIOSH and NRC reviews identified gaps in the literature with the hope of guiding future research. In recent years, investigators have begun to address some of these issues. For this commentary, only epidemiological studies concerning CTS or hand/wrist disorders published since 1998 were selected to illustrate this progress, and they are summarized in Tables 1 and 2. Despite some variation and even disagreement among these studies, a causal relationship is apparent between prolonged exposure to repetitive and forceful hand-intensive tasks, highly repetitive hand-intensive tasks, vibration, psychosocial stress at work, and the development of CTS or other hand/wrist WMSDs.[1,40,53,66,85,97,100,109] In addition, concurrent, comorbid medical conditions or past wrist trauma increase CTS risk.[9,53,66] The additional risk factors of awkward or sustained UE postures also contribute to hand/wrist tendinitis, strains, and sprains,[92,97] which are the most common UE WMSDs.[20,49] UE WMSDs have a higher prevalence and incidence in women, especially those who work in the service industries and who have psychosocial stress at work.[40,62,66] Age alone does not appear to account for increased incidence of hand and wrist disorders in the absence of other risk factors, but aging can increase risk of WMSDs.[40,53] While a substantial proportion of all WMSDs occur in the manufacturing industries nationally, they may be related to predominant nonmanufacturing industries locally, including manual labor, service industries, and office work.[40,85,100] Computer users who are exposed to heavy use (more than 20 h/wk) of the

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TABLE 1. Summary of recent epidemiolgical studies of work-related carpal tunnel syndrome.

Authors and Country	Sample	Study Design	Conclusions	Comments
Abbas et al, 1998[1] USA (11) Other (6)	17 peer-reviewed studies of work-related CTS published from 1980 to 1995	Meta-analysis using "best-subset" and "forward-method" regression analyses	Force and repetition were significant risk factors for CTS; other risk factors could not be evaluated due to infrequent use among the published studies	As in NIOSH and NRC reviews, this meta-analysis points out the need for longitudinal or case-control study designs
Atcheson et al, 1998[9] USA	297 patients with UE WMSD, 114 with CTS	Cross-sectional design using multivariate logistical regression analysis	Patients with CTS have a high prevalence of concurrent medical conditions that can cause CTS irrespective of work	Several of the medical conditions included may also be work-related (ie, inflammatory and degenerative conditions); study illustrates importance of considering whole worker in determining WMSD causality
Frost et al, 1998[53] Denmark	743 slaughterhouse workers exposed to high-force high-velocity tasks and 398 repairmen or chemical workers as controls	Retrospective cohort design comparing relative risk for CTS for each exposure group	Forceful and repetitive manual tasks increase risk for CTS in both dominant and nondominant hands; risk is increased with cumulative years on the job	Use of control group and control for nonoccupational risk factors, including concurrent medical conditions, strengthens this study; findings of bilateral effects may be explained by assistance with the nondominant hand during task performance
Nathan et al, 1998[80] USA	283 (558 hands) industrial workers	Prospective, 11-year study of CTS using calculations of prevalence; hands that underwent carpal tunnel release were excluded from analysis	Decreases in NCV occur naturally with aging and do not necessarily lead to symptoms of CTS	No description of occupations or exposure levels provided; although exclusions of hands that underwent surgery for CTS and of diagnostic outliers were discussed as having no effect on results, their occurrence in the population would seem of interest in assessing the impact of workplace factors on CTS
Padua et al, 1999[85] Italy	461 patients with idiopathic CTS from 3 different geographical regions	Cross-sectional correlational comparison of patients with CTS	Hand stress may contribute to CTS	Correlational analyses limited in determining causality; many confounding variables not controlled; subjective reports of hand stress vulnerable to bias
Davis et al, 2001[40] USA	4836 cases of work-related CTS from state worker's compensation database	Retrospective survey of cases from 1992 to 1997	Manufacturing industries have the highest rates of CTS; high-rate industries may be determined regionally and differ from national trends; exposure to high-force high-repetition or vibration contributes to CTS; high rate among office occupations suggests that computer operation may be a risk factor; gender-related differences are measurable	Highlights underreporting of work-related CTS in national (BLS) surveys; addresses the assertion that CTS in the workforce is a natural consequence of aging by controlling for age
Leclerc et al, 2001[66] France (wrist tendinitis results summarized in Table 2)	598 workers in assembly, clothing, and shoe industries, food (meat) industries, packaging, and supermarket cashiering	Prospective, 3-year study of the incidence of CTS using backward stepwise regression analysis	Gender differences may be due to nature of occupational tasks and/or baseline prevalence of CTS (twice as high in women); force and psychosocial factors contribute to CTS	Controlled for nonphysical and some nonoccupational risk factors (ie, smoking, age, gender); subject selection bias by industry type may have led to inclusion of more affected workers

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TABLE 1 (continued)

Authors and Country	Sample	Study Design	Conclusions	Comments
Stevens et al, 2001[106] USA	257 employees who use computers	Cross-sectional determination of frequency of CTS	Frequency of CTS among computer users is no different from general population	Major methodological flaws in this study include lack of any statistical analysis, failure to examine the self-reported non-CTS cases for median nerve NCV, failure to recognize potentially confounding worker characteristics evident in the report (ie, CTS workers reporting more frequent mouse use and non-CTS workers reporting more hours of conventional typewriter use)
Thomsen et al, 2002[109] Denmark	731 bank and postal workers	Prospective, 18-month study of CTS prevalence and incidence using multiple logistic regression analysis	Highly repetitive work with low force associated with CTS; CTS incidence was too low to determine effect of exposure differences	Strength of the study includes careful measures of task exposure; although the low CTS incidence did not permit analysis of exposure effects, the method may be used in future, larger studies
Andersen et al, 2003[4] Denmark	6943 technical trade union members who use computer workstations employed at 3500 different companies	Prospective, 1-year study of the prevalence and incidence of CTS using logistic regression analysis	Computer use does not pose a severe occupational hazard for developing symptoms of CTS	The size and diversity of the sample is a strength of this study; short follow-up time may have missed new CTS cases; measures of exposure by self-report may have introduced error; increased risk with increased hours of mouse use in a 1-year period would suggest that intensive mouse use could be a severe occupational hazard for developing CTS over time, given widespread use of graphical user interfaces

Abbreviations: BLS, Bureau of Labor Statistics; CTS, carpal tunnel syndrome; NIOSH, National Institute for Occupational Safety and Health; NCV, nerve conduction velocity; NRC, National Research Council; UE, upper extremity; WMSD, work-related musculoskeletal disorder.

TABLE 2. Summary of recent epidemiological studies of upper extremity WMSDs.

Authors and Country	Sample	Study Design	Conclusions	Comments
Feuerstein et al, 1998[49] USA	8147 federal worker's compensation claims for UE WMSD with 1994 federal work force for controls	Cross-sectional study of prevalence of UE WMSD in 1994 and economic costs (not summarized in this review)	CTS and hand/wrist tendinitis most prevalent hand/wrist diagnoses; 40% of affected workers had multiple diagnoses or made multiple claims	As the authors point out, nonspecific diagnoses associated with longer duration of symptoms and work disability than clearly diagnosed disorders and may not be taken seriously by health care providers; multiple diagnoses are commonplace
Silverstein et al, 1998[100] USA	State worker's compensation claims for 100 449 hand/wrist disorders, 30 468 elbow disorders and 55 315 shoulder disorders (elbow and shoulder not summarized in this review)	Retrospective, 9-year study of claim incidence rates and costs (not summarized in this review) stratified by occupation	Industries characterized by manual handling and repetitive work have high incidence rates of hand/wrist disorders	This study illustrates the importance of considering regional industries when estimating risk and approaching interventions (also see Davis et al in Table 1)

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TABLE 2 (continued)

Authors and Country	Sample	Study Design	Conclusions	Comments
Scheuerle et al, 2000[97] USA	145 sign language interpreters	Cross-sectional survey of self-report of pain/discomfort using simple correlation analysis	Sign language interpreters susceptible to hand/wrist WMSDs, including CTS	Statistical analysis would be strengthened with logistic regression model rather than simple linear correlations; study makes good use of self-report symptom surveys including hand and body diagrams
Islam et al, 2001[62] USA	56 409 compensable work-related injuries/illnesses with 632 282 state workers as controls	Retrospective, 1-year study comparing incidence rates for males and females	Females have greater risk of overexertion illnesses; Further research needs to identify specific work tasks associated with jobs performed by men and women	Findings are supportive of several other studies regarding susceptibility of women to work-related neuritis and other hand/wrist disorders and of those in the service industries
Leclerc et al, 2001[66] France (CTS results summarized in Table 1)	598 workers exposed to repetitive work in assembly, clothing and shoe industries, food (meat) industries, packaging, and supermarket cashiering	Prospective, 3-year study of lateral epicondylitis and wrist tendinitis using backward stepwise regression analysis	Combinations of risk factors, including biomechanical, psychosocial, and individual characteristics contribute to WMSD risk; workers with 3 or more UE disorders had higher incidence of lateral epicondylitis	Study supports repetitive, forceful hand use as contributing to WMSD; enthesopathies are associated with multiple diagnoses; illustrates the importance of considering workplace psychosocial and individual factors in determining risk
Gerr et al, 2002[57] USA	632 newly hired employees with >15 h/wk of computer use	Prospective, 3-year study of UE WMSD and musculoskeletal symptoms using regression and survival analysis	Hand/arm WMSD common among computer users, more than 50% reported symptoms within 1 year of starting a new job; 64% to 73% reporting symptoms had confirmed WMSD diagnosis	Control for confounding variables (eg, concurrent medical conditions) was carried out and strengthens study; results indicate that confirmed CTS develops more slowly than CTS symptoms or other WMSDs, such as tendinitis; combines self-report of symptoms with confirmation by physical examination, thereby reducing bias
Hagberg et al, 2002[59] Sweden	1283 computer users at 46 work sites	Cross-sectional survey of prevalence of WMSD symptoms and loss of productivity	UE WMSD prevalent among computer users with impact on productivity; prevention may reduce this impact	Main focus of study was decreases in productivity associated with WMSD symptoms; use of structured interviews reduced subject reporting bias; study supports others showing higher prevalence in women
Russo et al, 2002[92] Canada	211 sonographers with professional society membership	Cross-sectional survey of prevalence of WMSD symptoms	Findings suggest association between awkward, static postures and forceful hand-intensive activity and WMSD symptoms	92% response rate ensures representative sample; division of respondents into high and low level of pain and discomfort groups permitted analysis of exposure effects; use of nonpatients a strength of this study

Abbreviations: UE, upper extremity; WMSD, work-related musculoskeletal disorders; CTS, carpal tunnel syndrome.

mouse are at increased risk for CTS[4] and other UE WMSDs,[57] and increasing hours of computer work or beginning a new job with high computer use demands are associated with increased risk of WMSDs.[4,57,59]

While epidemiological studies enable identification of risk factors, high-risk occupations, and even, to some extent, dose-response relationships between risk factors and the prevalence and incidence of WMSDs, they can tell us nothing about the underlying pathophysiological mechanisms leading to these disorders. Furthermore, it is impractical as well as unethical to sample tissues from workers suffering from WMSDs or healthy control subjects. Therefore, studies of tissue pathophysiology must be carried out in animal models. In the next section of this review, we will summarize findings in animal models and, to the extent available, human studies that investigate the 1mechanisms of tissue injury, degeneration, and repair and associated behavioral effects in WMSDs.

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PATHOPHYSIOLOGY OF WMSDs

Evidence of Musculoskeletal Injury and Inflammation in WMSDs

Animal models of repetition-induced tendinopathies show paratendon inflammation and cellular proliferation, increased production of matrix components, tendon degeneration, and functional losses (Table 3). Human studies examining tendon and sheath biopsies collected from patients with chronic tendinopathies or CTS (Table 4) find marked tendon and sheath degeneration and fibrosis in combination with inflammatory or proliferative changes.[8,29,47,51,88] In animal models, marked tendon injury is dependent on force, frequency, and duration of repetitive exposure (Table 3). Tendon necrosis and matrix disorganization are found only in studies utilizing intensive repetitive kicking or intensive running combined with tendon compression.[10,31,101,102] Inflamma-

TABLE 3. Animal models of WMSDs, chronic repetition, and loading in which tendons were examined.

Authors	Model	Findings for Each Study Categorized Based on Tissue and Functional Changes
Backman et al, 1990[10]	• Rabbit model of Achilles tendinosis • Controlled Kicking: 150 rep/min, 2 h/session, 3 d/wk for 5-6 wk	• Tendon necrosis, tendon matrix reorganization*,‖ • ↑ vascularity, ↑ inflammatory cells and edema in paratendon† • Paratendon fibrosis§
Archambault et al, 1997[7]	• Rabbit model of Achilles tendinosis • Controlled kicking: 20 and 75 rep/min, 1-2 h/d, 3 d/wk for 6-8 wk	• Hypercellularity and ↑ inflammatory cells in tendons; ↑ TNF, IL-1† • ↑ mRNA of matrix components (eg, ↑ collagen)§
Archambault et al, 2001[6]	• Rabbit model of Achilles tendinosis • Controlled kicking: 75 rep/min, loading of 1.2 Hz, 20 N; 2 h/d, 3 d/wk for 11 wk	• No evidence of injury/degeneration* • ↑ mRNA expression of collagen type III and MMPs†
Messner et al, 1999[77]	• Rat model • Eccentric loading of Achilles tendon: 30 cycles/min, 1 h/d, 3 d/wk for 7-11 wk	• Fibrillation of epitendon* • ↑ vascularity of epitendon; ↑ SP and CGRP in epitendon and paratendon† • Limping gait¶
Carpenter et al, 1998[31] Soslowsky et al, 2000[102], 2002[103]	• Rat model • Treadmill running loading of supraspinatus tendon with or without external compression via Achilles tendon allograft: 17 m/min on a decline; 1 h/d, 5 d/wk, up to 16 wk	• Hypercellularity, ↑ tendon cross-sectional area† • Collagen disorganization, rounded tenocytes‡,§ • ↓ maximum biomechanical stress¶ • Tissue changes ↑ with exposure (compression or time)
Barr et al, 2000[15] Barbe et al, 2003[12] Barr and Barbe, 2004[14]	• Rat model • HRLF reaching and grasping task: 1 reach/15 sec, 45 mg of force; 2h/d, 3 d/wk for 8-12 wk	• Forearm flexor tendon microfray* • Hypercellularity (widespread ↑ in macrophages in tendons and associated CT in weeks 3-6); ↑ COX2, IL-1β in tendon and sheath; ↑ serum IL-1α† • ↓ macrophages and paratendon fibrosis in weeks 8-12§ • See Table 5¶
Topp and Byl, 1999[111]	• Primate model • Repetitive, forceful hand squeezing in owl monkeys: 15 squeezes/min, 300 trials/d, for 2-5 mo	• Tendon hypercellularity and disorganized collagen in digital flexor tendons of 1 of 3 monkeys attributed to anatomical anomaly • No signs of active inflammation in hand tendons • See Table 4‖

Abbreviations: WMSDs, work-related musculoskeletal disorders; rep, repetitions; TNF, tumor necrosis factor; IL-1, Interleukin-1; MMP, matrix metalloproteinases; SP, substance P; CGRP, calcitonin gene-related peptide; HRLF, high repetition low force; CT, loose areolar and synovial connective tissue; COX2, cyclooxygenase 2.
* Injury/degenerative changes.
† Inflammatory/proliferative changes.
‡ Adaptive tissue changes/tissue reorganization.
§ Repair with or without regeneration or scarring (fibrosis).
‖ Pathological remodeling.
¶ Functional changes (eg, behavioral or biomechanical).

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TABLE 4. Selection of human studies of WMSDs and chronic loading in which tissue changes were examined.

Authors	Model	Findings for Each Study Categorized Based on Tissue and Functional Changes
Alfredson et al, 2000[3] 2001[2]	ECRB tendon microdialysis and biopsies in 13 pts with lateral epicondylitis >6 mo or chronic Achilles tendinosis	• PGE_2 not upregulated in tendon • ↑ glutamate (mediates pain); ↑ NMDAR1 (a glutamate receptor)
Astrom et al, 1996[8]	Achilles tendon biopsies from 27 pts undergoing surgery for chronic Achilles tendonitis	• Slight inflammation, bursitis or fibrosis in 5 pts[†,§] • Fiber disorganization and clusters of tenocytes with rounded nuclei[‡,‖]
Fenwick et al, 2001[47]	Achilles tendon biopsies from 7 pts with chronic Achilles tendinopathy	• Hypercellular, hypervascular; ↑ TGF-β/TGF-βR[‖,†] • Disorganized tendon matrix[‖] • ↑ glycosaminoglycan[§]
Campligio et al, 1999[29]	Flexor tendosynovial biopsies from 50 pts with idiopathic carpal tunnel syndrome (CTS)	• Disorganization and degeneration of collagen fibers[*,‖] • ↑ vascularity & arteriosclerosis[†,‖] • Diffuse fibrosis of tendon sheath[§]
Freeland et al, 2002[52]	Flexor tendosynovial biopsies and serum examined in 41 pts with CTS	• ↑ malondialdehyde in serum and flexor tenosynovium* • ↑ PGE_2 and ↑ IL-6 in flexor tenosynovium[†,§]
Phalen, 1972[88]	Flexor synovial biopsies of 152 wrists of pts treated surgically for CTS	• 40 pts with nonspecific inflammation[†] • 83 pts with fibrosis[§]
Ljung et al, 1999a[67], 1999b[68]	ECRB muscle biopsies from 26 pts with lateral epicondylitis >7 mo	• Abnormal muscle NADH staining; muscle necrosis[*,‖] • No evidence of muscle inflammation • ↑ type 2A fibers and muscle fiber regeneration[‡]
Dennett and Fry, 1988[42]	First dorsal interosseous biopsies from 29 pts with painful chronic overuse syndrome	• ↑ inflammatory cells[†] • ↑ type 1 fibers; ↓ number and hypertrophy of type 2 fibers; mitochondrial changes[‡]
Fredericson et al, 1995[51]	MRI of bone in runners with tibial stress reaction or fracture	• Frank cortical stress fracture[*,‖] • Periosteal edema, progressive marrow involvement[†] • Correlation of pain with degree of bone involvement
Tinazzi et al, 1998[110]	Spinal, brainstem and cortical SEP recorded following ulnar nerve stimulation in 12 pts with CTS	• ↑ amplitude of ulnar SEP at level of spinal cord, brainstem, and cortex[#]
Druschky et al, 2000[43]	Cortex of 1 patient with unilateral CTS examined using magnetic source imaging	• ↓ cortical representation of injured median nerve and invasion of depressed areas by ulnar and radial representation[#]
Byl et al, 2000[24], 2002[27]	Cortices of 18 pts, 7 with focal hand dystonia, examined using noninvasive magnetic source imaging or magneto-encephalography	• Disorganized SEF in SI cortex; degradation of digit representation; ↓ volume of hand representative in cortex[#] • Focal hand dystonia[¶]
Butterworth et al, 2003[22]	Cortices of 9 pts with focal hand dystonia examined using MRI	• Degradation of digit representation in widespread sensory cortices[#] • Focal hand dystonia[¶]

Abbreviations: WMSDs, work-related musculoskeletal disorders; ECRB, extensor carpi radialis brevis; pts, patients; PGE_2, prostaglandin E_2; NMDAR1, N-methyl D-aspartate receptor; TGF-β, transforming growth factor-β; CTS, carpal tunnel syndrome; IL-6, interleukin-6; NADH, nicotine-adenine-dinucleotide reductase; SEP/F, somatosensory evoked potential/field response; MRI, magnetic resonance imaging.
* Injury/degenerative changes.
† Inflammatory/proliferative changes.
‡ Adaptive tissue changes/tissue reorganization.
§ Repair with and without regeneration or scarring (fibrosis).
‖ Pathological remodeling.
¶ Functional changes (eg, behavioral or biomechanical).
# Central nervous system reorganization.

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tory changes are more prevalent than degenerative changes in animal models of tendinopathies and suggest that inflammatory/proliferative changes appear early, before overt signs of tissue injury.[7,10,12,77,102] Discrete signs of injury may precede inflammation in tendons or their sheaths.[12,52] In models of chronic repetitive motion, tendon inflammation eventually subsides and is followed by a fibrotic response that may lead to complete tissue repair if loads or repetition are sufficiently low.[6,7,12,14]

Progressive functional impairments develop with chronic repetitive tasks and accompany signs of tissue injury (Table 3).[31,77,101,102] Neurogenic changes normally associated with pain are found in both human and animal models of tendinosis and may be another cause of behavioral decline.[2,3,77]

Although muscles appear to be more adaptive than tendons, chronic repetition results in inflammatory cell infiltration, myofiber splitting, and fibrotic replacement of injured myofibers in both human and animal models of WMSDs (Tables 4 and 5).[12,42,103-105] Studies by Stauber et al[103,104] indicate that repeated muscle strains at slow strain rates lead to tissue adaptation, but that repeated strains at fast velocities result in a variety of myopathic changes including fibrosis. Increasing the exposure and duration of repeated forced-lengthening leads to significant decreases in muscle mass and myofiber area and further increases in noncontractile tissues.[105]

In our model of UE WMSDs in the rat, we found evidence of injury and inflammation with performance of a high-repetition negligible-force (HRNF) reaching task (Tables 3 and 5).[12,13,15] Increased immunohistochemical expression of hsp 72, an indicator of cellular distress and injury, is elicited in the lumbricals and their connective tissues.[15] Macrophage infiltration is observed not only in the muscles of the entire reach forelimb, but also in those of the nonreach forelimb and the hindlimb. Macrophage infiltrates peak after 5 to 6 weeks of task performance and then decline, despite continued performance of the task,[12] presumably due to the normal course for resolution of the inflammatory response. The bilateral effect may be due to use of the nonreach limb for postural support or to a cytokine-mediated systemic inflammatory response.

Cytokines are proteins involved in mediating the immune response, hematopoiesis, inflammation, and bone resorption. Interleukin-1 (IL-1), for example, is a proinflammatory cytokine produced and secreted by immune cells (eg, infiltrating macrophages and neutrophils), as well as a variety of other cell types, including fibroblasts, myocytes, and synoviocytes, in response to tissue injury. The induction of IL-1 and other cytokines is orchestrated by a variety of paracrine and autocrine mechanisms. A serum increase of a proinflammatory cytokine is indicative of a chronic and/or systemic inflammatory reaction in the body.[12,13] We observed that serum levels of IL-1α increase significantly in rats that have performed the HRNF task for 8 weeks.[12,13] Thus, both a local (macrophage infiltration in the reach limb) and a systemic inflammatory response are occurring in response to continued performance of a high-repetition task. In contrast, serum IL-1α does not change in rats performing a low-repetition negligible-force (LRNF) task.[13] We hypothesize that the net cytokine production in the LRNF group allows for the maintenance of homeostasis through the resolution of an acute inflammatory response. The level of repeated incidents of mechanical injury to the tissues in the HRNF group, on the other hand, leads to a net production of IL-1α and is indicative of a chronic and systemic inflammatory phase.

The injury and inflammatory changes in our model are accompanied by motor behavior degradation.[12,13,33] In HRNF animals, motor performance declines and alternative movement patterns emerge. A maladaptive raking pattern is observed in 100% of HRNF animals 2 weeks after the peak inflammatory response. This pattern is characterized by a lack of digit closure and repeated clumsy attempts to gain control of the food pellet.[12] These results indicate that, although the inflammatory response subsides, motor degradation continues to progress.

The effects of repeated mechanical loading and cyclic strain on bone have been studied in humans and in animal models (Tables 4 and 6). Studies of rats running on treadmills[18,19,50,78] and performing repetitive jumping[114] have shown that increasing the intensity of weight-bearing exercise is associated with diminishing returns in biomechanical competence, mass, and bone morphology of vertebral and limb bones. Periosteal and marrow edema as well as tibial stress fractures have been reported in runners with shin splints.[51] We are only beginning to understand the mechanism(s) of pathophysiological bone responses to repetitive-reaching movements. In our rat model, periosteal bone sites of muscle and interosseous ligament attachments show evidence of pathological woven, or immature, bone formation in HRNF animals.[16] These changes are greater in the distal than in the proximal forelimb bones, greater in the reach than in the nonreach limb, and greater at muscle attachments to bone than at ligament attachment sites or sites without attachments.

Based on the studies reviewed above and summarized in Tables 3 through 6, WMSDs are induced by the performance of highly repetitive tasks with or without forceful exertions. Many tissue types are involved, including tendon, muscle, loose connective tissue, and bone. Early, discrete tissue injury stimulates an acute inflammatory response that may resolve with tissue repair in the presence of low repetition and low force, or that may be followed by tissue

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degeneration and fibrosis leading to scarring in the presence of high-repetition and/or high force or other extrinsic risk factors (such as tendon impingement). Furthermore, inflammatory effects may be systemic, which may explain some of the nonspecific pain syndromes affecting workers with complaints of WMSDs who are frequently not taken seriously by health care providers.[49] Behavioral declines in animal models coincide with the inflammatory response, but appear to persist despite tissue repair. This latter finding is consistent with WMSDs in humans and merits investigation of other causes of such persistent behavioral decline. We will now turn to evidence of peripheral nerve injury in WMSDs.

Evidence of Peripheral Nerve Injury in WMSDs

Most experimental work on the response of nerve to mechanical loading involves the study of acute or chronic loads, and may thus overlook the importance of repetition per se on the development of nerve lesions. Only 2 experimental studies examined this question, and they arrive at conflicting conclusions. Szabo and Sharkey[108] applied fluctuating pressures to rat tibial nerve and reported that only the mean level of pressure was important in causing conduction block. In contrast, Watanabe et al[117]elongated rat brachial plexus by 8% in static or cyclic loading and found that cyclic loading had more pronounced effects on grip strength, compound action potential amplitude, and integrity of the blood-nerve barrier. It is unclear whether this difference in findings is related to the type of loading (compression versus elongation) or to other factors.

The mechanisms of nerve injury via compression are complex. Compression may cause mechanical disruption of nerve structures, as well as indirectly compromise function by restricting vascular perfusion. Experimental evidence suggests that several processes are involved, depending on the magnitude and duration of nerve loading. Although described separately, it is likely that several of the following phenomena affect nerve anatomy and function in repetitive-motion injury.

Under localized compression, mechanical disruption of axons and myelin may occur. Dyck et al[45] found that endoneurial fluid, axoplasm, and myelin were displaced away from regions of rat peroneal nerve that were acutely pressurized. At the site of compression, there was an increase in the distance between nodes of Ranvier and distortion of myelin lamellae. These observations suggest that the elevation of pressure within the carpal tunnel may cause direct mechanical disruption of saltatory conduction or interfere with normal axoplasmic transport. In the median nerves of aged guinea pigs (a species in which spontaneous nerve compression occurs)[5,54] there is a similar distortion of myelin away from the carpal region, again suggesting that pressure has a direct effect on nerve function.[84]

Blockage of axoplasmic transport by nerve pressure has been demonstrated in several studies in rabbits.[86,95,35-38] Rydevik et al[95] showed that 50 mm Hg pressure applied to the vagus nerve for 2 hours was sufficient to reversibly block transport, and that the block achieved at greater pressures (200 and 400 mm Hg) persisted for 1 to 3 days following pressure release. Using a similar model, Dahlin and coworkers[35-38] showed that pressures as low as 30 mm Hg could block axoplasmic transport and induce histological changes after 7 days. Dahlin et al[34] also demonstrated that the transport mechanisms remained affected 14 days after compression at 200 mm Hg.

Normal nerve function requires metabolic energy, both to maintain the ionic gradients across the membrane necessary for propagation of the action potential and to power axoplasmic transport. In acute studies of anoxia, axonal conduction began to fail after approximately 11 minutes.[39,48] Pressures as low as 20 to 30 mm Hg reduce nerve blood flow,[94] so it is likely that the pressures observed in the carpal tunnel of patients with CTS (mean, 32 mm Hg)[55] may limit nerve perfusion. Motor conduction latency decreased immediately upon surgical release in patients with CTS, suggesting that pressure in the tunnel had restricted nerve perfusion prior to surgical release.[46]

The blood-nerve barrier is formed by the perineurial membrane and by endothelial cells in endoneurial capillaries, which are connected by tight junctions.[69] This barrier, which normally limits the passage of macromolecules, is disrupted by compression,[93] resulting in intraneural edema. Lundborg et al[70] report that compression of rat sciatic nerve at 30 mm Hg for 2 hours resulted in increased endoneurial pressure at 1 and 24 hours after compression was released. Powell and Meyers[90] found that endoneurial edema occurred within 4 hours after pressure release, and persisted for 28 days. Edema may further increase the pressure on endoneurial capillaries and restrict blood flow.[98] Disruption of the blood-nerve barrier has also been described in chronic experiments in which a nerve is banded with a cuff of silastic tubing (Table 5).[73,74]

Nerve compression can also cause axonal demyelination and degeneration. Rydevik and Nordborg[96] found evidence of demyelination 3 weeks after 2 hours of compression at 200 and 400 mm Hg in rabbit tibial nerve. Powell and Meyers[90] found demyelination and Schwann cell necrosis in rat sciatic nerve 7 days after acute compression at 30 mm Hg. Demyelination has also been reported in chronic nerve-banding experiments on rats and monkeys.[72,74,83] Mackinnon et al[74] found degeneration

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TABLE 5. Animal models of WMSDs, chronic repetition, lengthening, and compression in which peripheral neuromuscular tissues were examined.

Authors	Model	Findings for Each Study Categorized Based on Tissue and Functional Changes
Stauber et al, 1994,[104] 1996[103]	• Rat model • Forced-lengthening soleus muscle: slow (10 mm/s) or fast (25 mm/s) strain rates, 3/wk for 4-6 wk	• Hypertrophy, ↑ muscle mass, ↑ myofiber area (adaptation) after slow stretch; ↑ muscle mass, ↓ myofiber area after fast stretch‡ • Myofibers splitting and ↑ type A fibers (regeneration) after fast stretch; collagen struts after slow stretch; clear fibrosis after fast stretch§
Stauber et al, 2000[105]	• Rat model • Forced-lengthening soleus muscle: 50 strains/d, 5 d/wk for 6 wk, followed by 3 mo of cessation of chronic hyperactivity	• Hypervascularity† • ↓ muscle mass, ↓ myofiber area‡ • ↑ noncontractile tissue, ↑ collagen content§ • Incomplete recovery of tissue changes after 3 mo
Mackinnon et al, 1984[74] Mackinnon and Dellon, 1986[73]	• Rat model • Silastic tubing-induced chronic nerve compression of median nerves for 1-12 mo	• Nerve compression, nerve demyelination and degeneration;* hypervascularity† • Intraneural fibrosis, regenerating unmyelinated fibers, tissue changes ↑ over time§ • ↓ NCV¶
Mackinnon et al, 1985[75]	• Primate model • Silastic tubing-induced chronic nerve compression of median nerves for 4-12 mo	• ↓ neural tissue in fascicles, demyelination* and ↓ number of myelinated fibers • Intraneural fibrosis§
Barr et al, 2002[13]	• Rat model • LRLF reaching and grasping task: 1 reach/30 s, 45 mg of force, 2 h/d, 3 d/wk for 12 wk	• No increase in serum IL-1α (only serum examined)† • No motor changes¶
Barr et al, 2000[15], 2002[13] Barbe et al, 2003[12] Clark et al, 2003[33] Clark et al, 2004[32]	• Rat model • HRLF reaching and grasping task: 1 reach/15 sec, 45 mg of force, 2 h/d, 3 d/wk for 8-12 wk; HRHF reaching and grasping task; 1 reach/15 sec, 180 g of force, 2 h/d, 3 d/wk for 12 wk	• ↑ hsp 72 in distal forelimb and palm by week 3; nerve demyelination begins week 9* • Widespread ↑ in macrophages in nerve and all muscles examined in weeks 3-6; ↑ COX_2 and IL-1β in cells of muscles, tendons, CT of distal forelimb and palm; ↑ serum IL-1α† • ↑ intraneural fibrosis (CTGF and collagen type I) in weeks 10-12§ • ↓ NCV of median nerve; ↓ reach rate and task duration; maladaptive movement patterns arise; ↑ paw withdrawal response threshold to tactile stimulation¶

Abbreviations: WMSDs, work-related musculoskeletal disorders; NCV, nerve conduction velocity; LRLF, low-repetition low-force; IL-1α, interleukin-1α; HRLF, high-repetition low-force; hsp72, inducible form of heat shock protein 70/72; COX2, cyclooxygenase 2; IL-1β, interleukin-1β; CT, loose areolar and synovial connective tissue; CTGF, connective tissue growth factor.
* Injury/degenerative changes.
† Inflammatory/proliferative changes.
‡ Adaptive tissue changes/tissue reorganization.
§ Repair with and without regeneration or scarring (fibrosis).
‖ Pathological remodeling.
¶ Functional changes (eg, behavioral or biomechanical).

after 1 month of chronic banding of rat sciatic nerves with small-diameter cuffs, and evidence of fiber regeneration after 3 months (Table 5). They did not observe fiber degeneration when larger cuffs were used. O'Brien et al[83] report degeneration of fibers in rat sciatic nerve after 8 to 24 months using a large-diameter cuff. Signs of Wallerian degeneration have also been reported in the median nerves of aged guinea pigs.[5,54,84] Wallerian degeneration and regeneration are generally considered to occur only in advanced stages of CTS.[56,71] However, in our study of repetitive reaching, rat median nerves showed infiltrating macrophages, which remove damaged myelin,[32,87] by 3 weeks of task performance and myelin degradation by 9 weeks (Table 5).[33]

Chronic nerve compression may also induce neural fibrosis. Nerve banding experiments have shown that moderate chronic compression leads to thickening of the epineurium and the perineurium in rats and monkeys.[72-74,83] In our model of repetitive reaching, there was increased deposition of collagen in the epineurium by 8 weeks of task performance.[32,33] We also observed widespread expression of connective tissue growth factor, a mediator of fibrosis, by Schwann cells and intraneural fibroblasts. In 1 animal that had performed the task for 10 weeks, there was a

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connective tissue nodule surrounding the nerve at the wrist. Thus, chronic nerve compression leads to fibrotic changes within and surrounding the nerve. Fibrosis may affect nerve function by directly compressing the axons, by compressing the vascular supply, or by entrapping the nerve and thus preventing normal nerve gliding.[60,71] Such entrapment may lead to traction injury. Entrapped peripheral nerves are more susceptible to injury at other sites, for which the term "double crush syndrome" has been coined.[61,115] This increased susceptibility, which has been confirmed experimentally,[41,82] likely reflects defects in axonal transport affecting the entire length of the axon.[69]

Carpal tunnel pressure is elevated when the wrist is placed in flexion or extension or when performing actions such as making a fist or holding objects.[55,99] It is thus likely that repetitive hand movements cause compression of the median nerve. The early development of nerve pathology in CTS is thought to involve disruption of the blood-nerve barrier following ischemia, with the resulting edema leading to fibrosis, demyelination, and in severe cases, Wallerian degeneration.[56,69,71,107] Other effects of pressure on the nerve, such as distortion of myelin and axoplasm, and interference with axoplasmic transport may also play a role. Altered nerve function may explain the persistent behavioral changes in patients with WMSDs and may also contribute to reorganization of sensory and motor pathways within the central nervous system (CNS), which we discuss in the next section.

TABLE 6. Selection of rat models of WMSDs or chronic/excessive exercise in which bone tissues were examined.

Authors	Model	Findings for Each Study Categorized Based on Tissue and Functional Changes
Bourrin et al, 1994[18]	• Treadmill running, 5-wk-old rats • High magnitude reps, long-duration task: 105 min/d at 30 m/min by week 9; 11 wk 10° grade, 80% VO_2 max	• Site-specific cancellous bone adaptation‡ • ↑ bone loss (↑ activated osteoclasts and eroded surfaces) and ↓ osteoid thickness; ↓ longitudinal tibial bone growth‖
Bourrin et al, 1995[19]	• Treadmill running, 9-wk-old rats • Lower magnitude and duration than above: increase to 90 min/d at 20 m/min by week 2, for 5 wk, 0° grade, 60% VO_2 max	• ↑ bone formation (tibia) with ↑ osteoblasts; site-specific adaptation of trabecular network; ↓ activated osteoclasts (↓ bone resorption); ↓ serum calcium levels weeks 3-4‡
Forwood and Parker, 1991[50]	• Treadmill running • High rep, medium magnitude: 20 000 loading cycles/d, 2 h/d, 26.8 m/min, 10% grade, 5-10 d	• No histological evidence of microdamage* • Site specific ↓ or ↑ of apposition growth (LE bones)‡ • ↓ stiffness and ↑ twist angle of tibia‖
Mosekilde et al, 1994[78]	• Treadmill running • High rep, low force: 5 d/wk, 2 km/d for 4-10 mo	• ↓ cortical-endosteal bone resorption in femur; site-specific ↑ bone mass and strength‡
Umemura et al, 2002 [114]	• Repetitive jumping • Low rep, high force: 20/session, 3 30-s jump intervals, 1 session/d for 8 wk	• ↑ bone mass; mass ↑ with longer intervals between loading‡
Turner et al, 1994[113]	• Low rep, excessive loading: 2 Hz, 27-64-N loads, 36 rep/d, for 12 d	• Bending strains above 40 N ↑ bone forming surface, mineral apposition rate and bone formation‡ • ↑ woven bone at periosteal surface at 40 N or greater‖
Mosley and Lanyon, 1998[79]	• Dynamical axial loading of ulna • High strain rates, short duration: 2-Hz frequency, 1-20 N, 3 strain rates, 1200 loading cycles applied on days 4-8, 11-15	• Adaptive modeling along bone shaft in all groups: complex site-specific ↑ and ↓ bone formation and resorption; ↑ osteogenic response with ↑ strain rates‡
Barr et al, 2003[16]	• Rat model • High-rep, low-force, long-duration reaching-and-grasping task: 1 reach/15 min, 45 mg of force, 2 h/d, 3 d/wk for 12 wk	• ↑ osteoblasts in cortical bone by 12 wk‡,§ • ↑ woven bone at bone-periosteum at tendon/ligament attachment sites; ↑ activated osteoclasts and macrophages at same sites at 3-6 wk‖ • See Table 4¶

Abbreviations: WMSDs, work-related musculoskeletal disorders; rep, repetition; LE, lower extremity.
* Injury/degenerative changes.
† Inflammatory/proliferative changes.
‡ Adaptive tissue changes/tissue reorganization.
§ Repair with and without regeneration or scarring (fibrosis).
‖ Pathological remodeling.
¶ Functional changes (eg, behavioral or biomechanical).

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Evidence of CNS Reorganization in WMSDs

Neuroplasticity refers to the persistent anatomical or physiological changes in a neuron that occur during development, regeneration, experimental manipulations, or repeated activity across a synapse. There is evidence of such neural reorganization at multiple levels of the CNS following skill learning, chronic pain, peripheral inflammation, peripheral nerve injury, and performance of repetitive tasks (Tables 4 and 7).

Chronic pain, inflammation, and peripheral tissue injury result in repeated activation and/or chronic overstimulation of nociceptive afferents terminating in spinal cord dorsal horns. The sustained nociceptive afferent barrage causes a greater release of excitatory neuropeptides and amino acids from these terminals than that which occurs during acute events.[44] The nociceptors become hypersensitive,[76] expand their receptive fields, and increase the excitability of secondary neurons in the spinal cord. These changes contribute to the hyperalgesia associated with chronic pain and inflammation.

Pathological changes in the neural input to the CNS also result in reorganization of brainstem and cortical regions (Table 4). Examination of somatosensory-evoked responses following ulnar nerve stimulation in patients with chronic CTS shows increased amplitudes in the spinal cord, brainstem, and sensoricortical regions carrying information from the ulnar nerve ipsilateral to the median nerve lesion.[110] Magnetic source imaging of the cortex of a patient with CTS revealed an invasion of areas normally representing the median nerve with areas representing ulnar and radial nerves.[43] These results indicate that structural and physiological changes can occur throughout the central neuroaxis following chronic nerve compression.

The CNS can be profoundly affected by the performance of repetitive hand-intensive movements. There is strong evidence that repetitive tasks alone can lead to degradation of the somatosensory cortex in monkeys,[25,26,28,111] rats,[91] and humans (Table 4).[22,24,27] In the primate model of repetitive grasping, electrophysiological mapping of the primary somatosensory cortex (the region of the dorsal parietal cortex designated as area SI) reveals a dedifferentiation of the hand region with shifted or degraded digit-receptive fields.[23-25,111] These changes are associated with movement dysfunctions. However, use of proximal muscles and variable strategies result in less SI degradation and improved motor control.[111] In humans, degradation of hand representations also occurs with focal hand dystonia.[22,24,27] The severity of focal hand dystonia positively correlates with the ratio of the mean amplitude to latency of the somatosensory evoked potential (SEP) in the SI cortex.[27] Furthermore, degradation of the digit representation is not isolated to just SI, but also involves secondary somatosensory and posterior parietal cortices.[22] A loss of spatial discrimination in the form of gap detection and single-touch localization has also been observed.[11] Rehabilitation techniques for patients with focal hand dystonia that include sensory discriminative training have been reported to improve sensorimotor function.[23,30,118]

Findings of CNS reorganization associated with peripheral tissue injury and inflammation and with repetitive stereotyped movements have important implications in the rehabilitation of individuals with WMSDs. Along with scarring (fibrosis) and decreased function of peripheral nerves, somatotopic dedifferentiation of sensorimotor receptive fields probably contributes to maladaptive movement patterns and

TABLE 7. Animal models of WMSDs in which central nervous system changes were examined.

Authors	Model	Findings Related to Tissue and Functional Changes
Byl et al, 1996a[26], 1996b[28], 1997[25] Topp and Byl, 1999[111]	Repetitive, forceful hand squeezing in owl monkeys: 15/min, 300 trials/d for 2-5 mo; training continued until accuracy dropped to below 50%	Somatotopic dedifferentiation of hand representation in area SI: expansion and overlap of digit receptive fields ↓ speed and motor accuracy
Plautz et al, 2000[89]	Repetitive UE motor task: retrieval of food pellets from a small-diameter and large-diameter wells in squirrel monkeys	Small-diameter wells: task-related changes in movement representations in area MI during skill acquisition Large-diameter wells: no task-related cortical changes
Remple et al, 2001[91]	Repetitive power reaching in rats: progressive increase in maximum size pasta bundle that could be retrieved; 30-d training period	↑ Proportion of motor cortex occupied by distal wrist/digit representation, ↓ elbow/shoulder representation in power-reaching and control rats compared to nonreach rats

Abbreviations: WMSDs, work-related musculoskeletal disorders; SI, primary somatosensory cortex; UE, upper extremity; MI, primary motor cortex.

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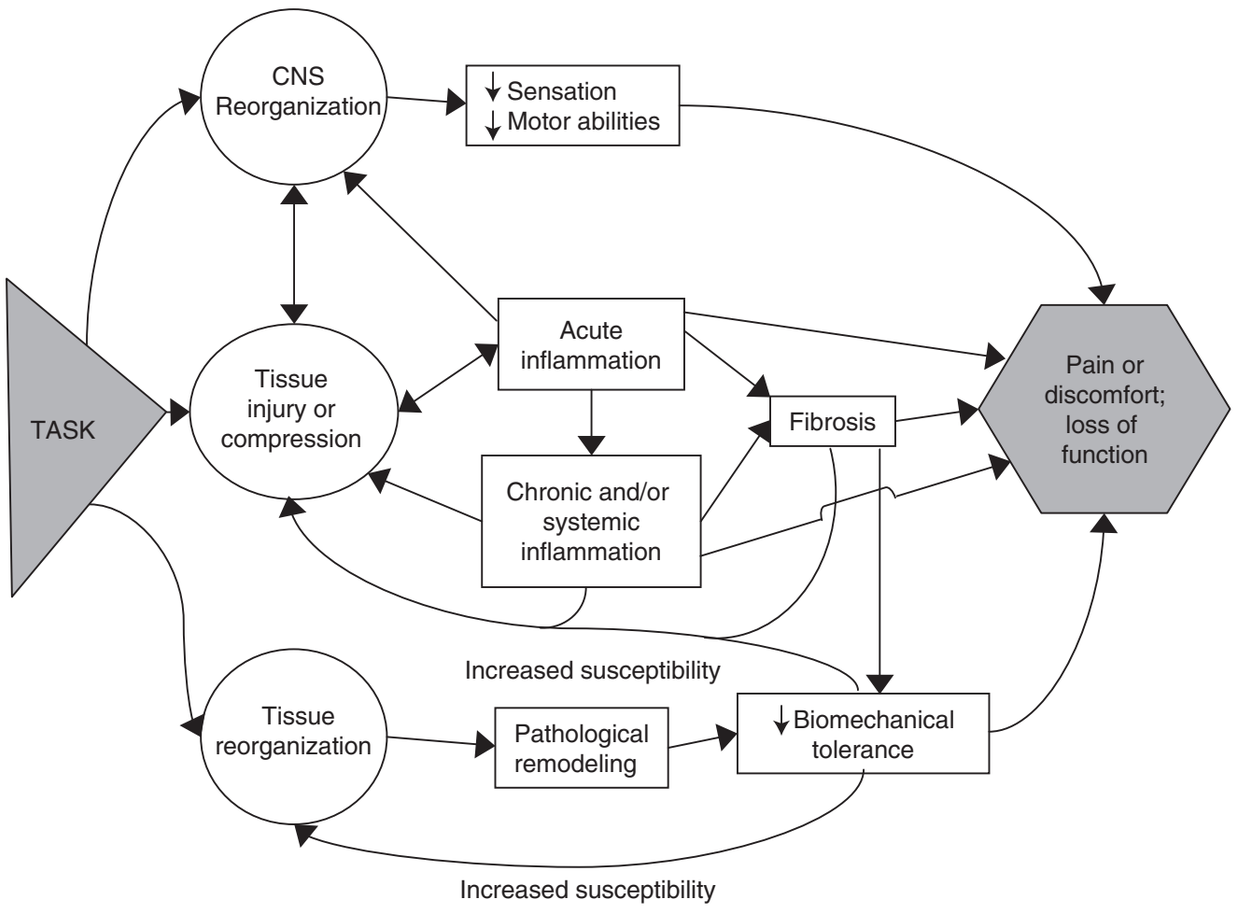

FIGURE. Schematic diagram showing the 3 primary pathways hypothesized to lead to work-related musculoskeletal disorders caused by repetitive and/or forceful hand-intensive tasks. Interrelationships between components of these pathways are indicated, which illustrates the pathomechanical complexity that may contribute to pain, discomfort, and functional loss. Clinicians need to be aware of all of these mechanisms to plan effective interventions or respond to unexpected or unsatisfactory treatment outcomes. See Summarizing Thoughts and Working Hypotheses section for a detailed explanation of these pathophysiological pathways. (CNS, central nervous system.)

the potential for increased peripheral tissue injury due to imprecisely controlled and inefficient movements. These behavioral consequences have been observed in both animals[12,13,15,23,26,28,33,111] and humans.[22,24,27,43,110] Failure by health care providers to recognize such central phenomena in patients could lead to poor treatment outcomes and contribute to long-term disability and loss of income.

SUMMARIZING THOUGHTS AND WORKING HYPOTHESES

Hand and wrist WMSDs represent a substantial proportion of work-related illnesses and are associated with relatively high medical costs and loss of work. They are caused by the chronic performance of highly repetitive hand-intensive tasks, especially those involving high levels of force. Based on this review of the literature, we hypothesize that the performance of repetitive and/or forceful hand-intensive tasks may induce WMSDs through 3 primary pathways: (1) CNS reorganization, (2) tissue injury or compression, and (3) tissue reorganization. These pathways are depicted in the Figure, which also indicates hypothesized connections to the pathomechanisms directly responsible for pain and dysfunction. The paragraphs that follow will elaborate upon these 3 pathways.

Central Nervous System Reorganization

Central nervous system changes can result from the performance of highly repetitive tasks, both in the presence and the absence of chronic pain, peripheral tissue inflammation, and/or peripheral nerve compression (Figure). In some cases, such as focal hand dystonia, such central reorganization may be unaccompanied by peripheral tissue injury.[111] Corroborating evidence exists for central reorganization in patients with focal hand dystonia and includes changes in SEPs at all levels of the central neuroaxis,[22,27,43,110] as well as loss of spatial discrimination.[11] Such neuroplasticity interferes with normal sensation and movement, which may further increase the effects of continued exposure to repetitive tasks.

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Peripheral nerve compression and tissue inflammation can also induce central neuroplasticity (Figure), although the relative contribution of such a mechanism with respect to the performance of repetitive motion alone may be impossible to discern when these conditions coexist. Sensorimotor degeneration in patients diagnosed with CTS is well known.[63] Three recent studies of sensorimotor function among office workers exposed to heavy computer use are particularly relevant to the persistent controversy surrounding the causal role of computers in WMSDs. Tremblay et al[112] found that female frequent computer users performed worse in manual acuity bilaterally and in manual dexterity of the right (dominant) hand than did occasional computer users. Jensen et al[64] found decreased vibrotactile sense in the median and ulnar nerve distributions and decreased pinch strength with the forearm pronated in symptomatic workers in jobs with heavy computer use, compared with asymptomatic workers in jobs with light computer use. No other differences were found in strength, endurance, or hand-eye coordination. Greening and Lynn[58] compared heavy computer users with WMSDs to at-risk office workers with heavy computer use and asymptomatic controls with light computer use and found decreased vibration sense in both the median and ulnar nerve distributions in the WMSD group, and in the median nerve distribution in the at-risk group. Keyboard use for 5 minutes resulted in further decreased vibration sense in subjects with WMSDs. Furthermore, most workers with WMSDs experienced decreased tolerance to suprathreshold stimulation compared to those without WMSDs.

While the results of the above studies could indicate the early onset of median nerve entrapment among workers with jobs requiring heavy computer use, they also may indicate alternative injury mechanisms. For example, involvement of the ulnar nerve in symptomatic individuals might indicate central reorganization due to altered peripheral nerve input.[110] Hyperalgesia and preserved motor function in the presence of impaired sensation might indicate central sensitization[76] or sensory cortical field expansion.[24,27] Positive findings in the nondominant hand might indicate a systemic inflammatory response.[12] For any of these alternatives, confirmation of a positive relationship between intensity of computer use and decreased conduction velocity of the median nerve would be diluted or absent, because the primary mechanism underlying symptoms would not necessarily include loss of peripheral nerve function. While computer use may not be a major cause of work-related CTS (an assertion still under heated debate), it may nonetheless be an important risk factor in the development of WMSDs.

Tissue Injury or Compression

Highly repetitive and/or forceful motions cause injury to the musculoskeletal system and peripheral nerves (Figure). This initial tissue injury is usually localized and discrete (Tables 3-6). The severity of injury is dependent on force, frequency, and duration of repetitive exposure. Serum markers of injury have been found in patients with WMSDs. Freeland et al[52] detected increased serum malondialdehyde, an indicator of cell distress, in patients with CTS. Kuiper et al[65] found higher levels of biomarkers of collagen anabolism in a group of student nurses with high numbers of patient-handling tasks.

The tissue injury leads to localized, acute inflammatory responses (Figure) that include edema, macrophage infiltration, and increased production of proinflammatory cytokines and other inflammatory mediators by injured cells and invading immune cells (Tables 3-6). Although the inflammatory process may resolve with complete repair of the injured tissues at low enough levels of repetition and force, tissue scarring can also accompany the healing process. Continued exposure to the initiating stimulus (such as a highly repetitive task) can lead to chronic inflammation and then to a chronic fibrotic state (Figure). Fibrotic changes within tissues may subsequently increase the susceptibility of those tissues to further injury with continued exposure, even to decreased levels of repetition and force.[41,61,82,115]

Animal studies also reveal the involvement of multiple body systems in WMSDs. Work in our laboratory shows a widespread increase in phagocytic macrophages in many musculoskeletal tissues, and a circulatory distribution of inflammatory mediators as a result of performance of highly repetitive motions.[12,13] Thus, inflammatory mediators may be widely distributed via the circulatory system and lead to a systemic inflammatory response to the task.

Although it remains to be seen whether serum markers of inflammation are present in patients with WMSDs, one possible consequence of the circulatory distribution of inflammatory mediators in WMSDs is a widespread increased susceptibility of tissues to previously innocuous physical stress (Figure). In such a case, tissue injury would occur at a lower exposure threshold. This circulatory mechanism might explain the nonspecific pain syndromes with which patients sometimes present and which are frequently dismissed by health care providers.[49]

Tissue Reorganization

Repetitive loading of bones, muscles, and tendons leads to adaptive remodeling of these tissues (Figure; Tables 3, 4, and 6). However, the consequence of excessive repetitive loading may be pathological remodeling/reorganization of the tissues. For example, we showed pathological remodeling of bone

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tissues into immature, woven bone at sites of tendon and ligament attachments in both the dominant and nondominant UE of rats performing highly repetitive reaching.[16] Furthermore, Soslowsky[102] showed that continued exposure to repetitive loading in a treadmill-running rat model of rotator cuff tendinitis leads to a decrease in the biomechanical tolerance of the tendon. Such a change can result in an increased susceptibility of the tissues to further reorganization and injury with continued exposure (Figure).

CONCLUSION

Hand and wrist WMSDs represent a substantial proportion of work-related illnesses and are associated with relatively high medical costs and loss of work. Based on our review of the literature and our own work in a rat model, we have identified 3 primary pathophysiological mechanisms involved in the development of WMSDs. All of these pathways, either in isolation or in combination, may cause pain, discomfort and/or loss of function in patients with WMSDs (Figure). In the case of both systemic (circulatory) and CNS mechanisms, effective treatment should extend far beyond the customary focus on musculoskeletal and peripheral nerve tissues specifically involved in occupational tasks. The wise clinician should consider all such mechanisms when confronted with a patient who has complex, confusing signs and symptoms or who experiences disappointing treatment outcomes.

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