The XXVII[th] Annual Occupational Ergonomics and Safety Conference
Nashville, Tennessee, USA
May 28-29, 2015

The Current State of Biomarkers Related to Low Back Pain and Their Relation to Established Risk Factors

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Abstract: WMSDs and LBP continue to be prevalent in and costly to the medical and workers' compensation systems alike. Current methods for assessing risk of WMSDs and LBP may be limited due to a reliance on *in vitro* tissue tolerances and a lack of correlation to observed risk levels. Select biomarkers offer distinct advantages as they are derived from tissues commonly involved in injury (muscle and collagenous tissue) and levels have been correlated with established risk factors. Several studies have demonstrated close relationships of exposure to risk factors and biomarker levels, and have applied these in occupational settings. Several limitations still exist for biomarkers and must be addressed before biomarkers may be integrated within current risk assessment programs. The purpose of this review is to advocate the use of biomarkers by discussing limitations of current methods, highlight select biomarkers which have been related to tissues involved in WMSDs and LBP, and suggesting areas of research which are necessary prior to the successful use of biomarkers in the workplace.

Keywords: Work-related musculoskeletal disorders, Lower back disorders, Biomarkers, Muscle, Collagen, Risk factors

1. Introduction

Work-related musculoskeletal disorders (WMSDs) continue to be common in many industrialized countries and represent a substantial burden to the medical and workers' compensation systems alike. Proportionally, overexertion injuries are the leading cause of WMSDs in 2014, comprising 25.3% of costs, an estimated $15.1 billion in direct costs ("2014 Liberty Mutual Workplace Safety Index," 2014). This category of injuries is encompasses lifting, pushing, pulling, holding, carrying, or throwing. The total indirect costs have been estimated to be in excess of $200 billion (da Costa & Vieira, 2010). Specifically lower back pain (LBP) is largest contributor to WMSDs. Lifetime incidence of LBP has been estimated to lie between 80-85% of people (Hoy et al., 2010). In New Zealand, over 50% of workers reported symptoms related to the lower back over a 12 month period (Widanarko et al., 2011). Recently, the National Occupational Research Agenda suggested that, in order to reduce the impact of WMSDs, multi-dimensional research is required to establish preventative strategies (Marras, Cutlip, Burt, & Waters, 2009).

A number of risk factors for LBP are well recognized. Early research demonstrated that that overexertion injuries are caused primarily by an inability of body tissues to withstand a given load (Kumar, 2001). Many of these tissue tolerance limits stem from *in vitro* studies of muscles, vertebrae, and connective tissues (Brinckmann, Biggemann, & Hilweg, 1988; Noyes, 1977). These studies demonstrated that the magnitude of load and frequency of repetition are the two task related factors which most contribute to WMSDs and LBP. Peak and cumulative loads on the spine have been associated with lost-time and lower back pain rates (Coenen et al., 2012; Village et al., 2005). In reality though, such a direct relationship is complicated by potential decreases in tissue tolerance over time (Marras, 2000) and the complex influences of diverse personal factors such as psychological state, age, gender, and obesity (Steering Committee for the Workshop on Work-Related Musculoskeletal "Work-Related Musculoskeletal Disorders: A Review of the Evidence," 1998). Compounding the difficulty of determining causation, sub-clinical WMSDs often lack pathological symptoms, making their identification prior to injury more difficult (Vällfors, 1985). Additional risk assessment tools that can account for known risk factors, while also detecting sub-clinical physiological changes, would enhance our ability to predict WMSD risk and could help in the future to substantially reduce the prevalence and adverse impacts of WMSDs.

Biomarkers, 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. LBP and low back

injuries are commonly associated with muscle, cartilage, and/or bone tissues of the spine (Brinckmann et al., 1988). When bodily tissues are injured a host of biomarkers are released both locally and systemically in an effort to aid the repair pathway (M. F. Barbe & Barr, 2006). Therefore, biomarkers may help describe the presence and/or progression of sub-clinical tissue damage (see Figure 1) prior to developing a WMSD, and thus may be used to enhance our ability to predict future injury risk. Biomarkers have even been suggested as part of a workers' compensation program (Christian & Nussbaum, 2013).

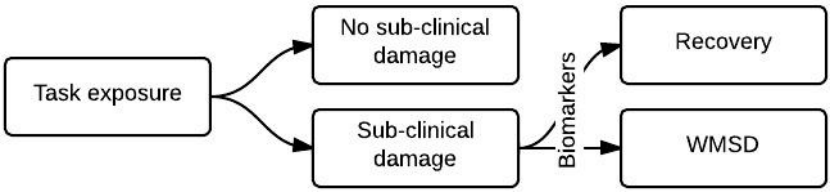

Figure 1. Conceptual model of the progression of WMSDs and the use of biomarkers in occupational settings. Current evidence supports the use of biomarkers for assessing levels of sub-clinical tissue damage (Christian & Nussbaum, 2015a).

2. Current Methods for Evaluating LBP Risk

Current methods for assessing WMSD and LBP risk can be categorized in physiological, physical, and psychophysical methods (Dempsey, 1998). Ideally, the use of these methods, alone or in combination, should enable potentially injurious tasks or occupations to be identified so that appropriate control measures can be implemented to reduce risk. Unfortunately, the epidemiological data to support their use is limited.

The Revised NIOSH Lifting Equation (RNLE) is arguably one of the more popular tools for assessing how acceptable and risky lifting tasks are. To do this the RNLE incorporates several lifting task parameters to determine risk relative to a task that is acceptable to 75% of females, has a maximum energy expenditure of 4.7 kcal/min, and a maximum spinal compressive force of 3400kN (Waters, Putz-Anderson, Garg, & Lawrence, 1993). In a study comparing multiple risk assessment methods for assessing risk of 93 vehicle production tasks, the RNLE had the lowest threshold for identifying tasks as medium and high risk (Lavender, Oleske, Nicholson, Andersson, & Hahn, 1999). Despite a demonstrated sensitivity for identifying high risk tasks of 73% (Marras, Fine, Ferguson, & Waters, 1999) and significant odds ratios for 'high-risk' tasks (Waters et al., 1999), one cross-sectional study demonstrated that tasks classified as 'high risk' did not result in significantly higher WMSD rates (Waters, Lu, Piacitelli, Werren, & Deddens, 2011). Further, recent evidence suggests that certain RNLE factors may not actually influence risk as predicted (Adams et al., 2010).

Another common tool used to evaluate the risk of lifting tasks is the Michigan 3-Dimenstional Static Strength Prediction Program (3DSSPP) predicts risk based on both strength and biomechanical factors, and can be applied to a wide variety of industrial tasks (Fischer, 2011). Outputs of this tool include a percentage of capable population, estimates of spinal compressive forces, and muscle demands, all of which are measured relative to previously determined 'safe' levels (Waters, Lu, Werren, & Piacitelli, 2011). To date, no epidemiological studies confirm the validity of 3DSSPP, but in comparison to the RNLE, 3DSSPP rated only 1% of the same simulated tasks as 'high-risk', indicating a lack of predictive power (Lavender et al., 1999).

Current methods have contributed to our understanding of task-related risk factors, and a variety of exposure assessment methods and tools exist, enabling direct comparisons between tasks. However, field studies have not confirmed predictive validity for many of these tools as risk assessment methods. There is a lack of empirical studies demonstrating sub-clinical physiological damage following task exposure as measured by many of these tools, and their ability to accurately predict LBP or WMSD risk has not been fully assessed. A method that can assess risk while accounting for personal factors, and which gives measures that are a direct result of physiological damage, would help overcome limitations of and enhance the current methods, thus improving our ability to evaluate workplace tasks and accurately predict LBP risk.

3. Overview of Biomarkers Related to Physiological Damage

Biomarkers may overcome some of the limitations of current methods, therefore offering distinct advantages. The 'gold standards' of assessing tissue damage (e.g. tissue biopsies and imaging technologies) are typically impractical, invasive, and costly to utilize. Select biomarkers are produced by tissues related to WMSDs and consequently act as surrogates for these 'gold standards'. They can be measured objectively and are, comparative to some measures such as electromyography, metabolic oxygen consumption, and kinematic equipment, less invasive. In a recent dissertation the author has outlined a set of criteria to guide the selection of biomarkers, which will be applied to the biomarkers discussed here: 1) changes in levels are a direct consequence of physiological damage and use, 2) existing literature suggests these

biomarker changes can be seen on a systemic level (as opposed to a local, which would involve obtaining biopsies), 3) biomarkers themselves occur as early as possible in biological pathways of damage and/or repair, and 4) there is evidence to suggest that confounding factors can be accounted for (Christian, 2014).

The major advantage of biomarkers, therefore, is a direct relation to true physiological damage as they are usually produced by, or as a consequence of, damaged tissues. With regard to relevant tissues for assessing LBP risk, this review will focus primarily on muscle and collagenous tissue. Both of these tissues are highly related to WMSDs (Kumar, 2001) and have been specifically identified as tissues involved in LBP, e.g. the lumbar flexors/extensors, annuli fibrosus, and nuclei pulposus (Chaffin, Andersson, & Martin, 1991).

3.1 Muscles

Approximately 25% of the WMSDs experienced in the United States are classified as 'overexertion' injuries ("2014 Liberty Mutual Workplace Safety Index," 2014). Muscle tissue is of particular interest since repetitive use of muscles, without adequate rest periods, can lead to histological damage (Clarkson & Hubal, 2002). A number of biomarkers related to muscle tissue have been identified. Creatine Kinase (CK) is arguably one of the most muscle biomarkers popular since it is ubiquitously found in all muscle cells and is released into the blood stream following eccentric contraction induced cell rupture (Newham, Jones, & Edwards, 1986). Typical increases following eccentric muscle exertion range anywhere from 4 to 40 fold, depending on the volume of muscle tissue that is damaged. Numerous other molecules are released during cell rupture, and can be measured as indicators of muscle damage. These molecules include myoglobin, aldolase, and troponin, to name a few, although their relation to WMSDs and LBP had been studies less (Brancaccio, Lippi, & Maffulli, 2010).

A recently developed view of muscle tissue implicates it as a secretory organ (Pedersen, 2013). Here, certain biomarkers are released relative to the *stress* imposed on muscle tissue, as opposed to actual physiological damage such as those discussed above. Interleukins are a family of molecules used to signal between tissues in the body. The source of some interleukins has been traced to muscle tissue. Interleukin-1 (IL1), -6 (IL6), and -10 (IL10) are all produced by and released from muscle tissue following exertions, regardless of physiological injury (Pedersen, 2013). Research suggests that their purpose is to modulate the inflammatory response of the body, and consequently their peak levels and temporal patterns depend on whether or not physiological muscle damage has occurred (Reihmane & Dela, 2013). Tumor necrosis factor α (TNFα) is also produced in muscle tissue, thought only as a result of physiological damage, and whose purpose is to recruit macrophages and neutrophils to clear damaged cells (Steensberg et al., 2002). Interestingly, the release patterns of IL6 are thought to help regulate TNFα production to appropriate levels (Petersen & Pedersen, 2005).

Research has demonstrated a number of biomarkers which are related to muscle tissue use and damage. As a major contributor to WMSDs and LBP, muscle tissue use and overexertion may be detected through the use of these (and other) biomarkers.

3.2 Collagen

Collagen molecules are found in many tissues in the body. In relation to WMSDs and LBP, collagen molecules are found in muscle connective tissue, annuli fibrosus, and nuclei pulposus (Chaffin et al., 1991). When (over)exertion occurs, these structures undergo deformation, and may tear or undergo degradation (Kumar, 2001). A number of biomarkers related to collagen have been identified. Procollagen type I/II C-propeptide (PI/IICP) is a subunit of the collagen molecule that is released when collagen is being synthesized, and is therefore often used to measure the synthetic rate of collagen. Often used in combination, type I/II collagen C-telopeptide (CTX-I/II) is released when degraded collagen molecules are broken down (Garvican, Vaughan-Thomas, Innes, & Clegg, 2010). These two biomarkers have, for example, been used to measure patient recovery following surgery for lumbar disc herniation to demonstrate collagen production (Kuiper et al., 2002).

Certain cytokines and inflammatory biomarkers have been identified in collagenous tissue too. Specifically IL1, and TNFα have both been identified in the intervertebral disc. Evidence suggests that their heightened presence within discs indicate the level of damage and degradation experienced by the collagenous tissues following compressive forces (Wang, Jiang, & Dai, 2007). This study also showed histological damage in the tissue relative to the biomarker expression. IL6 has also been localized to the intervertebral discs of patients with spinal cord injury. Here, IL6 patterns suggested that the nervous system plays a role in regulating inflammatory biomarker changes in response to degradation (Paulson, Goosey-Tolfrey, Lenton, Leicht, & Bishop, 2013).

Evidence suggests that certain biomarkers can be used to indicate the physiological status and/or injury of both muscle tissue and collagen molecules. If these biomarkers can be used as a risk assessment method for WMSDs and LBP they should also demonstrate a relationship to identified occupational risk factors.

4. Relation of Biomarkers to Established Risk Factors

While this paper argues that current methods provide an incomplete assessment of risk, their contribution to understanding various risk factors cannot be underestimated. Many of these risk factors were established in the early cadaver studies discussed above. With respect to WMSDs and LBP, two factors are of particular importance; magnitude of loads, frequency of loads, and the interaction of those factors (Brinckmann et al., 1988). If biomarkers are to be used for WMSD and LBP risk assessment their levels should be found relative to the extent of exposure to these risk factors.

Both load and frequency have been demonstrated to influence some of the biomarkers discussed above. Early studies using biomarkers did not carefully control exposure levels, but still demonstrated that CK and IL6 levels increased following strenuous exercise, such as running and cycling (Kim, Lee, & Kim, 2009; Reihmane, Jurka, Tretjakovs, & Dela, 2012; Toft et al., 2002). A feline model of lumbar ligaments was used, exposing spinal discs to high-frequency loading. Here, higher levels of lumbar loading results in greater levels of IL1 and 8 as well as TNFα in the intervertebral discs (Pinski et al., 2010). Another similar study used a rat model of WMSDs to show that, over 12 weeks of training, both load, frequency, and their interaction increased levels of muscle and tendon IL1, TNFα, and CTX-I (M. Barbe et al., 2013).

Studies involving humans have also begun to investigate the effect of specific risk factors on biomarker levels, both in controlled laboratory settings and workplaces. Two laboratory based studies are of particular importance. The first had participants lift a box of varying weights at a constant frequency over a period of two hours. Significant dose-response relationships of the box weight to CK, IL6, and TNFα were seen, suggesting that physiological damage caused by this repetitive task could be measured by the biomarkers (Yang, Marras, & Best, 2011). A study performed by the author expanded on the prior, implementing specific control methods to isolate the lower back and lumbar flexors/extensors during a one hour simulated lifting task. Each participant performed the task at 5 different levels, in which the load and frequency were varied. Both CK and IL6 demonstrated dose-response relationships to load *and* frequency (Christian & Nussbaum, 2015c). Together these studies support the use of biomarkers for assessing physiological damage.

Some studies have also examined biomarkers in occupational settings. Kuiper, van Dieën, Everts, Verbeek, and Frings-Dresen (2004) examined nurses for the associations of PICP and CTX to spinal shrinkage, a measure of cumulative spinal loading. They found a significant correlation between biomarker levels and the extent of spinal shrinkage. Another study by that group compared these biomarker levels between construction and sedentary workers, demonstrating greater levels of collagen turnover for construction workers (Kuiper, Verbeek, Everts, Straub, & Frings-Dresen, 2005). A similar study by the author followed high (constructions workers, nurses, landscapers, etc.) and low (sedentary office workers) occupational physical stress groups over an entire working week, and found that IL6 levels were higher at all time points (Christian & Nussbaum, 2015a).

Currently there appears to be a significant body of research suggesting select biomarkers are related to muscle and collagen damage that is commonly experience following exposure to highly strenuous tasks, and specifically that found as a precursor to WMSDs and LBP.

5. Limitations and Future Research

Despite the existing evidence for using biomarkers to assess WMSD and LBP risk, there are a number of important limitations which must be discussed. Biomarkers rarely act in isolation and are often influence by a wide range of confounding factors. Age (Toft et al., 2002), obesity (Mohamed-Ali et al., 1997), and gender (Edwards, Burns, Ring, & Carroll, 2006) are just some of the factors which have been demonstrated to affect biomarker levels. There are doubtless many others, and the extent of these needs to be determined and accounted for when measuring biomarkers for WMSD and LBP risk.

Prior to integrating biomarkers as part of a comprehensive risk assessment system, prospective studies of associations between changes in biomarker levels, exposure levels, and future WMSD and LBP development are needed. These type of epidemiological data are critical to bridging the gap between research and practice.

6. Conclusions

The factors relating to WMSDs and LBP have been well established in the literature. Commonly used tools try to make use of relationships between exposure to these risk factors and the physiological tissue damage that underlies WMSDs and LBP. Unfortunately these tools are limited in a number of ways. Biomarkers related to the tissues involved in WMSDs and LBP present a novel method with unique advantages over current methods for assessing risk. Studies have demonstrated that select biomarkers derived from muscle and collagenous tissue are found in the body in relation to exposure to these risk factors and in at-risk occupational groups. A number of limitations still exist though, namely determining the influence of confounding factors and prospective studies linking biomarkers levels to observed risk.

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