Musculoskeletal disorders (MSDs) occurring as a result of prolonged repetitive and forceful work tasks are a leading cause of long-term pain and physical disability, and include diagnoses such as median nerve compression, tendinopathies, and musculotendinous fibrosis disorders. In 2010, MSDs accounted for 29% of all workplace injuries and illnesses in the U.S. requiring time away from work, and are estimated to cost over $61.2 billion annually. However, the pathophysiology of these disorders is incompletely understood. We hypothesize that motor declines are associated with chronic low-grade inflammatory responses, but also fibrotic and degradative changes in forearm muscles and tendons. We sought in this study to examine the relationship between grip strength declines and muscle-tendon responses induced by long-term performance (24 weeks) of a high-repetition, low-force (HRLF) reaching task in a rat model, and to identify biomarkers indicative of underlying tissue changes. We observed that grip strength declined after training, and further in weeks 18 and 24, in reach limbs of HRLF rats. These declines correlated inversely with increased IL-6 and IL-1beta levels in flexor digitorum tissues, and with levels of IL-6, IL-10, TNFalpha and MIP3 in serum. Four fibrogenic proteins, TGFB1, CTGF, PDGFab and PDGFbb also increased in serum in HRLF weeks 18 or 24, concomitant with thickened peritendon, increased tendon levels of TGFB1 and muscle CTGF. Lastly, serum and tendon levels of a degradative enzyme (MMP2, a collagenolytic gelatinase), increased in HRLF rats by week 18. Serum IL-6, TGFB1, CTGF and MMP2 correlated significantly with muscle or tendon increases. Thus, motor declines were associated with low-grade systemic and musculotendinous inflammation throughout task performance, and significantly increased fibrogenic and degradative proteins with prolonged task performance. Serum IL-6, TGFB1, CTGF and MMP2 served as serum biomarkers of these underlying tissue changes.