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

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 non-neutral 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...
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. 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. However, CTGF production is also regulated by TNF-α, 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

8. Gallagher S, Heberger JR: Examining the interaction of force and repetition on


