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Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders

Ann E. Barr [a,*], Mary F. Barbe [a,b]

[a] *Physical Therapy Department, College of Health Professions, Temple University, 3307, North Broad Street, Philadelphia, PA 19147, USA*
[b] *Department of Anatomy and Cell Biology, School of Medicine, Temple University, Philadelphia, PA, USA*

Abstract

Work-related musculoskeletal disorders (MSDs) cause substantial worker discomfort, disability and loss of productivity. Due to the difficulty in analyzing the tissues of patients in the early stages of work-related MSD, there is controversy concerning the pathomechanisms of the development of these disorders. The pathophysiology of work-related MSD can be studied more easily in animal models. The purpose of this review is to relate theories of the development of tissue injury due to repeated motion to findings of recent investigations in animals that address the role of the inflammatory response in propagating tissue injury and contributing to chronic or recurring tissue injury. These tissue effects are related to behavioral indicators of discomfort and movement dysfunction with the aim of clarifying key time points for specific intervention approaches. The results from animal models of MSD are discussed in the light of findings in patients, whose tissues are examined at a much later phase of MSD development. Finally, a conceptual model of the potentially negative impact of inflammation on tissue tolerance is proposed along with suggestions for future research directions.

Keywords: Work-related musculoskeletal disorders; Repetitive motion disorders; Inflammation; Animal models; Pathophysiology; Tissue injury

1. Introduction

Illnesses due to repeated trauma accounted for 65% of the 333,800 newly reported cases of occupational illnesses in US private industry and for one in three lost work time illnesses in 2001 [13,14]. Work-related musculoskeletal disorders (MSDs) continue to cause substantial worker discomfort, disability and loss of productivity in US industry. In spite of numerous epidemiological studies demonstrating a positive relationship between exposure to repetitive and/or forceful motion and the prevalence of MSDs, the mechanisms of pathophysiology, particularly in the early stages of MSD development, are understood incompletely [12,35]. In part, this is due to ethical constraints in obtaining biopsies from healthy working populations in order to study the natural history of MSDs. Animal models provide an opportunity to examine such tissue effects at a much earlier time point and under experimental conditions in which exposure can be controlled. Several animal studies have been published in recent years which indicate that inflammation plays a role in the development of work-related MSD [4,6,16,42]. Other studies in both animals and patients have questioned the role of inflammation in the development of MSD [1,23,45]. Such divergent findings in the literature perhaps reflect the complex and multifactorial causes of work-related MSD. However, the question of the role of inflammation in MSD tissue pathophysiology, behavioral decline and chronic disability needs to be addressed if effective injury prevention and early treatment programs are to be established.

The purpose of this review is to relate theories of the development of tissue injury due to repeated motion to findings of recent investigations in animals that address the role of the inflammatory response in propagating tissue injury and contributing to chronic or recurring tissue injury. These tissue effects will be anchored to behavioral degradation with the aim of clarifying key

* Corresponding author. Tel.: +1-215-707-5964; fax: +1-215-707-7500.
E-mail address: aebarr@temple.edu (A.E. Barr).

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time points for specific interventions. Future directions in both animal and clinical research will be suggested.

2. Pathomechanical theories of the development of work-related MSDs

The National Research Council and Institute of Medicine report on work-related MSDs provides a conceptual model for the multifactorial influences leading to the development of MSD that proposes that internal tissue tolerances may be exceeded by external loads in the workplace [35]. External loads are translated into internal loads that induce physiological responses that may in turn influence tissue tolerance. The cumulative load theory of MSD development proposes that biological tissues undergo progressive mechanical degradation as a result of load accumulation over time [29]. This theory does not explain how many workers are able to perform repetitive and forceful tasks throughout their working lives without sustaining significant musculoskeletal injury [22]. Such individuals are perhaps more fit to perform work tasks due to individual variation. On the other hand, tissue tolerance may be sufficient up to a certain threshold below which its integrity is preserved and above which injury results. This latter possibility is known as the overexertion theory of MSD development, in which the combined effects of risk factors for MSD exceed tissue tolerance capacity and cause injury [29]. Numerous epidemiological studies support this concept and suggest that combinations of risk factors are more than additive in exceeding tissue tolerance thresholds [12,35,41].

Preliminary work in our laboratory indicated that tissue microtrauma resulted in an inflammatory reaction. Based on these results and those of others [4,15,16,31,32,43], a conceptual schematic for the development of MSD was presented in a previous review article and proposed that when continued task performance is superimposed upon injured and inflamed tissues, a vicious cycle of injury, inflammation and motor dysfunction ensues [10]. Investigation of this process has been undertaken in our laboratory in a rat model. The inflammatory response to mechanical tissue injury has been examined because it is a fundamental reaction to tissue injury with both physiological and functional consequences.

3. Tissue injury and the inflammatory response

The purpose of an inflammatory response in MSD would be to phagocytose injured cells and tissues. With repetitive and/or forceful tasks, the initiating stimuli for inflammatory responses include physical agents such as repeated over-stretch, compression, friction and anoxia [36,46]. These insults lead to mechanical injury of cellular membranes and intracellular structures and a localized release of proteins such as collagen, fibronectin and cytokines [15,43,44]. The nature of the inflammatory response following tissue injury depends upon both the time elapsed since injury as well as the extent of tissue damage. The following paragraphs will describe the sequence of events in the inflammatory response as well as the injury conditions under which they may occur.

Acute inflammation, which is depicted schematically in Fig. 1, is usually of short duration and sudden onset. The typical sequence of events is an initial transient arteriolar constriction followed by vasodilation, increased vascular endothelial permeability, exudation of fluid and plasma proteins, and transmigration of leukocytes from vessels into the injured tissues. The vasodilation gives rise to *calor* (heat) and *rubor* (redness), while the exudation and leukocyte infiltration give rise to *tumor* [19]. *Dolor* (pain) and *functio laesa* (loss of function) are associated with increased pressure on nerves as a result of tissue edema.

There are several causes of increased vascular permeability. The shortest-lived and most reversible follows the release of chemical mediators, such as histamine from mast cells and bradykinin, prostaglandins and serotonin from injured cells. A more long-lived endothelial cell retraction is induced by inflammatory mediators, such as tumor necrosis factor alpha (TNFα) and interleukin-1 (IL-1), following their release from injured cells. Sustained endothelial injury occurs with over-stretch or compression of vessels. Endothelial injury can also occur when leukocytes adhering to endothelium prematurely release toxic, oxygen free radicals and proteolytic enzymes. Finally, leakage from regenerating capillaries occurs during angiogenesis and repair [39].

Increased vascular endothelial permeability leads to transmigration of phagocytic leukocytes into tissues along chemical gradients in a process called chemotaxis. Which cells transmigrate during inflammation depends on the stimulus as well as the mediators and chemotactic agents released. While neutrophils are often the first to respond during an acute inflammatory response (first 6–24 h), followed by monocytes/macrophages in 24–48 h, macrophages are the predominant immune cells that respond to tendon and muscle injuries [19,27,32,40]. Chemotactic factors for leukocytes include fibronectin and collagenase fragments, and cytokines such as IL-1α and IL-6 [33,37,39].

There are three primary outcomes of acute inflammation: complete resolution with restoration of normal tissue structure, healing with scar formation, and chronic fibrosis. After mild trauma and limited tissue destruction, complete resolution with restoration of injured tissue to normal structure and function usually

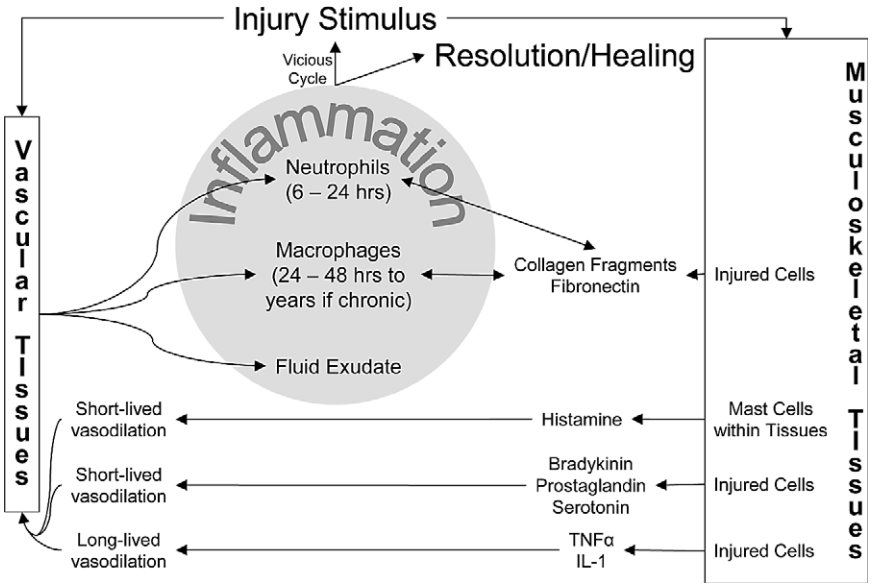

Fig. 1. Sequence of events in acute inflammation in response to a mechanical injury stimulus. Mechanical injury can damage both vascular and musculoskeletal tissues and lead to the mobilization of leukocytes (neutrophils and macrophages) by circulatory distribution and/or by chemotaxis induced by the presence of collagen fragments and fibronectin at the injury site. Even when the vasculature is spared mechanical injury, the release of inflammatory mediators from tissue mast cells and injured cells causes vasodilation and leukocyte mobilization. Ideally, acute inflammation resolves and injured tissue heals either completely or with the formation of a fibrous scar. In the case of a persistent injury stimulus or severe tissue disruption, the inflammatory response itself may cause further injury and inflammation, thereby setting up a vicious cycle with subsequent incomplete healing and/or chronic inflammation.

occurs. Healing with scar formation may occur after substantial tissue destruction in tissues with little capacity for regeneration, such as skeletal muscle, or after prolonged edema, in which case the edematous tissue fills with fibrinous exudates, cell infiltrate, and then converts to fibrotic connective tissue [19,31]. Finally, an acute response may be prolonged chronically concurrent with fibrosis [19].

Chronic inflammation can begin 2–4 days after the onset of the acute response and can last for weeks to months or years due to the persistence of the initiating stimulus, interference of the normal healing process, repeated bouts of acute inflammation, or low-grade smoldering due to continued production of immune response mediators [47]. The histological characteristics of chronic inflammation are the increased presence of macrophages, and increased numbers of fibroblasts and other tissue matrix cells, such as osteoclasts and chondrocytes, via cytokine and growth factor-induced proliferation [19,32]. Fibroblasts are associated with secretion of both collagen and collagenase leading to fibrosis and reactive tissue remodeling. Phagocytic cells can also contribute directly to tissue injury through the release of proteolytic enzymes and free radicals [32].

Systemic effects can occur during both acute and chronic inflammation. The classic characterizations of macrophage functions are primary immune defense, and removal of apoptotic cells and debris through phagocytosis. However, macrophages also produce cytokines, which have long range effects on virtually any distant cell type through circulatory distribution [20,21]. These cytokines induce production of prostaglandins and other inflammatory mediators locally and at distant sites. For example, the fever associated with acute inflammation is due to the circulation of IL-1 and TNFα to the hypothalamus following production of these cytokines by macrophages during phagocytosis [21,32]. IL-1 also stimulates the proliferation and release of leukocytes from bone marrow [26], further increasing their circulating numbers. Systemic IL-1 is a potent activator of osteoclasts, fibroblasts and chondrocytes by inducing proliferation of these cells, and subsequent bone resorption and cartilage matrix degradation [24,38].

The ultimate goal of the inflammatory process is to replace injured tissue with healthy, regenerated tissue, a fibrous scar, or both. Removal of the initiating stimulus or a decrease of chemical mediators terminates the inflammation and leads to resolution. However, comorbid factors, such as repeated bouts of injury, inadequate blood supply to the regenerating tissue, poor host nutritional status, presence of infections, and the presence of metabolic disorders, may modify the quality and speed of the inflammatory-healing response. In the paragraphs that follow, recent evidence in the literature regarding the inflammatory response of various tissues in animal models of repetitive and/or forceful loading is summarized.

4. Evidence of inflammation in the development of MSD

There are a number of animal studies that have related exercise loading of tendons to early tissue changes. Backman et al. [5]reported on the use of a kicking model in rabbits that induced Achilles tendonitis, as evidenced by the thickening and increased vascularity of paratenon with accompanying edema and fibroblast proliferation, in less than 5 weeks. Archambault et al. [4] refined this model and confirmed histological evidence of an inflammatory response in the paratenon. These investigators also observed increases in the proinflammatory mediators IL-1 and TNFα as well as in the transcript levels of matrix molecules (Type I collagen and proteoglycans) in 6–8 weeks. When the kicking protocol was prolonged to 11 weeks, no signs of injury were detected on histological examination of tendon and paratenon [3]. These findings show that tissue inflammation and tissue remodeling may occur early in MSD development, before overt signs of tissue impairment or functional decline. Furthermore, tissue repair at a later time may be complete if loads are sufficiently low.

In another model of Achilles tendon disorder, eccentric loading of the Achilles tendon of anesthetized rats was performed repeatedly for up to 11 weeks [34]. Tests of functional ambulation showed that some rats developed permanent limps after 3 weeks. On gross examination, the Achilles tendon of a limping rat showed epitenon fibrillation and hypervascularization. Hypervascularization was also noted in the epitenon of half of the trained animals. The main conclusions from this study are that functional declines may or may not accompany tissue injury, and the early phases of tissue injury are proliferative (i.e., inflammatory) rather than degenerative. In addition, the persistence of injured tissue up to 11 weeks suggests that this loading protocol was sufficient to cause chronic tissue disruption.

Soslowsky and colleagues have developed a rat model of running-induced rotator cuff tendinopathy [16,42]. In addition to the evidence for inflammation (i.e., tendon thickening and hypercellularity), maximum stress was decreased in the tendons of experimental animals compared to controls. These changes were present after 4 weeks of running and persisted through 16 weeks. The introduction of an additional tissue stress by an intrinsic insult (bacterial collagenase injected into the tendon) or an extrinsic compressive procedure (Achilles tendon allograft positioned in the subacromial space) increased the magnitude of these pathological responses. These studies clearly show evidence for decreased biomechanical tissue tolerance in an exercise-induced tendinopathy. The latter study illustrates the combined effects of multiple etiological factors in the development of exercise-induced tendinopathy.

Repetitive tasks have been shown to result in chronic inflammation of tendons, muscles and associated connective tissues with continued presence of subsets of macrophages [6,25] and residual scarring and fibrosis [18,43,44]. Jarvinen et al. [25] have speculated that the mechanisms leading to tissue repair are prevented by the continued cycle of tissue trauma in repetitive motion injury. This review of studies using animal models of exercise-induced musculoskeletal injury leaves questions regarding the association of tissue changes to motor dysfunction. When considering the development of MSD, loss of function is the hallmark that prompts clinical intervention. With this in mind, we have developed a model of upper extremity MSD in which rats are trained to reach and grasp voluntarily either small food pellets [6] or a handle that is pulled until a predetermined force threshold is reached [17].

This model yielded evidence of musculotendinous damage and fibrotic scarring in the forearm flexors of the reach limbs of high repetition, negligible force (HRNF) rats at 6 weeks [6]. Subsequent fibrotic scarring of these damaged tissues was evident by 8 weeks (Fig. 2b). Immunohistochemical analyses showed that this tendon disruption is accompanied by an increase in activated exudate macrophages by 6 weeks of task performance (Fig. 2d). There were also increases in macrophages in loose connective tissues, peripheral nerves, and bone-periosteum at the sites of muscle and ligament attachments of these HRNF animals [6,11,18]. Fig. 3 illustrates the time course of these inflammatory cell increases. For the HRNF group, the increase in the numbers of macrophages peaked significantly above control levels at 6 weeks and declined toward control levels at 8 weeks [6]. New results show that the number of ED1 immunoreactive macrophages increased significantly again at 12 weeks in the HRNF group (Fig. 3a).

The same tissues of the reach limbs of low repetition, negligible force (LRNF) animals underwent a non-significant response similar in timing but lower in magnitude (Fig. 3b) [9]. In the high repetition, high force (HRHF) animals, the inflammatory response was increased above control levels at 12 weeks concurrent with fibrosis [17,18].

Nonreach limb tissues of these same animals showed a similar time course of inflammation (Fig. 3) [6]. One possible explanation for this bilateral effect is the use of the nonreach limb. Another possible explanation is a cytokine-mediated systemic response that stimulates cell proliferation and inflammation in relatively non-stressed tissues. This hypothesis was investigated through ELISA analyses of the serum of these animals.

In the HRNF group, serum levels of IL-1α increased significantly above control levels in week 8 [6,9]. IL-1α did not change significantly in the LRNF group with task performance. Histological examination of tissues from the HRNF group showed that several anti-

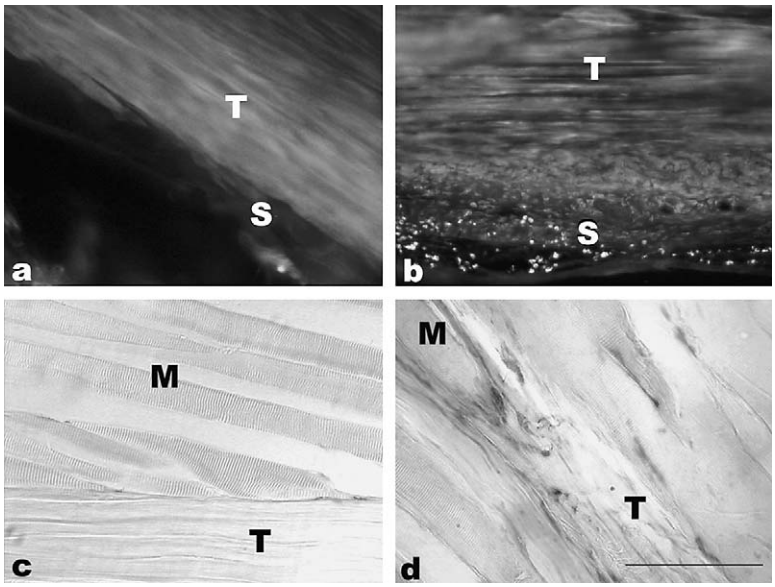

Fig. 2. Photomicrographs showing musculotendinous tissues in the flexor region of the wrist of control (a and c), 8 week (b) and 6 week (d) trained animals. The synovial sheath for the control limb (a) shows smooth, even borders. The synovial sheath for the reach limb of the 8 week trained animal shows hypercellularity, disruption of parallel fiber arrangement, and fibroblast proliferation with increased connective tissue growth factor expression. Many cells in the hypercellular region of the musculotendinous junction of the 6 week rat (d) express ED-1, indicating that they are macrophages engaged in phagocytosis, as compared to controls (c). T, tendon; S, synovium; M, muscle.

inflammatory cytokines were upregulated by 8 weeks of task performance [2,7,8]. This finding led to the conclusion 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.

5. Behavioral changes associated with inflammation in MSD

Two behavioral indicators in the rat model of upper extremity MSD offer insight into the behavioral consequences of inflammation. Reach rate (reaches/minute) is an indicator of the animals' ability to maintain task pace. Duration (hours of participation/day) is an indicator of overall animal comfort. The HRNF group underwent a significant decline in reach rate in week 6, which coincided with the peak inflammatory response, and a return toward baseline in week 8 [6,9]. The LRNF group did not exhibit any change in reach rate over 8 weeks [9]. The HRNF group showed a significant decline in duration in week 5 [6], whereas the LRNF group showed no decline in duration (unpublished results). The HRHF group shows a continual significant decline in reach rate and duration beginning at 3 weeks and persisting through 12 weeks of task performance [18].

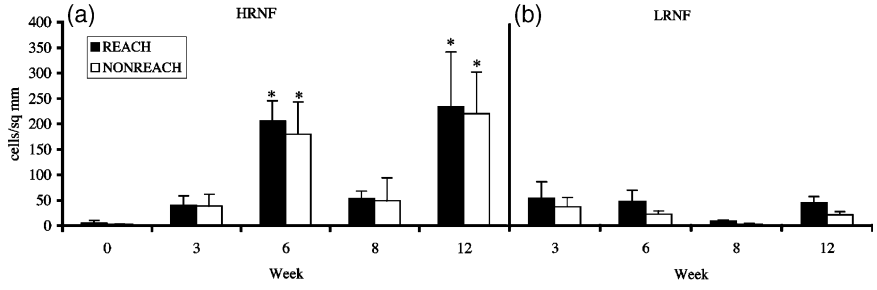

Fig. 3. Bioquantitation of ED1-expressing macrophages (+SEM) in combined upper extremity tissues of rats that performed high repetition, negligible force (HRNF) reaching (a) or low repetition, negligible force (LRNF) reaching (b). Tissues examined include muscle, tendon, loose connective tissue, nerve and bone. Note the peak cell counts in week 6 and week 12 for the HRNF group ($^{*}p < 0.01$). No significant differences were found in the LRNF group over 12 weeks.

6. Conceptual schematic for the role of inflammation in MSD

Our results are consistent with other animal models in that inflammatory cells and mediators are present in the musculotendinous tissues in as early as 6 weeks after a repetitive task regimen is initiated. Other tissues and anatomical regions have been examined and the inflammation is found to be widespread. Serum analyses gave evidence for a systemic inflammatory response. There is a clearly demonstrated dose–response relationship between repetition-force and tissue and behavioral responses. From a pathophysiological perspective, the results in these three groups can be summarized quite simply. The LRNF animals experienced a mild acute inflammatory episode that resolved in due course with no perceptible decrease in function. The HRNF animals experienced acute and chronic inflammatory changes with possible residual tissue scarring and transient decreases in function. The HRHF animals experienced persistent acute and/or chronic, smoldering inflammation with progressive tissue scarring and steadily declining function.

Based on these findings, we have constructed a conceptual schematic that describes the role of inflammation in the development of MSD (Fig. 4). Significant time points for behavioral indicators of tissue pathophysiology are included and highlight the gap between the typical moment of clinical intervention and the onset of possibly irreversible tissue damage. The schematic also indicates key time points for different kinds of interventions.

In relation to the theories of MSD development, our work and that of others lend credence to the over-exertion theory as both an initiating as well as a propagating injury stimulus. This is evident in even the LRNF group with the lowest load accumulation. While cumulative loading of viscoelastic tissues in the short-term may increase the likelihood that applied loads will result in tissue injury, it is nonetheless an over-exertion

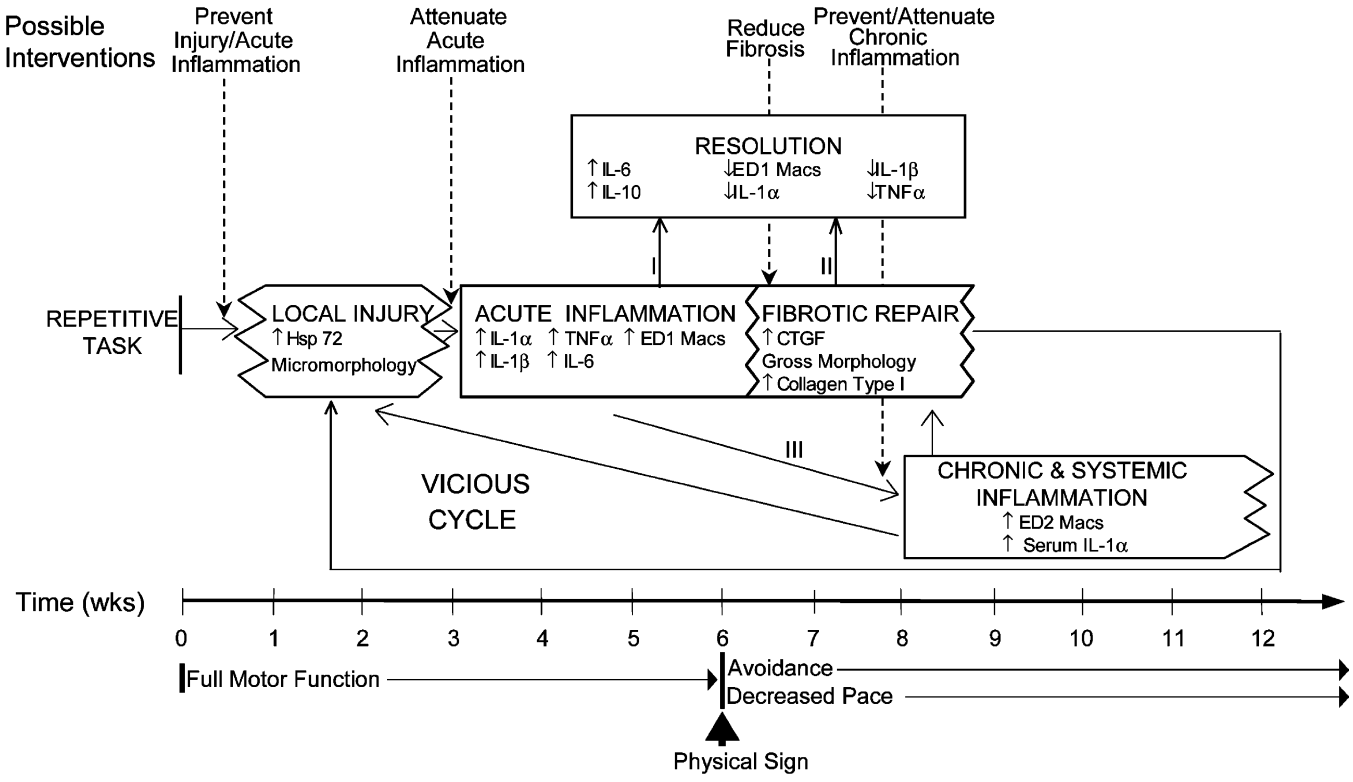

Fig. 4. Conceptual schematic showing the steps in inflammation-mediated development of MSD. The vertical zigzagged boundaries indicate uncertainty as to the specific time frame for transitions between progressive steps. The time line at the bottom of the figure relates these inflammatory events to observations of behavioral indicators in a rat model. At the top of the figure are indicators of key time points for specific types of possible clinical interventions. At the very bottom of the figure is indicated the physical sign (behavior degradation) that reflects underlying pathophysiology. Results from experiments using a rat model of upper extremity MSD [2,6–11,17,18] are listed at each step. The three possible exposure-dependent outcomes in this schematic are indicated as follows: I. acute inflammation followed by resolution and restoration of normal tissue, as in the LRNF group; II. acute inflammation followed by fibrotic repair, as in the HRNF group; and III. acute inflammation followed by chronic systemic inflammation, with or without fibrotic repair, and initiation of a vicious cycle of further injury and inflammation, as in the HRHF group. Note that the onset of tissue inflammation toward a pathway of potentially irreversible scarring may be already underway at the time of the physical sign, which may limit the effectiveness of clinical interventions in restoring normal tissue function. LRNF, low repetition, negligible force; HRNF, high repetition, negligible force; HRHF, high repetition, high force.

event that initiates an inflammatory response. Repeated bouts of injury, inflammation and fibrosis will eventually contribute to decreasing tissue tolerance over time such that lower levels of exertion will lead to tissue damage, which will further decrease tissue tolerance and functional performance. Thus, a vicious cycle of injury leading to long-term functional disability is established.

The observed systemic inflammatory response may further exacerbate the decline in tissue tolerance. As in other immune system responses, the presence of proinflammatory mediators, such as IL-1, in the serum means that these cytokines can be transported relatively rapidly to areas of localized injury. The sensitivity of the inflammatory response may increase when serum cytokines are present such that previously innocuous tissue insults may induce an acute inflammation in a shorter time course, thereby amplifying the inflammatory response. Therefore, not only tissue tolerance decreases over time, but it also fluctuates as localized and systemic inflammatory factors are stimulated and resolved. This change in tissue tolerance is characterized in Fig. 5.

Such decreasing tissue tolerance may explain why analyses of human tissue, such as flexor tendon synovium in carpal tunnel syndrome and extensor carpi radialis brevis tendon in lateral epicondylitis [1,23,30], do not find active acute inflammatory indicators, but instead find anti-inflammatory mediators and fibrotic proliferation. These patient populations are tested long after acute inflammation has resolved. While the designation of such soft tissue injuries as noninflammatory informs clinicians of effective treatments for patients seen so late in the process, we disagree that the early pathomechanical initiator of these conditions is noninflammatory. The mere presence of fibrotic tissues and anti-inflammatory mediators in the tissues of patients with MSD strongly suggests a preceding proinflammatory episode.

7. Future directions

Future experiments in animal models should investigate the long-term effects of continued task performance on the inflammatory cycle of MSD development. In addition, effective treatments can be predicted and tested in such animal models based on the nature (i.e., acute vs. chronic) of the inflammation at the various stages of MSD development depicted in Fig. 4.

Finally, investigators should look to transfer the knowledge gained from studying animal models to humans. Kuiper et al. [28] followed serum markers of Type I collagen synthesis prospectively among student nurses performing lifting tasks. The group with higher task exposures was found to have higher serum indicators of collagen synthesis, which indicates extracellular matrix remodeling in soft tissues. The presence of this marker in serum is consistent with a hypothesis of a serum-mediated increase in system response gain. Experiments in human subjects can be conducted to examine serum for inflammatory mediators with exposure to repetitive, forceful tasks. These kinds of experiments would enable investigators to relate work factors directly to the inflammatory response in order

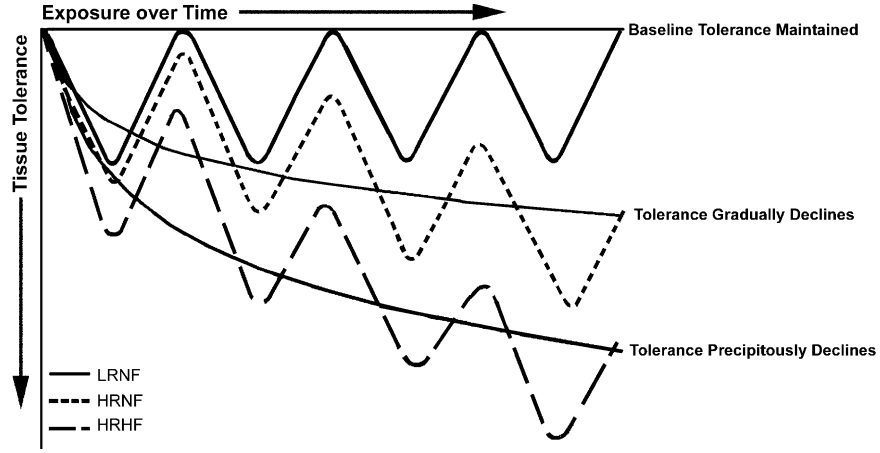

Fig. 5. Conceptual model of the hypothesized long-term effects of repeated tissue inflammation on tissue tolerance. This model is consistent with the overexertion theory of MSD development. In cases where the tissue exposure level remains below a critical threshold (upper curve, as in the LRNF group), repeated bouts of inflammation will be successful in resolving tissue disruption and restoring normal tissue tolerance through healing. When tissue exposure exceeds a critical threshold, incomplete tissue healing may result with subsequent reduction in tissue tolerance (lower two curves). Depending on the degree of exertion, this decline in tissue tolerance may be gradual (as in the HRNF group) or precipitous (as in the HRHF group). In addition to the overall decline in tissue tolerance, inflammatory episodes will result in transient periods of even lower tissue tolerance, resulting in the fluctuations in tissue tolerance depicted. The modification of tissue exposure level during these transient tissue tolerance minima may have an important impact on the maximization of tissue tolerance. LRNF, low repetition, negligible force; HRNF, high repetition, negligible force; HRHF, high repetition, high force.

to more fully understand the relationship between workplace risk factors, injury, and inflammation. With knowledge gained from animal studies of the tissue response that corresponds to the serum response, such studies may provide clinicians with clues as to the effectiveness of the treatments being provided to their patients. Another major step in the application of results from animal models would be the development of methods that permit the non-invasive measurement of inflammatory mediators in the working human. We look forward with excitement to the next phase of research in this area.

Acknowledgements

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Ann E. Barr, PT, PhD is an Assistant Professor in the Physical Therapy Department, College of Allied Health Professions, Temple University, Philadelphia, PA. In collaboration with colleagues in the Physical Therapy Department, Drs Mary Barbe and Brian Clark, as well as co-investigators in the Department of Anatomy and Cell Biology of Temple School of Medicine, Dr Barr conducts research in the area of work-related musculoskeletal disorders. She and her colleague, Dr. Barbe, have developed a novel in vivo injury model of work-related musculoskeletal disorder in the rat that encompasses the investigation of tendosynovial, musculoskeletal and nerve tissues in the context of a repetitive, posturally constrained, voluntary hand and wrist intensive motor task. Results of recent published studies indicate that work-related carpal musculoskeletal disorders develop through mechanisms that include injury, inflammation, fibrosis and subsequent nerve compression. These results have led to plans for the study of indicators of systemic inflammatory mediators in the serum of patients work-related musculoskeletal disorders. Her grant funding sources over the past several years include the Foundation for Physical Therapy, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Temple University. Her current funding is from the National Institute of Occupational Safety and Health (CDC).

Dr. Mary F. Barbe, PhD, Associate Professor, has a joint appointment in the Physical Therapy Department, College of Allied Health Professions and the Department of Anatomy and Cell Biology, School of Medicine, Temple University, Philadelphia, PA. In collaboration with Drs. Ann Barr and Brian Clark as well as investigators in the Department of Anatomy and Cell Biology, Dr Barbe uses a rat model of work-related musculoskeletal disorder to examine motor behavioral and pathophysiological changes associated with repetitive, forceful upper limb motor tasks. This model is used to examine the exposure-response relationship between motor task repetition rate and force and physiological and behavioral indicators of injury. Recent findings include tissue changes associated with inflammation in muscle, tendon, loose areolar connective tissue, synovial connective tissues and peripheral nerves throughout the reach limb, as well as signs of tendon fray in the flexors of the distal reach limb. There was also evidence that the inflammation was sytemic, which has led to plans for the study of indicators of systemic inflammatory mediators in the serum of patients with work-related musculoskeletal disorders. Her grant funding sources over the past several years include National Science Foundation, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Temple University. Her current funding is from the National Institute of Occupational Safety and Health (CDC).