Biomarker Changes over a Working Week in High Physical Stress Jobs

Marc Christian[1] and Maury A. Nussbaum[1,2]

[1]Department of Industrial & Systems Engineering, Virginia Tech, Blacksburg, VA USA
[2]Virginia Tech – Wake Forest School of Biomedical Engineering & Sciences, Blacksburg, VA USA

A proposal for funding by the OSHRC

A. Significance

Background - Work-related musculoskeletal disorders (WMSDs) continue to be prevalent and costly. According to a conservative NIOSH estimate, the costs attributed to WMSDs total >$13 billion/year [1]. Overexertion remains the top cause of occupational injuries, involving nearly 25% of the total number [2]. Lifetime incidence rates of low-back pain (LBP) specifically are about 80-85% in industrialized countries [3], though these rates vary substantial between industry sectors and genders. Male construction workers contribute the most cases, with an overall WMSD prevalence of 17.6% [4], and the majority of cases (54%) involving the lower back pain [5]. These problems present a significant burden to individual workers, the construction industry, and the medical system.

Diverse ergonomic/biomechanical approaches exist to estimate occupational LBP risks, given a measurement or estimation of task exposure. Psychophysiological methods are often used to subjectively assess a worker's ability to perform a task [6], or the resulting discomfort [7], in an attempt to determine risk of injury. The primary limitations of these methods are the large inter-individual variability [8] and unclear relation to true tissue damage [9]. Physiological assessments rely on measures of physical, chemical, or biological factors influenced by physical stress [10], to establish exposure limits that minimize the potential for injury. Again, however, the specific relationships with injury risk are largely unknown. Physical methods are often used, for example to determine loads on the spine and other kinetic/kinematic variables such as force, repetition, angle, etc. [11]. While some of these factors have been associated with increased risk of injury [12], generalization of exposure limits is difficult due to variable tissue tolerances between people. A method that can overcome the limitations of current methods by directly and objectively assessing physiological damage, especially when it is sub-clinical, would be of substantial benefit in predicting and ultimately controlling WMSDs.

Biomarkers: A Potential Tool for WMSD Risk Assessment - Biomarkers are molecules that, "can be objectively measured and evaluated as an indicator of physiological change" (pg. 1) [13]. Currently, their main use in physiological medicine centers on measuring injury recovery and tracking disease progression [14-16]. Recent reviews suggest that select biomarkers are released into the systemic blood supply following short term injury of joints, muscles, and connective tissues, due to the rupture of cells, thus providing a valid measure of physical injury [17, 18]. The origin and biological purpose of a biomarker can also indicate more specific injury characteristics [19, 20], and by measuring levels of specific biomarkers we may be able to evaluate the extent and type of injury following physically demanding tasks. However, some fundamental aspects of biomarker responses have yet to be investigated, representing a current impediment to eventual occupational application.

A recent OSHRC pilot grant allowed us to begin to investigate natural diurnal changes in biomarkers, which is important as earlier work has suggested the importance of time-of-day when interpreting biomarker levels [21, 22]. This pilot work also began to assess the influence of personal factors such as age, weight, and physical lifestyle [17], which have been shown to influence baseline biomarker levels. Accounting for these factors in future studies is critical to minimizing confounding, and validly associating biomarker changes with tissue damage. In this pilot work, participants in young (18-30yrs), old (50-65yrs), normal weight (BMI: 18.5-25), and obese (BMI: 30-40) categories were recruited and followed over 24hrs, with 6 blood draws occurring at approximately even intervals. The preliminary results (see Fig. 1) suggest important diurnal changes, and that these are influenced by BMI. An eventual NIOSH proposal is planned to expand participant numbers so that age and gender can be accounted for as well. Sensitive and relative biomarker changes have also been observed due to various physical exertion levels [23-25]. Establishing these differences in working populations, and assessing sensitivity to differing physical work demands, is needed before biomarkers can be related to

injury risk. By investigating these issues, we can help to establish biomarkers as a valid tool for determining injury risk.

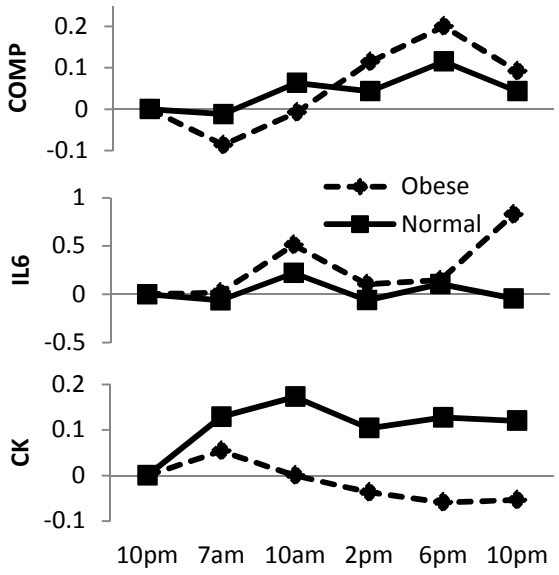

Figure 1. Fold changes for COMP, IL6, and CK over 24hrs between 7 normal-weight and 9 obese people.

Conclusions and Proposed Work - While current methods for assessing WMSD risks have had numerous benefits, a number of important limitations remain. Use of biomarkers to predict such risk is a potential alternative, since it is a relatively non-invasive method that uses objective and quantitative measures that are directly related to physical damage. Recent studies have demonstrated a mechanosensitive change in biomarker levels following task exposure (see below), supporting the feasibility of using biomarkers in the occupational domain. At present, though, the occupational use of biomarkers is hindered by a lack of knowledge concerning basic properties. These include the effect of time of day and personal factors, which our noted pilot work has begun to explore. In addition, though, work is needed to assess the level of sensitivity of biomarkers to differences in occupational physical exposures. Assessing this sensitivity is considered a critical step to support future use of biomarkers in the workplace, and to this end we propose a second preliminary study.

In the **Proposed Work**, *we will quantify biomarker changes throughout a working week, and assess biomarker sensitivity by comparing results between physically active worker groups and a sedentary population*. As discussed above, short-term studies have shown that physical activity leads to altered biomarker levels. By observing changes throughout the week, we can determine if there are measurable differences in markers of physiological damage between the groups, thereby supporting the applicability of biomarkers within the workplace. This study will help lay the foundation for future prospective studies that will seek to associate biomarker changes with the incidence of WMSDs.

NORA Priority Research Areas - The proposed research addresses three NORA Priority Research Areas: **Low Back Disorders**, **Exposure Assessment Methods**, and **Risk Assessment Methods**. Within the **National Construction Agenda**, we specifically address the topic of **Musculoskeletal Disorders**, subsections 7.3 and 7.4, which aim to develop practical methods for assessing exposure and associating exposure with development of WMSDs [26].

B. Innovation

The use of biomarkers to assess physically demanding work is quite new, with very limited existing evidence reported. Biomarkers allow for a specific and quantitative individual analysis of physiological damage due to workplace tasks, and show high potential in predicting future risk of injury, due to a direct relation to physiological damage. This project will investigate a fundamental property of biomarkers, which has yet to be explored in humans (i.e., sensitivity to workplace physical demands). Results from the proposed study, along with our earlier pilot work, will help lay a foundation for a more widespread use of biomarkers in the workplace. Using biomarkers provides several potential advantages over current methodologies, as

described above. In the future, it is likely that these can be combined with existing ergonomic/biomechanical methods to develop innovative approaches to assessing and controlling WMSD risks.

C. Approach

The purpose of this study is to determine whether selected biomarkers are sensitive to occupational physical demands. We propose to examine *three specific biomarkers*: Cartilage oligomeric matrix protein (COMP), Interleukin-6 (IL6), and Creatine phosphokinase (CPK). Each of these biomarkers gives insight into a unique aspect of physiological damage, respectively to cartilage, collagen, and muscle.

With injury to collagenous tissue, changes in several biomarkers have been observed [27-29]. Cartilage oligomeric matrix protein (COMP) is a molecule that is produced ubiquitously in high-collagen tissues [30]. At a molecular level, COMP binds to collagen fibers, helping to anchor them and providing additional mechanical strength [31]. There is a mechanosensitive increase of COMP with respect to differential loading protocols [23, 32], which corresponds to an increased need for mechanical strength. Interleukin-6 (IL6) is an inflammatory protein that is up-regulated and released into the bloodstream in correspondence to the volume and duration of muscle mass use [20]. Additionally, IL6 appears to induce production of collagen fibers [28], which will increase mechanical strength of tissues similarly to COMP. Together, these two biomarkers provide insight into the state of collagenous tissue following mechanical exposure, and thus lend themselves well to use as predictive biomarkers for repetitive and overuse injuries.

Muscles are the crucial structure of the body that provide strength and force for movement. Although controlled damage, known as 'microtrauma', has beneficial effects such as in weight training [33], debilitating injuries due to overexertion injuries are common [34]. Creatine phosphokinase (CPK) is an muscle localized enzyme that buffers phosphate molecules required for force production [35]. During injury, muscle cells rupture, thus leaking CPK into the blood supply [36]. Eccentric muscle exercise is especially damaging and greatly increases CPK concentrations in the blood [37, 38]. Yang et. al [24] showed a clear dose-response relationship of IL6 and CPK with hand-held loads during a 2hr lifting task. Thus, while IL6 can be used as a measure of total muscle use, CPK indicates physical damage.

Proposed Work – Sensitivity of Biomarkers to Occupational Physical Demands

The purpose of this study is to determine if biomarker levels are sensitive to occupational physical demands, by comparing these levels among two groups. Specifically, we will assess levels among sedentary workers and a population with high levels of routine physical demands and risks of LBP (i.e., construction workers). Existing evidence is rather limited. One study positively associated IL6, along with other biomarkers of physiological damage, with increased upper-body musculoskeletal use [39], while another demonstrated that markers of collagen degradation were associated with lower-limb disorders [40]. In addition, a recent study showed dose-response relationships with load weight in the context of simulated manual material handling [24]. Our proposed work expands upon this evidence, by quantifying trends in biomarker levels across a working week (e.g., biomarker accumulation, and the effect of nightly rest). Future longitudinal studies can then investigate biomarker levels and incidence of WMSDs. Our **hypotheses** in this Study are that **1) different changes in biomarker levels will be observed between sedentary and active population, both within days and across a**

working week, **2) these differences will be associated with the amount of physical work performed and perceived discomfort ratings in isolated body areas**.

Design and Methods – A total of 16 participants will be recruited for a 5-day procedure. This sample size is based on what can be completed with requested and available funds. Participants will include eight individuals recruited from each of two job sectors: construction and sedentary. Before beginning the procedure, participants will provide informed consent and complete the validated International Physical Activity Questionnaire (long form). This questionnaire will be used to classify individuals as physically active (3 days/week with a total of 1500 MET-min/week, *or* 7 days/week with a total of 3000 MET-min/week) or sedentary (anything below physically active criteria) [41, 42]. A background questionnaire will be used to determine individual characteristics, such as age, gender, BMI, and history of musculoskeletal disorders.

Monday, Wednesday, and Friday, both before and after work, a blood sample will be obtained (this schedule assumes a "normal" work week). After each work shift, regional discomfort ratings [7] will be assessed for the major body areas addressed in the Standardized Nordic Questionnaire [43]. The Hollmann questionnaire will also be used to assess physical workload with respect to biomechanics of the lumbar region [44]. Between sample days, participants will be requested to perform their jobs normally. Over a working week, 6 blood samples and sets of questionnaires will thus be obtained.

Participants will be asked to restrict their physical activity outside of their job during the weekend prior to and the week of the study. The Monday morning draw will thus act as a baseline level. Participants in the physically active populations will be recruited from the local region, including local construction companies. Predominantly male construction workers are expected, though we will not exclude females. Workers in sedentary jobs will be recruited from VT and the local region, and, to the extent possible will be matched to the construction group in terms of gender, age, and anthropometry. Exclusion criteria include having any current or recent (within 3 years) history of musculoskeletal disorders, any inflammatory, heart, or blood-borne diseases, current smokers, diabetics, excessive anti-inflammatory drug use, and those who are anemic.

Analysis - Blood samples will be spun down immediately following a draw to obtain serum and frozen at -20C until analysis. Biomarker concentrations will be determined from serum samples for each time point using enzyme linked immunosorbent assays (ELISA): 1) COMP (BioVendor®, Chandler, NC); 2) IL-6 (BioVendor®, Chandler, NC); and 3) CPK (Antibodies-Online®, Atlanta, GA). As in previous studies, concentration levels will also be normalized ([baseline-timepoint]/baseline). Mixed-factor ANOVAs will be employed to assess the effects of time and group on the *dependent variables* (biomarker concentrations, normalized change values, perceived discomfort ratings, and reported job physical stress levels). We will also explore, using regression, the associations between biomarker responses, perceived discomfort rating, and reported physical workload. Significant effects will be concluded when $p<0.05$.

Based on earlier evidence, and consistent with **hypothesis 1**, we expect to find consistent patterns in biomarkers throughout the working week. Specifically, increases in biomarkers levels are expected over the course of the week, with (incomplete) reductions found in the morning samples. We also expect to find larger increases and less complete reductions in biomarkers among the high physical workload groups (**hypothesis 2**). Finally, we expect that patterns in biomarker changes will be directly associated with similar patterns of physical workload and perceived discomfort.

Limitations - A potential limitation of this work is that there are many other factors that could influence biomarker levels but that are not controlled (e.g. caloric intake, amount of prior sleep). However, we have selected biomarkers that are primarily associated with cartilage damage,

collagen synthesis, and muscle use/damage, which should minimize these potential confounding effects. Physical activity outside of work could also influence biomarker levels, though we are attempting to minimize this by asking participants to restrict their activity outside of work.

Expected Results and Contribution

The main purpose of this study is to contribute to the future use of biomarkers as an occupational tool to measure and control the risk of WMSDs. In industrialized countries, WMSDs in general and low back disorders specifically are prevalent and costly problems. These conditions are strongly associated with strenuous lifting activities [45] and more generally physically demanding occupations. Current methods do not allow for a direct and objective quantification of physiological injury. By using biomarkers, perhaps in concert with current methods, we may gain more insight into the extent and source of physical damage related to occupational physical demands and develop better methods to control these adverse outcomes. The proposed study will provide fundamental new information about biomarker changes associated with strenuous physical work, which can then be used to better interpret and/or design future studies. Changes over a working week will also demonstrate the applicability of biomarkers in the workplace, while associations with perceived discomfort and physical workload will speak to their sensitivity. The proposed work will help provide a strong foundation for this budding area of using biomarkers in an industrial setting.

Deliverables

As described in the RFP, we will provide updates as requested, a summary upon completion, and professional poster. We plan to use the preliminary results generated in from this proposal and those from the diurnal study (Fig. 1 and below) as the basis for a proposal to NIOSH (e.g., R21-type).

D. Prior OSHRC Funding

We received a Kevin Granata Pilot Grant in the February RFP, for $8,000. In this, we proposed to do small-scale preliminary work to examine both diurnal changes in biomarkers and to assess sensitivity to occupational physical demands. Due to the large inter-individual variability we found in the diurnal patterns we decided to expand those participant numbers. Thus, all pilot project funds (and personal funding supplied by the PI) were used to investigate the diurnal changes demonstrated in Fig. 1, which Figure shows only a subset of the results (analysis is ongoing). The present funding is sought to complete pilot work on sensitivity

E. References

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F. Budget

Itemized budget:

-6 ELISA kits:

2 x COMP ($555, http://www.biovendor.com/country30/product/immunoassays/cartilage-oligomeric-matrix-protein-human-elisa) $1,110.00

2 x IL6 ($595, http://www.biovendor.com/country30/product/immunoassays/interleukin-6-human-elisa) $1,190.00

2 x CPK ($757.14, http://www.antibodies-online.com/kit/626365/Creatine+Kinase+CK+ELISA/) $1,514.28

TOTAL: **$3,814.28**

-Shipping for ELISA kits:

6 x one-day, on ice shipping..... **~$185.72**

-Participant compensation:

16 x $100 ($15/blood draw + $10 for completion)..... $1,600.00

Total funding requested from OSHRC.....$5,600.00

Budget justification:

ELISA kits:

-Each ELISA kit can run 40 samples, which means we have (2kits/biomarker * 40samples/kit =) **80 samples/biomarker**.

-Study has 16 participants, at 6 samples each, i.e. (13 x 6 =) **96 samples**

-ELISA kits are currently the cheapest method for determining levels of specific enzymes, proteins, and molecules. The detection limits for COMP, IL6, and CPK are 0.4ng/ml, 0.92 pg/ml, and 0.1ng/ml

respectively, which are excellent for our application. We minimize the cost by performing all the analyses in house. Dr. Kevin Edgar has generously lent us a lab bench to use in the ICTAS 1 building. Even the graduate student in charge of performing the data collection has been certified as a phlebotomist.

-Shipping for the ELISA kits is generally expensive. Since each kit is only produced on request/order, they are shipped out as soon as they become available. Thus each kit is usually shipped separately. In addition, the kits are shipped via one-day express, and require special cooling packaging. Contents of the kits can degrade in high temperatures. This usually adds on substantial costs.

****Note on the budget:**

Substantially more resources are required to complete the work proposed here, including funds for phlebotomy supplies, lab supplies, conference travel, etc. We are requesting that just the ELISA kits and participant compensation be funded, and the remaining costs will be covered by the PI (Nussbaum).

G. Timeline and Project Management

	2012		2013							
	N	D	J	F	M	A	M	J	J	A
Study 1										
Recruitment										
Testing										
Analysis										
Reporting										

Dr. Maury Nussbaum will serve as the PI for this project. He is the primary advisory to Marc Christian, a graduate student in ISE, whose dissertation work will be addressing the use and application of biomarkers in the occupational setting. Mr. Christian will have a primary role in collecting, processing, and analyzing the study results, as well as in report and paper generation.