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Responsiveness of selected biomarkers of tissue damage to external load and frequency during repetitive lumbar flexion/extension

Marc Christian [a], Maury A. Nussbaum [a, b, *]

[a] Virginia Tech, Department of Industrial & Systems Engineering, 250 Durham Hall (0118), Blacksburg, VA 24061, USA
[b] Virginia Tech – Wake Forest School of Biomedical Engineering & Sciences, Blacksburg, VA, USA

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ABSTRACT

Quantifying biomarkers related to tissues commonly injured in occupational settings may be useful for exposure assessment or predicting injury risk. Here, serum levels of Cartilage Oligomeric Matrix Protein (COMP), Interleukin-6 (IL6), and Creatine Kinase (CK) were obtained before and after participants completed a repetitive lumbar flexion/extension task. The task was done for one hour, using five combinations of external load and frequency. COMP levels did not change over time or between exposure conditions. IL6 levels were significantly affected by time and by external load, while CK levels were significantly affected by the load × frequency interaction. Greater external load and frequency (for CK only) resulted in greater peak values of IL6 and CK, and both biomarkers recovered by 24 h after task completion. Since IL6 and CK levels exhibited a dose–response relationship to exposure levels, they may have potential use in the occupational domain.

Relevance to industry: This study investigated the effects of external load and frequency, during repetitive lumbar flexion/extension, on biomarkers that reflect tissue injury. Responses of biomarkers related to muscle use and damage (IL6 and CK) support earlier epidemiological evidence, and these may have future value in predicting occupational injury risk.

1. Introduction

Work-related musculoskeletal disorders (WMSDs) remain prevalent and continue to impose a substantial financial burden in numerous industries (Da Costa and Vieira, 2010). Lower back pain (LBP) and lower back disorders (LBDs) specifically account for the largest proportion of direct costs (Liberty Mutual Research Institute for Safety, Anon, 2013). Understanding the etiological risk factors and consequent physiological changes underlying LBP and LBDs is crucial to developing tools and/or methods that can identify high-risk jobs and/or tasks. Biomarkers, specifically those related to physiological damage, may be useful adjuncts to existing exposure and risk assessment methods, since by definition they are "[molecules] that can be objectively measured and evaluated as an indicator of a physiological…process" (Jain, 2010, pg. 1). Prior to integrating biomarkers in occupational settings, however, a clear understanding of the associations between risk factor exposure(s) and resulting biomarker levels is needed.

Early cadaver studies demonstrated that the likelihood of spinal tissue failure increased with greater load (Jäger and Luttmann, 1989), loading frequency (Yoganandan et al. 1994), and their interaction (Brinckmann et al. 1988). Similar dose–response relationships have been demonstrated in muscle tissue, where long-term exposure to high loads and repetitive tasks can result in histological changes such as cellular rupture (Kuipers, 1994; Brancaccio et al. 2010), tendon fraying (Barbe et al. 2003), and other structural abnormalities (Dennett and Fry, 1988). Epidemiological evidence has also associated exposure to high load and repetition with a greater risk of developing LBDs (Marras et al. 1995). Current tools used to assess LBP, LBD, and/or WMSD risk often incorporate an estimate of load and repetition rate, such as the Strain Index (Moore and Garg, 1995), Revised NIOSH Lifting Equation (Niosh, 1994), and Rapid Entire Body Assessment (Hignett and Mcatamney, 2000). While some evidence supports the use of these tools for identifying high-risk occupational tasks (Rucker and Moore, 2002; Waters et al. 2011), other evidence suggests limitations, specifically since there can be highly variable estimates of risk

* Corresponding author. Industrial and Systems Engineering, Virginia Tech, Blacksburg, VA, USA.
E-mail address: nussbaum@vt.edu (M.A. Nussbaum).

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levels between assessment tools for the same task (Lavender et al. 1999; Drinkaus et al. 2003). Biomarkers derived from the tissues commonly injured in WMSDs, and more specifically LBP and LBDs, may overcome at least some limitations of current methods, since biomarkers can objectively determine physiological changes (Carp et al. 2008; Jain, 2010). Initial work is needed, however, to verify the sensitivity, specificity, and predictive validity of biomarkers in the occupational context.

Injury to soft tissues, such as cartilage and muscle, is a common etiological factor underlying many WMSDs (Kumar 2001), and levels of three particular biomarkers derived from cartilage and muscle have been shown to be sensitive to physical exposures. Cartilage Oligomeric Matrix Protein (*COMP*) is expressed in cartilage tissue via a mechanosensitive promoter region, wherein it functions to provide mechanical strength to collagen fibers (Giannoni et al. 2003; Amanatullah et al. 2012). Diverse forms of physical activities have been found to increase COMP levels, including walking and running tasks (Mündermann et al. 2005; Kim et al. 2007, 2009; Niehoff et al. 2010) and repeated drop landings (Niehoff et al. 2011), and longitudinally over the course of an athletic season in soccer players (Hoch et al. 2012). This evidence indicates COMP sensitivity to both acute and more prolonged cartilage loading. Interleukin-6 (*IL6*) is a systemic cytokine released from muscle tissue, proportionally to the volume utilized, following exposure to damaging and non-damaging exercise, where it has both pro- and anti-inflammatory effects, respectively (Reihmane and Dela, 2013). The main source of systemic IL6 levels following exercise is contracting muscle tissue (Keller et al. 2005). Consistent with this, diverse forms of physical activity result in increased IL6 levels, including running (Reihmane et al. 2012) and cycling (Toft et al. 2002) in humans, and repetitive reaching in rats (Barbe et al. 2008). The enzyme Creatine Kinase (*CK*) is found primarily in muscle cells, where it buffers cellular phosphate molecules. Consequently, CK leaks into the systemic blood supply in proportion to the mass of muscle tissue that is injured during eccentric contractions (Brancaccio et al. 2010). Multiple studies have demonstrated that CK increases relative to the intensity of muscle exercise (Toft et al. 2002; Kim et al. 2009; Yang et al. 2011), and CK levels also correlate with the intensity of delayed onset muscle soreness (Chen et al. 2013). Despite a clear relationship with several forms of physical demands, additional studies are needed to evaluate the effects of occupationally-relevant levels and types of physical exposures on biomarkers, before these biomarkers can be considered feasible for predicting LBP, LBD, and WMSD risk.

Several recent studies have assessed changes in biomarkers in response to controlled exposure parameters relevant to occupational tasks, specifically load and frequency. Barbe et al. (2008, 2013) investigated the effect of repetitive reaching on biomarkers of injury in rats. The former study specifically varied repetition rate and found that higher repetition rate led to significantly greater systemic and tissue levels of inflammatory markers (Barbe et al. 2008). The latter study expanded upon this by varying the level of force. An interactive effect of repetition rate and force was found, with high force and high repetition rate yielding greater systemic and tissue levels of inflammatory markers (Barbe et al. 2013). Both studies also used histological results to verify the presence of tissue damage in connective and muscle tissue. Other work, by Splittstoesser et al. (2012) and Yang et al. (2011), examined biomarker levels following exposure to a 2-h lifting task among humans. The lifting task elicited significant increases in IL6 and CK (and other biomarkers) from baseline levels (Splittstoesser et al. 2012). The latter study found that IL6 and CK levels increased by ~2.5 pg/ml and 3–5 fold, respectively, after lifting an 11.3 kg box repeatedly for two hours (Yang et al. 2011).

Both of these sets of studies demonstrate important relationships between occupationally-relevant task parameters (e.g., load and frequency) and biomarker levels indicative of tissue damage, however there are some limitations which drove the design of the work presented here. Studies performed in rats have several advantages (e.g., a highly controlled setting and the ability to harvest tissues specifically involved in the task), yet generalizability to humans performing occupational tasks is uncertain. The noted lifting studies using humans overcome both of these concerns. Yet, these lifting studies involved physical demands in multiple body regions, and it is thus unclear whether systemic levels of biomarkers are influenced specifically (or in a dose–response fashion) by loading of tissues in the lower back. Determining the systemic biomarker contribution of tissues in the lower back during lifting tasks was considered to be of particular importance, given the high prevalence and costs of occupational injuries to these tissues. To the authors' knowledge, however, no study to date has investigated the effects of both external load and frequency on these biomarkers in humans, using an experimental setup designed to emphasize responses in the lower back tissues.

In summary, existing evidence suggests that changes in biomarkers derived from tissues commonly involved in LBP, LBDs, and/or WMSDs more generally has the potential to reflect underlying physiological damage. The purpose of the current study was to examine changes in three biomarkers (COMP, IL6, and CK) in response to loading of the lower back tissues at different levels of external load and frequency. A constrained lumbar flexion/extension task was employed, and was used to partially isolate physical loads to tissues in the lower back. To enhance external validity, occupationally-relevant levels of the task parameters (external load and frequency) were used. We hypothesized that task-induced changes in biomarkers levels would differ significantly with external load and repetition rate, and with possible interactive effects. Results of this study were intended to aid in understanding the influence of occupational risk factors on tissue responses, specifically in the lower back, and to inform future work investigating the use of biomarkers in occupational settings.

2. Methods

2.1. Overview

A repeated-measures design was used, involving one preliminary session and five experimental sessions. In each experimental session, participants completed a task requiring repeated lumbar flexion/extension, and which was done in five distinct conditions of external load and task frequency. Blood samples were obtained before, after, and during recovery from the task, and these samples were assayed for levels of COMP, IL6, and CK. All sessions were separated by a minimum of one week, to allow biomarkers to subside from previous experimental exposures (Toft et al. 2002; Kim et al. 2009) and to minimize a repeated bout effect for CK (Chen et al. 2013), thereby reducing potential carryover effects.

2.2. Participants

Six participants (two females, four males) were recruited from among the local student population as a convenience sample. Mean (SD) age and body mass index (BMI) were 23.7 (2.2) years and 23.5 (1.9) kg/m^2 respectively. Participants were required to have BMI < 25, and this restriction was used to accommodate constraints of the experimental apparatus (described below). To avoid the influences of pre-existing medical conditions and/or medications, participants were excluded based on the self-reported presence of: anemia, diabetes, inflammatory conditions (arthritis, Crohn's