The XXV Annual Occupational Ergonomics and Safety Conference
Atlanta, GA, USA
June 6-7, 2013

Biomarkers as a Potential Tool for Assessing Work-Related Musculoskeletal Disorder Risk

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

Corresponding author's Email: nussbaum@vt.edu

Author Note: Marc Christian is a current PhD student in the Industrial and Systems Engineering program at Virginia Tech. He received his bachelor degree in biochemistry and mathematics from the College of Wooster. Biomarkers, and their potential use in the workplace, are the focus of his current dissertation research. Maury Nussbaum is a Professor of Industrial and Systems Engineering at Virginia Tech. His research addresses occupational injury prevention and consumer product design. Please send requests to: Dr. Maury Nussbaum, 250 Durham Hall (0118), Blacksburg, VA 24061.

Abstract: In excess of three million work-related musculoskeletal disorders (WMSDs) occur annually in the US, resulting in a total annual cost of approximately $200 billion. These clearly represent a substantial burden to individuals, industry, and the medical system. Overexertion injuries comprise the largest percentage of WMSDs (~25%), whose origin can be often traced to an inability of biological tissue to tolerate a given load. Many current methods for assessing WMSD risks have not formally been evaluated for predictive validity, and thus their outputs have an unclear relation to physiological tissue damage. This limitation presents a current impediment in our ability to accurately assess occupational tasks in terms of WMSD risk. Biomarkers, however, can provide objective measures or indicators of physiological change, and growing evidence suggests that the origins, biological purposes, and levels of specific biomarkers can provide particular information regarding the state (or status) of collagenous and muscular tissue. These biomarkers may thus be helpful in assessing WMSD risk by identifying tissue damage, especially when it is sub-clinical, and the use of biomarkers may overcome some shortcomings of current ergonomic methods. However, there are several limitations in current knowledge regarding these biomarkers, and workplace-related impediments to their use, which must be addressed prior to their eventual application. This review will highlight the current state of knowledge concerning select biomarkers of collagen and muscle damage with regard to their potential advantages, research gaps limiting their current use, how and where biomarkers could be used in ergonomic evaluations, and workplace considerations necessary prior to implementing biomarkers as a WMSD risk assessment method.

Keywords: biomarker, musculoskeletal disorder, cartilage, interleukin, creatine kinase

1. INTRODUCTION

Work-related musculoskeletal disorders (WMSDs) continue to present a substantial economic burden for employers, workers' compensation, the medical system, and adverse health effects on employees. In 2011 alone, about 3 million workplace injuries were reported in the US (BLS, 2011). Among these, overexertion injuries in particular accounted for the majority of WMSDs (~25%), with indirect costs estimated as high as $200 billion (da Costa & Vieira, 2010). Diverse tools have been developed to assess workplace tasks, but discrepancies between prevailing theories of injury causation and risk assessment methods suggest limitations in their sensitivity and specificity.

Current theory suggests that overexertion injuries are caused primarily by an inability of body tissues to withstand a given load (Kumar, 2001). Such a direct relationship, though, is complicated by potential decreases in tissue tolerance over time (Marras, 2000) and influences of diverse personal factors such as psychological state, age, gender, and obesity (Steering Committee for the Workshop on Work-Related Musculoskeletal Injuries, 1998). Many tissue tolerance limits stem from *in vitro* studies of muscles, vertebrae, and connective tissues (Brinckmann & Hilweg, 1989; Noyes, 1977). Despite general agreement that the etiology of overexertion injuries is multivariate in nature (da Costa & Vieira, 2010; Marras, 2000), few current exposure and risk assessment methods account for multiple causal pathways. Compounding the difficulty of determining causation, sub-clinical WMSDs often lack pathological symptoms, making their identification prior to injury more difficult (Vällfors, 1985). These discrepancies between pathways of injury causation and risk assessment methods may limit the applicability of current methods to accurately determine WMSD risk.

2. BACKGROUND ON BIOMARKERS

Biomarkers are defined as molecules or proteins "that can be objectively measured and evaluated as an indicator of physiological change" (Jain, 2010, pg. 1), and are closely aligned with theories of WMSD causation. Since changes in select biomarkers can indicate sub-clinical physiological injury, they may act as surrogates for the "gold standards" that involve costly imaging technologies and invasive tissue biopsies. Three biomarkers will be discussed here: Cartilage oligomeric matrix protein (COMP), Interleukin-6 (IL6), and Creatine kinase (CK), as these are a primary current research focus of the authors, and their biological roles are relatively well established. It should be noted, though, that myriad other biomarkers exist.

COMP is a protein endemic to cartilagenous tissue, the main purpose of which appears to be the stabilization of collagen fibers to support the extracellular matrix under mechanical stress (Muller, Michel, & Altenburg, 1998). Cartilage degrades under mechanical stress, which ruptures cells and triggers the release of COMP into the bloodstream (Neidhart et al., 1997), while simultaneously a mechanosensitive promoter region responds by inducing COMP synthesis in cartilage tissue (Amanatullah et al., 2012), replenishing the supply to provide additional mechanical strength. A number of studies have demonstrated that COMP levels are sensitive to physical loading, for example during running (Kim, Lee, & Kim, 2007), walking (Mündermann, Dyrby, Andriacchi, & King, 2005), and drop landings (Erhart-Hledik et al., 2012). Thus, COMP is considered appropriate to represent the state of cartilagenous tissue, and temporal changes in COMP may help predict future cartilage injury.

Inflammatory cytokines, such as IL6, commonly act as signaling molecules, inducing both pro- and anti-inflammatory effects to aid recovery (Nielsen & Pedersen, 2007). The source of the majority of systemic IL6 has been traced to active muscle (Toft, Falahati, & Steensberg, 2011), where its expression is proportional to the intensity, duration, and mass of muscle used (Pedersen & Febbraio, 2008). The purpose of IL6 is to suppress previously expressed inflammatory proteins (Starkie, Ostrowski, Jauffred, Febbraio, & Pedersen, 2003) and to induce collagen synthesis in tendons to aid recovery (Andersen, Pingel, Kjaer, & Langberg, 2011). Increases in IL6 expression have been demonstrated in conjunction with general exercise (Wallberg, Mikael Mattsson, Enqvist, & Ekblom, 2011), cyclic loading of the lumbar spine in felines (D'Ambrosia et al., 2010) and humans (Yang, Marras, & Best, 2011), and in various types of lumbar disc herniation (Takahashi et al., 1996). IL6 expression has also been correlated with the severity of upper-extremity WMSDs (Carp, Barbe, Winter, Amin, & Barr, 2007), making it a promising candidate for identifying sub-clinical muscle damage, inflammation, and WMSD risk.

CK has long been used in the medical community (Jain, 2010), as it is a muscle-specific enzyme that is released into the bloodstream following eccentrically induced cell rupture (Newham, Jones, & Edwards, 1986). Consistent with this, transient CK increases have been shown throughout a marathon race proportional to the distance covered (Kim, Lee, & Kim, 2009) and in response to repetitive lifting (Splittstoesser, Marras, & Best, 2012; Yang et al., 2011). Furthermore, CK levels are often correlated with ratings of delayed onset muscle soreness (Magal et al., 2010). One study demonstrated that CK may even be a more reliable indicator of muscle damage than magnetic resonance imaging (Sorichter et al., 1995). Such evidence suggests that CK is a useful indicator of muscle damage that, in combination with IL6, indicates the state of muscle tissue.

3. POTENTIAL CONFOUNDING FACTORS OF BIOMARKERS

Despite the observed changes in COMP, IL6, and CK following exposure to WMSD risk factors discussed above, the complexity of biological signaling pathways suggests that biomarkers are likely to be influenced by other factors besides physical stress, for example age, obesity, and gender. If biomarkers are to be used in the workplace as a WMSD risk assessment tool, they should be able to account for differences between workers as well as the tasks they perform.

Numerous health decrements are associated with the process of ageing, such as a decreased muscle capacity (Degens & Korhonen, 2012), bone mineral content (Gomez-Cabello, Ara, Gonzalez-Aguero, Casajus, & Vicente-Rodriguaz, 2012), general low-grade systemic inflammation (Pedersen et al., 2000), and an overall impaired tissue recovery ability (Uciechowski & Rink, 2009). Older adults generally have higher baseline levels of IL6 and a blunted peak value of CK compared to younger adults following eccentric exercise (Toft et al., 2002). While age-related changes in COMP levels have not been studied, it has been suggested as a biomarker of age-associated arthritis (Zivanovic et al., 2011).

Obesity, defined as a BMI $\geq$ 30, is correlated with increased biomechanical stresses, and there is medical evidence for increased systemic inflammation and inhibited tissue repair capacity due to the abundance and volume of adipose tissue (Nieman et al., 1999). BMI was the attribute most highly correlated with IL6 in a population-based survey (Christian et al., 2011) due to the large proportion of systemic IL6 expressed in adipose tissue. Further, higher IL6 levels occur following exercise among individuals who are obese compared to non-obese individuals (Galassetti et al., 2011). The effects of obesity on CK and COMP have not been established; however, the latter is expected to be positively correlated with BMI due to

greater cartilage loading.

Finally, there is evidence that females are at an increased risk for developing WMSDs (da Costa & Vieira, 2010). Following a maximum exercise protocol, females showed a continual increase in IL6 after 60 minutes, while levels in males began to decrease, indicating possible differences in tissue recovery (Edwards, Burns, Ring, & Carroll, 2006). CK levels appear to be primarily increased in males following concentric exercise (Stupka et al., 2000), possibly due to greater muscle mass or differences in strength. If biomarkers are to be used as a risk assessment tool, they should be sensitive to differential WMSD risks between genders when performing comparable tasks (at least in some circumstances).

The evidence presented above suggests that our understanding of factors that influence biomarkers is incomplete. Before biomarkers can be implemented as part of an ergonomics program, more research is clearly needed to understand the influence of other contributing factors, for example so that levels can be adjusted to reflect primary influences of physiological damage. Existing studies have typically not controlled for differences between individuals, which may partially explain the discrepancies between evaluations using current risk assessment methods and observed WMSD incidence. An ability to account for these differences may enable an improved WMSD risk assessment.

4. FOR THE USE OF BIOMARKERS IN THE WORKPLACE

A potential advantage of biomarkers over current risk assessment methods is that they could be used in both proactive ergonomic programs, as recommended by the National Institute of Occupational Safety and Health (NIOSH) (Cohen, Gjessing, Fine, Bernard, & McGlothlin, 1997), and as part of workers compensation litigation scenarios. Although the former is preferred, the latter may be a useful byproduct of a biomarker monitoring system. Proper implementation of a biomarker-based ergonomics program in the workplace will, however, require certain protocols to support valid conclusions about WMSD risk.

Under the assumption that biomarkers do validly predict the risk of WMSDs, a biomarker monitoring program would enable an employer to determine, as an example, which tasks or workstations exceed safe levels of sub-clinical physiological injury. Unlike many current risk assessment methods, which mainly consider task-related parameters, biomarker analyses may account for differential physiological damage between workers based on individual tissue tolerances and, therefore, could support job reassignment versus redesigning a task. Establishing a detailed medical history at the time of employment, and keeping this updated throughout the working career is important to interpret biomarker levels. For example, and besides age, BMI, and gender, a history of MSDs and pain has been shown to predict future WMSDs (Eriksen, Bruusgaard, & Knardahl, 2004) and increase baseline biomarker levels (Carp, Barr, & Barbe, 2008). Establishing temporal associations between biomarker levels within individuals is also essential. Physiological damage after task exposure can only be inferred when biomarker levels are compared to a baseline measure, whether these are pre-employment levels or at the beginning of a working day, week, or month. Baseline levels should generally be obtained after at least 48 hours (i.e. a weekend) of limited physical activity, to allow for biomarkers to completely subside from previous exposures (Kim et al., 2009; Yang et al., 2011). Pre-employment physical testing is also common and has been shown to predict WMSD risk (Rosenblum & Shankar, 2006). In an analogous application, prior to task or workstation assignment, workers could be exposed to physically demanding tasks while determining biomarker levels before and after exposure. Continuous biomarker monitoring would also elicit useful information regarding the physiological damage and WMSD risk experienced over longer periods (days, weeks, and even months of task exposure). However, cost may be a limiting factor for the implementation of biomarker monitoring, and a more randomized testing scheme applied to detect general trends of WMSD risk may be more feasible.

It should be noted that identifying potentially hazardous levels of sub-clinical physiological damage is only one step in a proactive ergonomic program. After identifying tasks or workstations with high WMSD risk, current ergonomic assessment tools could be used to determine task parameters (forces, repetitions, postures, etc.) that contribute most to this risk. Together, this information can then be used to more effectively assign workers to tasks or workstations, implement worker rotation schedules, add worker aides, or redesign tasks as necessary to reduce the risk of WMSDs. Follow-up biomarker analyses can then be used to objectively assess the efficacy of the ergonomic intervention in terms of WMSD risk.

As mentioned previously, a workplace biomarker monitoring program may also help ensure the legitimacy of workers compensation claims. In order to receive compensation, an employee must report the injury to the employer, who often requires that a medical doctor document the presence of an injury. Doctors must account for a multitude of factors, such as event(s) leading to the injury, prior medical history, and workplace exposures, in order to verify the work-relatedness of the injury. In litigation cases, a judge must then evaluate all the evidence and testimonies to decide if workers compensation is justified (Rogers, 2000). This is especially difficult when assessing an overexertion injury that arose from an accumulation of sub-clinical damage, as the contribution of work-related exposure is not always clear. When a claim is legitimate, comparing biomarker levels before and after the injury will support the worker's claim. By using the same

information gleaned during regular biomarker monitoring, a number of false claims could be detected. For example, should an off-the-job injury occur, this may be detected by treating an end-of-day biomarker level as the baseline and comparing before-work levels the next day. Since biomarker levels typically subside after removal of physical stress, an increase while off-the-job could indicate other potential injury sources. When required by the employer, an employee must submit an accurate medical history to minimize exacerbation of past injuries with job placement. Should pre-employment levels be higher than expected, even after accounting for personal factors and previous injuries, this may indicate omitted or false information and warrant further investigation. Exaggeration of injuries could also be detected by biomarkers, if levels experienced after injury do not match those typically seen in research. Biomarker levels may also be used during injury recovery, by helping to determine return to work status. It is important to note that, due to the potential for confounding of biomarker levels, biomarkers will likely only indicate the need for further investigation before a medical professional can assess and a judge can rule on a claim.

5. ETHICAL AND LEGAL CONSIDERATIONS FOR IMPLEMENTATION OF A BIOMARKER PROGRAM

Before biomarkers can be instituted as part of a comprehensive ergonomics program, a number of ethical issues must be considered. A recent report offered a model of ethical concerns surrounding the use of biomarkers in the workplace, and was developed by interviewing seven groups of stakeholders: workers, occupational health physicians, occupational health nurses, researchers, employers, union representative, and public insurance representatives (Caux, Roy, Guilbert, & Viau, 2007). It is not surprising that confidentiality was the greatest concern when using blood samples. As biomarkers reflect the medical status of a worker, similar to medical histories, this information must be kept confidential, possibly by anonymizing results. Interpretation of blood samples ranked second, in that the complexity of biological systems suggests most biomarkers may indicate other medical conditions besides physiological damage. Thus, when biomarker levels are obtained it is important to limit the interpretation to the physiological damage and WMSD risk they represent. This reiterates the importance of submitting an accurate medical history and keeping it up to date. The Americans with Disabilities Act (ADA) of 1990 states that employers may not inquire about any form of disability prior to making an employment offer and further must make adequate accommodations for workers disabled on the job (Department of Justice, 1990). Consequently, any pre-employment screening to determine biomarker baseline levels and obtain the medical background must occur only after an employment offer has been accepted. To adequately protect the employer and employee, consent must be obtained for all the possible uses of biomarkers. This includes details on the exact biomarkers to be investigated, limitations of the interpretation of them, and their purpose in protecting the employee from WMSDs but also in protecting the employer in the case of potentially job-related injury. Although the Genetic Information Nondiscrimination Act (GINA) of 2008 explicitly excludes biomarkers as defined here, it addresses the necessity to limit analysis of blood samples to the biomarkers described when obtaining consent from the employee. In unionized workplaces, employers will need to work closely with the union representatives to ensure the rights and confidentiality of the workers are maintained. As long as these concerns regarding confidentiality, consent, and interpretation are addressed, biomarker monitoring may be a valuable component to an ergonomic evaluation program.

6. CONCLUSIONS

Biomarkers show promise as a new WMSD risk assessment tool that may offer advantages over some current methods, since biomarkers can objectively indicate physiological damage on an individual basis. Prior to implementation in an ergonomic program, though, a clearer understanding is needed of biomarker changes related to WMSD risk and the influence of confounding factors. If care is taken to establish temporal patterns relative to a baseline, biomarkers may be integrated as part of a proactive ergonomic WMSD risk assessment tool and simultaneously aid employers in some workers compensation litigation scenarios. In these contexts, biomarkers might best be combined with traditional risk and exposure assessment tools to identify contributing factors to WMSD risk. Finally, there are a number of important ethical and legal limitations that need to be considered when contemplating the use of biomarker-based WMSD risk assessment.

7. REFERENCES

Amanatullah, D. F., Lu, J., Hecht, J., Posey, K., Yik, J., Di Cesare, P. E., & Haudenschild, D. R. (2012). Identification of a 3Kbp Mechanoresponsive Promoter Region in the Human Cartilage Oligomeric Matrix Protein Gene. *Tissue Engineering Part A, 18*(17-18), 1882-1889. doi: 10.1089/ten.tea.2011.0497

Andersen, M. B., Pingel, J., Kjaer, M., & Langberg, H. (2011). Interleukin-6: a growth factor stimulating collagen synthesis in human tendon. *Journal of Applied Physiology, 110*(6), 1549-1554. doi: 10.1152/japplphysiol.00037.2010

BLS. (2011). Occupational injuries and illnesses: industry data.

Brinckmann, M.P., & Hilweg, D. (1989). Prediction of the compressive strength of human lumbar vertebrae. *Clinical Biomechanics, 4*, iii-iv.

Carp, S., Barbe, M. F., Winter, K. A., Amin, M., & Barr, A. E. (2007). Inflammatory biomarkers increase with severity of upper-extremity overuse disorders. *Clinical Science, 112*(5), 305-314. doi: 10.1042/cs20060050

Carp, S., Barr, A. E., & Barbe, M. F. (2008). Serum biomarkers as signals for risk and severity of work-related musculoskeletal injury. *Biomarkers in Medicine, 2*(1), 67-79. doi: 10.2217/17520363.2.1.67

Caux, C, Roy, D, Guilbert, L, & Viau, C. (2007). Anticipating ethical aspects of the use of biomarkers in the workplace: A tool for stakeholders. *Social Science & Medicine, 65*(2), 344-354.

Christian, L. M., Glaser, R., Porter, K., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. K. (2011). Poorer self-rated health is associated with elevated inflammatory markers among older adults. *Psychoneuroendocrinology, 36*(10), 1495-1504. doi: 10.1016/j.psyneuen.2011.04.003

Cohen, A, Gjessing, C, Fine, L, Bernard, B, & McGlothlin, J. (1997). *Elements of Ergonomics Programs*. Cincinnati, OH: NIOSH.

D'Ambrosia, Peter, King, Karen, Davidson, Bradley, Zhou, Bing, Lu, Yun, & Solomonow, Moshe. (2010). Pro-inflammatory cytokines expression increases following low- and high-magnitude cyclic loading of lumbar ligaments. *European Spine Journal, 19*(8), 1330-1339. doi: 10.1007/s00586-010-1371-4

da Costa, B. R., & Vieira, E. R. (2010). Risk Factors for Work-Related Musculoskeletal Disorders: A Systematic Review of Recent Longitudinal Studies. *American Journal of Industrial Medicine, 53*(3), 285-323. doi: 10.1002/ajim.20750

Degens, H., & Korhonen, M. T. (2012). Factors contributing to the variability in muscle ageing. *Maturitas, 73*(3), 197-201. doi: 10.1016/j.maturitas.2012.07.015

Edwards, K.M., Burns, V.E., Ring, C., & Carroll, D. (2006). Individual differences in the interleukin-6 response to maximal and submaximal exercise tasks. *Journal of Sports Sciences, 24*(8), 855-862.

Erhart-Hledik, J. C., Favre, J., Asay, J. L., Smith, R. L., Giori, N. J., Mundermann, A., & Andriacchi, T. P. (2012). A relationship between mechanically-induced changes in serum cartilage oligomeric matrix protein (COMP) and changes in cartilage thickness after 5 years. *Osteoarthritis Cartilage, 20*(11), 1309-1315. doi: 10.1016/j.joca.2012.07.018

Eriksen, W., Bruusgaard, D., & Knardahl, S. (2004). Work factors as predictors of intense or disabling low back pain; a prospective study of nurses' aides. *Occupational and Environmental Medicine, 61*(5), 398-404. doi: 10.1136/oem.2003.008482

Galassetti, P.R., Rosa, J.S., Heydari, S., Oliver, S.R., Flores, R.L., Pontello, A.M., & Ibardolaza, M. (2011). Inflammatory Cytokine Profiles During Exercise in Obese, Diabetic, and Healthy Children. *Journal of clinical research in pediatric endocrinology, 3*(3), 115.

Gomez-Cabello, A., Ara, I., Gonzalez-Aguero, A., Casajus, J. A., & Vicente-Rodriguaz, G. (2012). Effects of Training on Bone Mass in Older Adults. *Sports Medicine, 42*(4), 301-325.

Injuries, Steering Committee for the Workshop on Work-Related Musculoskeletal. (1998). *Work-Related Musculoskeletal Disorders: A Review of the Evidence*. Washington, DC: National Academy Press.

Jain, K. K. (2010). *The Handbook of Biomarkers*. New York: Springer. Americans with Diasbilities Act (1990).

Kim, H. J., Lee, Y. H., & Kim, C. K. (2007). Biomarkers of muscle and cartilage damage and inflammation during a 200 km run. *European Journal of Applied Physiology, 99*(4), 443-447. doi: 10.1007/s00421-006-0362-y

Kim, H. J., Lee, Y. H., & Kim, C. K. (2009). Changes in serum cartilage oligomeric matrix protein (COMP), plasma CPK and plasma hs-CRP in relation to running distance in a marathon (42.195 km) and an ultra-marathon (200 km) race. *European Journal of Applied Physiology, 105*(5), 765-770. doi: 10.1007/s00421-008-0961-x

Kumar, S. (2001). Theories of musculoskeletal injury causation. *Ergonomics, 44*(1), 17-47.

Magal, M., Dumke, C. L., Urbiztondo, Z. G., Cavill, M. J., Triplett, N. T., Quindry, J. C., . . . Epstein, Y. (2010). Relationship between serum creatine kinase activity following exercise-induced muscle damage and muscle fibre composition. *Journal of Sports Sciences, 28*(3), 257-266. doi: 10.1080/02640410903440892

Marras, W. S. (2000). Occupational low back disorder causation and control. *Ergonomics, 43*(7), 880-902.

Muller, G., Michel, A., & Altenburg, E. (1998). COMP (cartilage oligomeric matrix protein) is synthesized in ligament, tendon, meniscus, and articular cartilage. *Connective Tissue Research, 39*(4), 233-244.

Mündermann, Annegret, Dyrby, Chris O., Andriacchi, Thomas P., & King, Karen B. (2005). Serum concentration of cartilage oligomeric matrix protein (COMP) is sensitive to physiological cyclic loading in healthy adults. *Osteoarthritis and Cartilage, 13*(1), 34-38. doi: DOI: 10.1016/j.joca.2004.09.007

Neidhart, M., Hauser, N., Paulsson, M., Dicesare, P. E., Michel, B. A., & Hauselmann, H. J. (1997). Small fragments of cartilage oligomeric matrix protein in synovial fluid and serum as markers for cartilage degradation. *British Journal of Rheumatology, 36*(11), 1151-1160.

Newham, D. J., Jones, D. A., & Edwards, R. H. T. (1986). Plasma creatine kinase changes after eccentric and concentric contractions. *Muscle & Nerve, 9*(1), 59-63. doi: 10.1002/mus.880090109

Nielsen, A. R., & Pedersen, B. K. (2007). The biological roles of exercise-induced cytokines: IL-6, IL-8, and IL-15. *Applied Physiology Nutrition and Metabolism-Physiologie Appliquee Nutrition Et Metabolisme, 32*(5), 833-839. doi: 10.1139/h07-054

Nieman, D.C., Henson, D.A., Nehlsen-Cannarella, S.L., Ekkens, M., Utter, A.C., Butterworth, D.E., & Fagoaga, O.R. (1999). Influence of obesity on immune function. *Journal of the American Dietetic Association, 99*(3), 294-299.

Noyes, F.R. (1977). Functional properties of knee ligaments and alterations induced by immobilization: a correlative biomechanical and histological study in primates. *Clinical Orthopaedics and Related Research, 123*, 210.

Pedersen, B. K., Bruunsgaard, H., Ostrowski, K., Krabbe, K., Hansen, H., Krzywkowski, K., . . . Schjerling, P. (2000). Cytokines in aging and exercise. *International Journal of Sports Medicine, 21*, S4-S9. doi: 10.1055/s-2000-1444

Pedersen, B. K., & Febbraio, M. A. (2008). Muscle as an endocrine organ: Focus on muscle-derived interleukin-6. *Physiological Reviews, 88*(4), 1379-1406. doi: 10.1152/physrev.90100.2007

Rogers, P. (2000). Injured Workers and Medical Evidence: A Judge's Perspective. In T. Mayer, R. Gatchel & P. Polatin (Eds.), *Occupational Musculoskeletal Disorders*. Philadelphia, PA: Lippincott Williams & Wilkins.

Rosenblum, K.E., & Shankar, A. (2006). A study of the effects of isokinetic pre-employment physical capability screening in the reduction of musculoskeletal disorders in a labor intensive work environment. *Work: A Journal of Prevention, Assessment and Rehabilitation, 26*(2), 215-228.

Sorichter, S., Koller, A., Haid, CH, Wicke, K., Judmaier, W., Werner, P., & Raas, E. (1995). Light concentric exercise and heavy eccentric muscle loading: effects on CK, MRI and markers of inflammation. *International journal of sports medicine, 16*(5), 288.

Splittstoesser, R. E., Marras, W. S., & Best, T. M. (2012). Immune Responses to Low Back Pain Risk Factors. *Work-a Journal of Prevention Assessment & Rehabilitation, 41*, 6016-6023. doi: 10.3233/wor-2012-1053-6016

Starkie, R., Ostrowski, S.R., Jauffred, S., Febbraio, M., & Pedersen, B.K. (2003). Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. *The FASEB Journal, 17*(8), 884-886.

Stupka, N., Lowther, S., Chorneyko, K., Bourgeois, J. M., Hogben, C., & Tarnopolsky, M. A. (2000). Gender differences in muscle inflammation after eccentric exercise. *Journal of Applied Physiology, 89*(6), 2325-2332.

Takahashi, H., Suguro, T., Okazima, Y., Motegi, M., Okada, Y., & Kakiuchi, T. (1996). Inflammatory cytokines in the herniated disc of the lumbar spine. *Spine, 21*(2), 218.

Toft, A. D., Falahati, A., & Steensberg, A. (2011). Source and kinetics of interleukin-6 in humans during exercise demonstrated by a minimally invasive model. *European Journal of Applied Physiology, 111*(7), 1351-1359. doi: 10.1007/s00421-010-1755-5

Toft, A. D., Jensen, L. B., Bruunsgaard, H., Ibfelt, T., Halkjær-Kristensen, J., Febbraio, M., & Pedersen, B. K. (2002). Cytokine response to eccentric exercise in young and elderly humans. *American Journal of Physiology-Cell Physiology, 283*(1), C289-C295.

Uciechowski, P., & Rink, L. (2009). Neutrophil Granulocyte Functions in the Elderly. *Handbook on Immunosenescence*, 439-455.

Vällfors, B. (1985). Acute, subacute and chronic low back pain: clinical symptoms, absenteeism and working environment. *Scandinavian journal of rehabilitation medicine. Supplement, 11*, 1.

Wallberg, Linnea, Mikael Mattsson, C., Enqvist, Jonas, & Ekblom, Björn. (2011). Plasma IL-6 concentration during ultra-endurance exercise. *European Journal of Applied Physiology, 111*(6), 1081-1088. doi: 10.1007/s00421-010-1737-7

Yang, Gang, Marras, William S., & Best, Thomas M. (2011). The biochemical response to biomechanical tissue loading on the low back during physical work exposure. *Clinical Biomechanics, 26*(5), 431-437. doi: 10.1016/j.clinbiomech.2011.01.005

Zivanovic, S., Rackov, L. P., Zivanovic, A., Jevtic, M., Nikolic, S., & Kocic, S. (2011). Cartilage Oligomeric Matrix Protein - inflammation biomarker in knee osteoarthritis. *Bosnian Journal of Basic Medical Sciences, 11*(1), 27-32.