Serum Biomarkers as Predictors of Stage of Work-related Musculoskeletal Disorders

Mary F. Barbe, PhD
Sean Gallagher, PhD, CPE
Steven N. Popoff, PhD

Musculoskeletal disorders (MSDs) are a leading worldwide cause of long-term pain and physical disability,[1] with diagnoses including tendinopathies, nerve compression syndromes, and muscular and joint disorders.[2,3] Studies in people with upper extremity work-related MSDs (WMSDs) find evidence of inflammation, fibrosis, and degeneration in serum and musculotendinous tissues, although the timing of each is unknown.[4-7] Serum biomarkers that might aid in pinpointing the stage of these disorders are being investigated.

Several risk factors have been identified, including forceful exertions, repetitive motion, and nonneutral body postures. A recent systematic review showed a consistent pattern of force-repetition interaction for musculoskeletal disorder risk, with low-force repetitive tasks demonstrating a modest increase in MSD risk, whereas high-force repetitive tasks result in rapid escalation in MSD risk, which is indicative of tissue fatigue failure.[8]

We have developed a rat model of voluntary reaching and handle-pulling for food reward,[9] in which reach rates and force levels were determined from epidemiologic studies. One goal of our laboratory is to identify biomarkers for monitoring disease progression of WMSDs and appropriate targeting of treatments. We recently examined whether serum inflammatory cytokines exhibit force × repetition interaction responses using this rat model.[10] Serum tumor necrosis factor–α (TNF-α) shows a significant force × repetition interaction (P = 0.0003) with task performance (Figure 1, A). No increases in TNF-α were seen in low-force groups, but high increases were observed in rats performing high-repetition, high-force tasks.[11-13] These results indicate that serum TNF-α follows the fatigue-failure theory during acute phases of ≤3 months. TNF-α and related cytokines may provide the best gauge of overall acute tissue damage resulting from repetitive, forceful exertions and may be the best biomarkers of this phase of WMSDs.

The timing of the inflammatory versus fibrotic responses with WMSDs is also of clinical interest. Studies have detected serum biomarkers of inflammation in patients with upper extremity WMSDs of short duration (≤3 months), including TNF-α,[4-6] again suggesting a role for inflammatory cytokines early in the course of upper extremity WMSDs. However, studies examining tissues from patients with upper extremity WMSDs during surgical intervention show increased tissue fibrogenic proteins and fibrotic histopathology, which is indicative of deranged extracellular matrix production and degeneration in tissues by this time point.[7]

Therefore, we extended our rat studies to examine the effects of performing a high-repetition, low-force task for 24 weeks. Serum TNF-α levels increased early after training but declined by week 18 (Figure 1, B). In contrast, serum interleukin-10 (IL-10), an anti-inflammatory cytokine, increased steadily until week 18. This may be

Topics from the frontiers of basic research presented by the Orthopaedic Research Society.

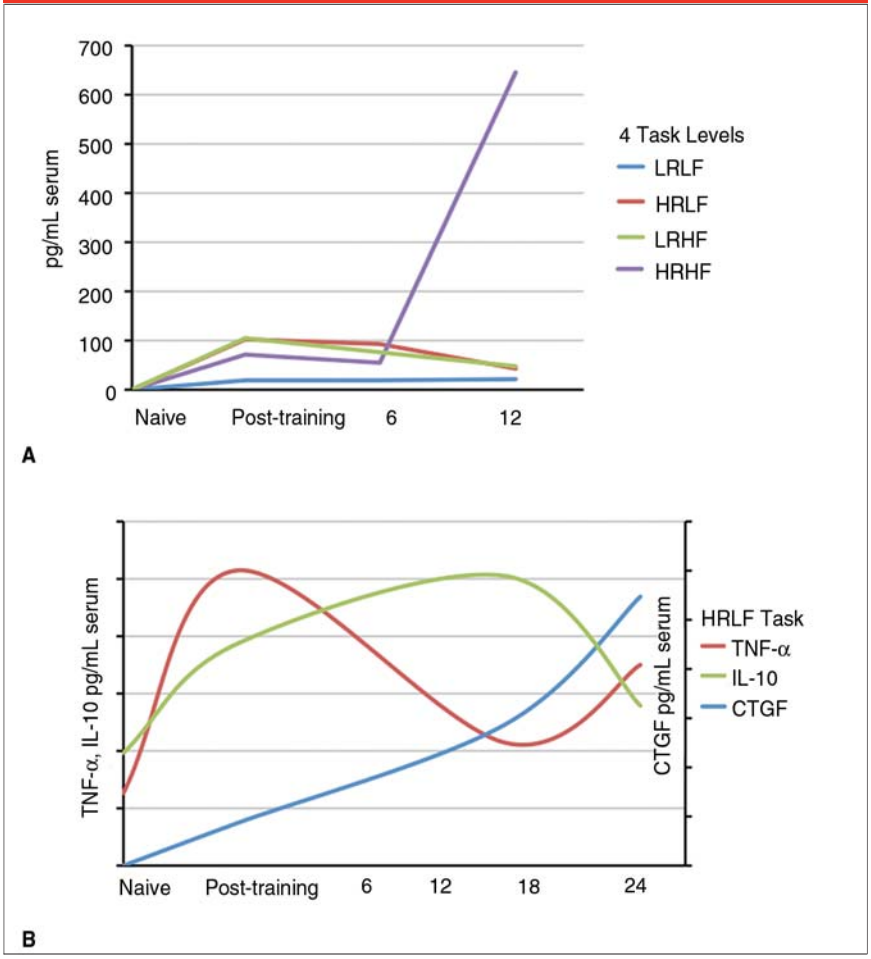
From the Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA (Dr. Barbe and Dr. Popoff), and the Department of Industrial and Systems Engineering, Auburn University, Auburn, AL (Dr. Gallagher).

None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Barbe, Dr. Gallagher, and Dr. Popoff.

J Am Acad Orthop Surg 2013;21: 644-646

http://dx.doi.org/10.5435/JAAOS-21-10-644

Figure 1



Graph of serum biomarkers in a rat model of upper extremity work-related musculoskeletal disorders. **A,** Serum levels of tumor necrosis factor (TNF)-α in rats performing one of four tasks for 12 weeks. **B,** Schematic illustration showing temporal changes in serum levels of TNF-α and interleukin-10 (IL-10) (left axis) and connective tissue growth factor (CTGF) (right axis) in rats performing high-repetition, low-force (HRLF) tasks for 24 weeks. HRHF = high-repetition, high-force; LRHF = low-repetition, high-force; LRLF = low-repetition, low-force

one reason for the decreasing TNF-α because IL-10 plays a key role in limiting immune responses.

We next examined serum for connective tissue growth factor (CTGF), an important mediator of fibrosis. Studies have shown that CTGF increases in tissues under conditions of overload or injury and that it is a key player in the pathogenesis of fibrosis.[14] We observed increased serum and tissue CTGF by week 24, compared with controls (P = 0.03) (Figure 1, B). It is known that transforming growth factor–β1 induces CTGF expression, leading to fibroblast proliferation and collagen deposition.[14] However, CTGF production is also regulated by TNF-α,[15] which is an interesting fact considering their temporal relationship (Figure 1, B). Importantly, because the CTGF level is normally low in sera of healthy individuals, it may serve as a predictive biomarker for patients in the fibrotic stage of WMSDs.

Our results indicate that most serum inflammatory cytokines, including TNF-α, demonstrate force-repetition interactions. These findings support the use of key pro-inflammatory cytokines as biomarkers of acute tissue damage and the fatigue failure hypothesis as a mechanism underlying WMSDs. We have also observed significantly increased serum and tissue CTGF levels that correlated with tissue fibrosis. Additional studies are underway to determine whether elevated CTGF is an essential mediator of fibrotic events. If so, one could envision CTGF as a potential therapeutic target to prevent fibrosis and reduced function and as a serum biomarker of tissue fibrogenic changes occurring with WMSDs.

References

1. Horton R: GBD 2010: Understanding disease, injury, and risk. *Lancet* 2012; 380(9859):2053-2054.
2. Piligian G, Herbert R, Hearns M, Dropkin J, Landsbergis P, Cherniack M: Evaluation and management of chronic work-related musculoskeletal disorders of the distal upper extremity. *Am J Ind Med* 2000;37(1):75-93.
3. Rempel D: Ergonomics: Prevention of work-related musculoskeletal disorders. *West J Med* 1992;156(4):409-410.
4. Carp SJ, Barbe MF, Winter KA, Amin M, Barr AE: Inflammatory biomarkers increase with severity of upper-extremity overuse disorders. *Clin Sci (Lond)* 2007; 112(5):305-314.
5. Rechardt M, Shiri R, Matikainen S, Viikari-Juntura E, Karppinen J, Alenius H: Soluble IL-1RII and IL-18 are associated with incipient upper extremity soft tissue disorders. *Cytokine* 2011; 54(2):149-153.
6. Riondino S, La Farina F, Martini F, Guadagni F, Ferroni P: Functional impairment in video terminal operators is related to low-grade inflammation. *Int Arch Occup Environ Health* 2011;84(7): 745-751.
7. Barbe MF, Barr AE: Inflammation and the pathophysiology of work-related musculoskeletal disorders. *Brain Behav Immun* 2006;20(5):423-429.
8. Gallagher S, Heberger JR: Examining the interaction of force and repetition on

musculoskeletal disorder risk: A systematic literature review. *Hum Factors* 2013;55(1):108-124.

9. Fedorczyk JM, Barr AE, Rani S, et al: Exposure-dependent increases in IL-1beta, substance P, CTGF, and tendinosis in flexor digitorum tendons with upper extremity repetitive strain injury. *J Orthop Res* 2010;28(3):298-307.

10. Gallagher S, Massicotte VS, Barr-Gillespie AE, Barbe MF: The interaction of force and repetition on systemic inflammatory cytokine response in a rat model. *Proceedings of the Human Factors and Ergonomics Society*, 2013, p 57.

11. Barbe MF, Elliott MB, Abdelmagid SM, et al: Serum and tissue cytokines and chemokines increase with repetitive upper extremity tasks. *J Orthop Res* 2008;26(10):1320-1326.

12. Rani S, Barbe MF, Barr AE, Litivn J: Role of TNF alpha and PLF in bone remodeling in a rat model of repetitive reaching and grasping. *J Cell Physiol* 2010;225(1):152-167.

13. Xin DL, Harris MY, Wade CK, Amin M, Barr AE, Barbe MF: Aging enhances serum cytokine response but not task-induced grip strength declines in a rat model of work-related musculoskeletal disorders. *BMC Musculoskelet Disord* 2011;12:63.

14. Leask A, Parapuram SK, Shi-Wen X, Abraham DJ: Connective tissue growth factor (CTGF, CCN2) gene regulation: A potent clinical bio-marker of fibroproliferative disease? *J Cell Commun Signal* 2009;3(2):89-94.

15. Beddy D, Mulsow J, Watson RW, Fitzpatrick JM, O'Connell PR: Expression and regulation of connective tissue growth factor by transforming growth factor beta and tumour necrosis factor alpha in fibroblasts isolated from strictures in patients with Crohn's disease. *Br J Surg* 2006;93(10):1290-1296.