



# The biochemical response to biomechanical tissue loading on the low back during physical work exposure

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## ABSTRACT

**Background:** Our understanding of low back disorder causality is limited in that how biomechanical loading acting on various spinal tissues initiates the pain pathway is not clear. Previous studies suggest that cytokines may be important in mediating the inflammatory responses in patients with back pain. This study quantified the acute biochemical responses to physical work stressing the low back and assessed the relationships between these systemic responses and specific lumbar spine tissue loads.

**Methods:** Twelve healthy males were tested under control and two weight-lifting conditions (light and heavy). Venous blood was sampled at various time points before and after the physical work and analyzed for cytokine, granulocyte, and creatine kinase levels. Biomechanical data were collected during the tasks and a biologically-assisted lumbar spine model was used to calculate spinal loads at various lumbar spine levels and trunk muscle forces.

**Findings:** Levels of interleukin-6, granulocytes, and creatine kinase all increased after both weight-lifting tasks, with the greatest changes observed with the heavier lifting task. Similarly, plasma levels of interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$  both increased following the heavier lifting task. These inflammatory responses were significantly correlated with specific spinal tissue loads.

**Interpretation:** This study suggests that it may be possible to use inflammatory cytokines as biomarkers to monitor the physiological responses of the human body to biomechanical loading. Identifying the possible sources of cytokine up-regulation using an advanced biomechanical model may help a more effective understanding of the causal pathways that lead to low back disorders.

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## 1. Introduction

Despite many years of research our understanding of low back disorders (LBD) causality is still very limited (NRC, 2001). The scientific literature suggests that LBD are strongly associated with occupational tasks (Andersson, 1981; Chaffin and Park, 1973), especially manual materials handling jobs that require lifting, pushing, and pulling (Chaffin and Park, 1973; Hoozemans et al., 2002). While biomechanical loading associated with physical work is believed to be the primary cause of LBD, the nature of this relationship is not entirely clear.

The traditional approach to understanding and controlling LBD risk compares spinal loads from biomechanical models to the physical tolerance of the spine tissues typically derived from cadaver studies (NIOSH, 1981, 1994). This logic suggests that the risks of tissue failure and the subsequent development of LBD are increased only when spinal loads exceed the tissue's structural tolerance. However, there

are several problems with this approach. First, the material properties derived from cadaveric tissues can be very different from those of living tissues (Bass et al., 1997; Keller et al., 1990). Second, data from cadaver studies primarily represent vertebral body or endplate fractures, whereas LBD are thought to originate from many tissues in the lumbar region including muscle, ligament, facet joints, and fascia (Deyo and Weinstein, 2001). Finally, research suggests that pain from tissue injury can be initiated at the cell level and perceived when the overall tissue structure is still intact (Scholz and Woolf, 2002). Therefore, the traditional mechanical load-tolerance model might better represent LBD pathways if it included tissue biochemical (inflammatory) tolerance limits.

In recent years, it has been recognized that cytokines play an important role in mediating the inflammatory responses caused by forces imposed on cells or tissues of the musculoskeletal system. Investigations have shown increased synthesis of interleukin (IL)-1 $\beta$  and IL-6 after fibroblasts are repetitively stretched (Skutek et al., 2001; Tsuzaki et al., 2003). Animal studies report increased expression of IL-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , IL-6, and IL-8 after 60 min of cumulative cyclic loading of the supraspinous ligaments (King et al., 2009), whereas, reaching and grasping tasks have resulted in elevated

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cytokines locally and systemically (Barbe et al., 2008; Elliott et al., 2009). In human subjects, local inflammatory responses are characterized by the invasion of neutrophils into the injured muscle as early as 2 h after exercise (MacIntyre et al., 2000). Increased levels of IL-1 $\beta$ , TNF- $\alpha$ , IL-8, IL-6, and IL-10 have been found both in muscle biopsies and in plasma following intense eccentric exercise (Fielding et al., 1993; Nieman et al., 2003).

Furthermore, the relationship between cytokines and LBD has been investigated in many studies. Herniated lumbar discs from patients with radiculopathy show IL-1, IL-6, IL-8, TNF- $\alpha$ , and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) release (Ahn et al., 2002; Kang et al., 1996; Takahashi et al., 1996). Degenerated discs from patients with low back pain may produce significantly more IL-6, IL-8 and PGE<sub>2</sub> than patients with sciatica (Burke et al., 2002). In patients with back disorders, cytokines were also found in vertebral endplates (Ohtori et al., 2006) as well as the facet joints (Igarashi et al., 2004). Moreover, both static (Palmer and Lotz, 2004; Wang et al., 2007) and dynamic (Wang et al., 2007) loads have been shown to up-regulate cytokine expression in intervertebral discs in animal models. Collectively, these findings suggest that mechanical loading from physical work, when acting on the various low back structures, may cause micro- or small injuries to local cells or tissues (e.g. myofibril damage or disc cell death), which will increase the production of pro-inflammatory cytokines. These cytokines may mediate acute inflammatory responses in the local tissue, which include tissue destruction, nociceptor stimulation, and cytokine secretion. These responses, if limited, are essential to normal tissue repair (Toumi and Best, 2003). When mechanical stimulus continues to present, chronic inflammation may develop to cause further tissue degeneration. Both acute and chronic inflammations therefore may result in the development of low back pain.

The purpose of this study was two-fold; to determine the acute biochemical responses to physical work stressing the low back and to assess the relationships between biochemical responses and specific lumbar spine tissue loads predicted by advanced biomechanical modeling techniques. If we are able to understand how *specific* tissue loadings are associated with systemic up-regulation of pro-inflammatory cytokines, it may be possible to better predict the onset of LBD and develop more scientifically-based treatment and prevention strategies.

## 2. Methods

### 2.1. Experimental design

#### 2.1.1. Overview

A laboratory experiment was conducted to assess the acute biochemical responses to specific biomechanical loading of low back tissues. Subjects performed lifting and lowering tasks under different load magnitude conditions. Biomechanical data were used as inputs to a subject-specific three-dimensional lumbar spine model to determine muscle forces and subsequent spinal loads. Blood samples were drawn at various time points before and after the experimental tasks to estimate acute systemic biochemical responses. Subjective discomfort data were also collected at the same time points to provide a pain-related outcome measure (not reported here).

#### 2.1.2. Study design

The study was a repeated measures design that included two lifting sessions with different load weights and one non-lifting control session. The load weights consisted of 2.3 kg and 11.3 kg, which represented approximately the 30th and 75th percentiles of exposure in manual materials handling jobs, respectively (Marras et al., 1993, 1995). Blood draws were taken at baseline, 0 h after, 2 h after, and 24 h after the experimental task based on observed responses to aerobic exercise (Brenner et al., 1999; Bruunsgaard et al., 1997). For the control session, subjects assumed their normal daily activities but were not permitted to perform any lifting tasks. Blood samples were collected at the same time

as the lifting sessions. The ordering of the conditions was randomized, with only one condition tested each day. Subjects were given at least one week to rest and recover after each session to minimize any carryover effects. All sessions started at the same time of day to minimize any potential diurnal effects.

### 2.2. Subjects

Twelve healthy, young males with no history of back pain or back injury were recruited. Prior to participation, subjects were informed about the details of the study and signed consent forms approved by the University's Institutional Review Board. The average (standard deviation, SD) age was 24.3 (5.0) years old. The average weight and height were 69.1 (9.1) kg and 173.2 (6.7) cm, respectively. There were eight Caucasians, three Asians, and one African-American. No subject had a manual materials handling job within one year of the study.

### 2.3. Experimental task

The experimental task consisted of a series of lifting and lowering of weighted boxes at a certain frequency. Based on previous industrial surveillance studies (Marras et al., 1993, 1995), the lift origin vertical height was 88 cm and the horizontal moment arm distance was 63 cm. Lift destination vertical height was set at 75% of the subject's shoulder height to lessen the stress on shoulder muscles and therefore decrease the possibility of mechanical and biochemical responses due to shoulder loading. The lift destination shelf was located at 90° clockwise to the lift origin stand. At the first computer-generated tone the subject lifted the box from the origin to the destination. At the next tone the subject lowered the box from the destination shelf back to the origin. The frequency of the task was 12 per minute, which resulted in 6 lifting and 6 lowering exertions every minute. The duration of the task was 2 h without breaks.

### 2.4. Apparatus

The position and movement of the lumbar spine during the lifting tasks were measured using a Lumbar Motion Monitor (LMM). The LMM is a series of electrogoniometers that track instantaneous changes in trunk position, velocity and acceleration in three-dimensional space. Motion characteristics of the upper and lower extremities were recorded by magnetic-based motion tracking sensors (Xsens Technologies B.V., Enschede, The Netherlands).

Electromyographic (EMG) data were collected at 1000 Hz with a Model 12 Neuradata Acquisition System (Grass Technologies, West Warwick, RI, USA). Bipolar surface electrodes were placed over the right and left pairs of the latissimus dorsi (RLD and LLD), erector spinae (RES and LES), rectus abdominus (RRA and LRA), external obliques (REO and LEO), and the internal obliques (RIO and LIO). The muscle sampling locations have been described previously (Mirka and Marras, 1993). The myoelectric data were low-pass filtered at 500 Hz, high-pass filtered at 30 Hz, notch filtered at 60 Hz, rectified, averaged using a 20 ms sliding window filter and then normalized relative to the values collected during maximum voluntary contractions (MVCs). To measure external spinal loads, the method developed by Fathallah et al. (1997) was employed. A combination of a force plate (Bertec 4060A; Bertec, Worthington, Ohio, USA) and two electrogoniometers was used to determine continuous three-dimensional forces and moments about the L5/S1 intervertebral joint. All signals were simultaneously collected using customized data acquisition software and entered into an EMG-assisted biomechanical model.

### 2.5. Experimental procedures

Antecubital venous blood samples were acquired at the General Clinical Research Center (GCRC) of the University. Baseline draws

were at 8 am to account for any day-to-day variability of the biochemical measures. For the weight-lifting sessions, the subject was transported to the Biodynamics Laboratory for biomechanical data collection after the baseline blood draw. Anthropometric measurements were recorded and surface electrodes were placed on ten trunk muscles (Marras, 1990). The subject was then placed in a rigid pelvic support structure that allowed him to perform maximum isometric exertions for the ten trunk muscles. Maximum voluntary EMG data were used to normalize the EMG data collected from the experimental trials. The subject was then fitted with a LMM and was instructed to stand on a force plate to calibrate the biomechanical model. Biomechanical data were collected every 15 min. At the end of the two-hour task, the subject was transported back to the GCRC for the 0 h after task blood draw. After the 0 h blood draw, the subject was provided lunch and rest before the 2 h after task blood draw. Twenty-four hours following the lifting task, the subject returned for a final blood draw.

### 2.6. Biomechanical variables

The biomechanical data collected during each lifting session were used as inputs to the EMG-assisted spine model to predict three-dimensional spinal loads and muscle forces. Over the past 25 years, our laboratory has developed an EMG-assisted three-dimensional dynamic spine model that determines how the vertebral joints and surrounding tissues of the lumbar spine are loaded under realistic occupational conditions (Marras and Granata, 1997a). The model has been validated for robustness in sagittal bending (Granata and Marras, 1993), lateral bending (Marras and Granata, 1997b), axial twisting (Marras and Granata, 1995), lowering exertions (Davis et al., 1998), and repetitive lifting (Marras et al., 2006). The model has also been adjusted to incorporate compression and shear calculations at each level of the lumbar spine (Knapik and Marras, 2009). In the current study, baseline (non-lifting) biomechanical measures were obtained by modeling the data collected when the subjects were in an upright standing posture before the lifting trials started. The methods used to model the non-lifting data were the same as those used for the lifting exertions. Biomechanical measures (model output) included peak compression, anterior–posterior (A/P) shear, and lateral shear forces at each inferior and superior endplate level from L5/S1 to T12/L1, as well as the muscle forces for ten power producing trunk muscles.

### 2.7. Biochemical variables

Variables included IL-1 $\beta$ , TNF- $\alpha$ , IL-8, IL-10, IL-6, PGE<sub>2</sub>, white blood cell count (WBC), granulocyte percentage (GRANp), granulocyte absolute count (GRANa), and creatine kinase (CK). For each draw, 15 ml of venous blood was acquired from the antecubital vein using standard phlebotomy techniques. Samples were immediately analyzed for WBC, GRANa, GRANp, and CK. Samples for cytokines and PGE<sub>2</sub> were immediately centrifuged, aliquoted, and placed in  $-80^{\circ}\text{C}$  freezer storage until analysis. These samples were assayed in duplicate using Human Proinflammatory-4 II Ultra-Sensitive, Human IL-10 Ultra-Sensitive, and PGE<sub>2</sub> 96-well Kits (Meso Scale Discovery, Gaithersburg, MD, USA) per kit instructions. Changes in body hydration status due to sweating and drinking water may cause changes in plasma volume, which will affect the accuracy of the measurements of plasma protein concentrations. Therefore, adjustments to raw concentration values of the biochemical variables were made according to previous methods (Dill and Costill, 1974).

### 2.8. Data analyses

For each biochemical variable, change from baseline value was calculated by subtracting the baseline from the values of subsequent time points (0, 2 and 24 h post) for each experimental condition. Mean

and SD of the changes from baseline value were also obtained for each weight condition at each time point. The SAS mixed procedure with repeated measures (SAS Institute Inc., Cary, NC, USA) was used to test the main and interaction effects of weight and time. Post-hoc analyses identified significant contrasts between different levels of the main and interaction effects. All factors were considered significant at an alpha level of 0.05.

Maximum spinal loads and muscle forces during the two-hour lifting period were obtained for each subject under each weight condition. Maximum compression, A/P, and lateral shear forces across all levels of the lumbar spine were also identified for each subject under each weight condition. A correlation matrix containing the Pearson correlation coefficients ( $r$ ) between the maximum tissue loads and the maximum change of biochemical variables was generated.

## 3. Results

### 3.1. Biochemical responses

The main and interaction effects of weight and time on IL-6, WBC, GRANp, GRANa, and CK were all significant. For IL-1 $\beta$ , IL-10, and TNF- $\alpha$ , only time had a significant effect. No significant effects of weight, time or their interaction were found for IL-8 and PGE<sub>2</sub> (Table 1).

Post-hoc analyses showed that IL-6 levels increased immediately following the 2.3 kg lifting task (1.811 pg/ml) compared to the baseline (1.077 pg/ml,  $P=0.0441$ ), while lifting 11.3 kg resulted in IL-6 elevations at both the 0 h (3.667 pg/ml) and 2 h post (3.219 pg/ml) time points compared to the baseline (1.098 pg/ml,  $P<0.0001$ ). When compared to the same time points between weight conditions, the changes in IL-6 levels at 0 h and 2 h after lifting 11.3 kg were significantly higher than the diurnal changes under the control condition ( $P<0.0001$  for both time points) and the 2.3 kg lifting condition ( $P<0.0001$  for 0 h post and  $P=0.0016$  for 2 h post, respectively, Fig. 1).

IL-1 $\beta$  had a 70% increase at 2 h post (0.366 pg/ml) from baseline (0.214 pg/ml) after lifting 11.3 kg ( $P=0.0245$ , Fig. 2), while TNF- $\alpha$  showed an 18% increase at 2 h post after the same task (7.507 pg/ml vs. 6.347 pg/ml at baseline,  $P=0.0033$ , Fig. 3). TNF- $\alpha$  levels for the 11.3 kg condition were also higher than the 2.3 kg condition 24 h after the lifting task ( $P=0.041$ ).

IL-10 had a significant main effect of time, however, it was essentially driven by the diurnal fluctuation of the control condition. The IL-10 responses after the 2.3 and 11.3 kg lifting tasks were not significant over time.

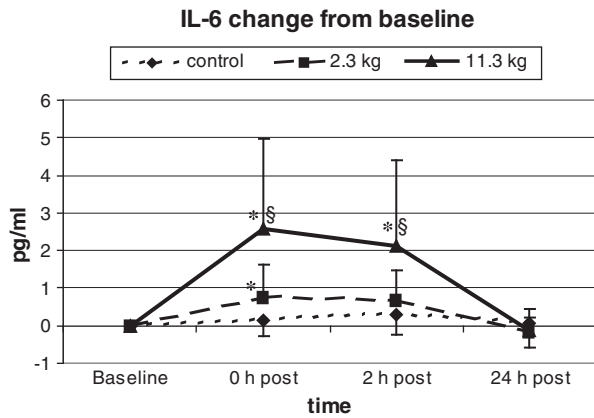
The absolute granulocyte count increased from baseline at 0 h and 2 h post under both lifting conditions ( $P<0.001$ ). The 11.3 kg condition also showed significant change from 0 h (3.8 K/ $\mu\text{L}$ ) to 2 h post (5.0 K/ $\mu\text{L}$ ,  $P=0.0007$ ), resulting in a linear increase from baseline (2.6 K/ $\mu\text{L}$ , Fig. 4). At 24 h post-lifting the response of granulocytes returned to the baseline for both lifting conditions. When compared to the same time points of the control condition, both lifting tasks resulted in greater changes at 0 h and 2 h post ( $P<0.05$ ). At 2 h post the increase in granulocytes from baseline under the 11.3 kg condition (2.3 K/ $\mu\text{L}$  change) was almost

**Table 1**

$P$ -values of the effects of load weight and time since task exposure on biochemical variables.

	Weight	Time	Weight $\times$ Time
IL-1 $\beta$	0.2092	0.0225*	0.8192
TNF- $\alpha$	0.1952	0.043*	0.5619
IL-6	<0.0001*	<0.0001*	0.0011*
IL-10	0.9398	0.0132*	0.6662
WBC	<0.0001*	<0.0001*	0.0004*
GRANp	<0.0001*	0.0011	<0.0001*
GRANa	<0.0001*	<0.0001*	<0.0001*
CK	<0.0001*	0.0038*	0.02*

\* Indicates a significant effect ( $P<0.05$ ).



**Fig. 1.** IL-6 response to different weight conditions over time. The data represented are mean (SD) of the change from baseline values. \*Significantly different from baseline,  $P < 0.05$ . <sup>§</sup>Significantly different between weight conditions at the same time point (0 h post: 11.3 kg vs. control and 11.3 kg vs. 2.3 kg; 2 h post: 11.3 kg vs. control and 11.3 kg vs. 2.3 kg),  $P < 0.01$ .

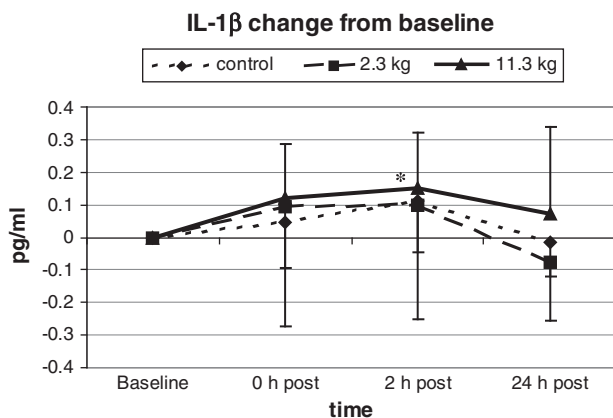
twice the response to the 2.3 kg condition (1.2 K/ $\mu$ L change), demonstrating a dose–response relationship. The responses of total WBC and granulocyte percentage were similar to the absolute count of granulocytes.

CK levels continued to increase from baseline until 24 h post-lifting, with the 2.3 kg task showing a 27% increase from 140 U/L to 178 U/L ( $P = 0.0214$ ) and the 11.3 kg condition resulting in an increase of 116% from 114 U/L to 246 U/L ( $P < 0.0001$ , Fig. 5). For the 11.3 kg condition, the changes in CK were also higher than the control condition at 2 h and 24 h post time points ( $P = 0.0214$  and  $P < 0.0001$ , respectively).

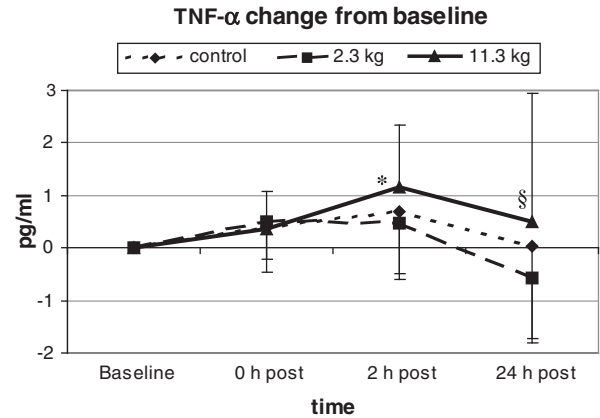
### 3.2. Biomechanical loading

Table 2 shows the maximum spinal loads across all the levels of the lumbar spine and the maximum muscle forces for each experimental condition. Compressive forces were higher for the 11.3 kg condition compared to the control and 2.3 kg conditions at each level ( $P < 0.0001$ ). However, even for the 11.3 kg condition forces were generally below the 3400 N tolerance threshold expected to result in endplate microfractures (NIOSH, 1981, 1994). Compressive forces tended to be greatest at lower levels (L5/S1 superior endplate and L4/L5 inferior endplate) and decreased at upper levels of the lumbar spine.

A/P shear forces peaked at the L2/L3 superior and the L1/L2 inferior endplate levels. When lifting 2.3 kg, A/P shear forces from the L2/L3 superior to the T12/L1 inferior endplates reached the 1000 N shear



**Fig. 2.** IL-1 $\beta$  response to different weight conditions over time. The data represented are mean (SD) of the change from baseline values. \*Significantly different from baseline (11.3 kg: 2 h post vs. baseline),  $P < 0.05$ .



**Fig. 3.** TNF- $\alpha$  response to different weight conditions over time. The data represented are mean (SD) of the change from baseline values. \*Significantly different from baseline (11.3 kg: 2 h post vs. baseline),  $P < 0.01$ . <sup>§</sup>Significantly different between weight conditions at the same time point (24 h post: 11.3 kg vs. 2.3 kg),  $P < 0.05$ .

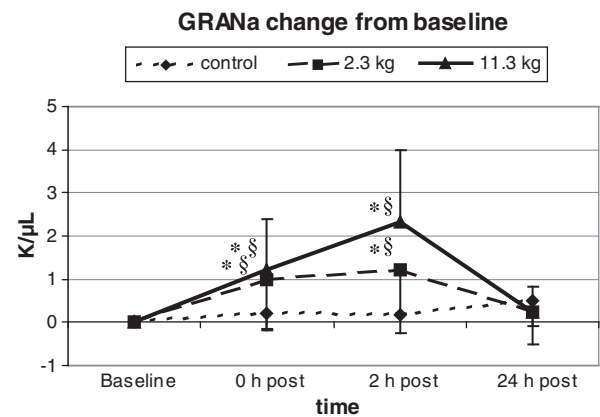
tolerance threshold reported in the literature (Cyron and Hutton, 1978; McGill, 1997). The 11.3 kg condition resulted in A/P shear forces greater than 1000 N throughout almost the entire lumbar spine.

Lateral shear forces tended to increase from lower to upper lumbar spine with the highest value at the T12/L1 superior endplate. However, the magnitude of these forces was well below the level that would be expected to lead to damage (Cyron and Hutton, 1978; McGill, 1997).

The peak forces generated in most trunk muscles were lower than 200 N, except for the RES and LES, whose forces were about 500 N for the 2.3 kg condition and 800 N for the 11.3 kg condition.

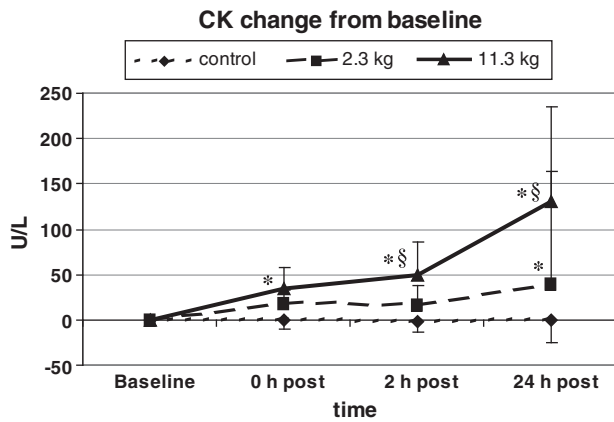
### 3.3. Correlation analysis

Correlations between the maximum spinal loads and muscle forces and the biochemical responses are displayed in Table 3. IL-1 $\beta$  had significant correlations with the maximum muscle forces of RLD, LLD, RIO, and LJO, while IL-10 showed similar moderate correlations with RRA, REO, and LEO. The relationships between TNF- $\alpha$  and biomechanical variables were all non-significant. In contrast, IL-6 levels were correlated with all biomechanical variables compared to other biochemical measures. The highest correlation was seen between the maximum A/P shear force and IL-6 ( $r = 0.695$ ). Both IL-8 and PGE<sub>2</sub> had low correlations with biomechanical variables. All the hematological measures (WBC, GRANp, and GRANa) and CK had many moderate correlations with spine loading and muscle forces.



**Fig. 4.** GRANa response to different weight conditions over time. The data represented are mean (SD) of the change from baseline values. \*Significantly different from baseline,  $P < 0.001$ . <sup>§</sup>Significantly different between weight conditions at the same time point (0 h post: 2.3 kg vs. control and 11.3 kg vs. control; 2 h post: 2.3 kg vs. control, 11.3 kg vs. control and 11.3 kg vs. 2.3 kg),  $P < 0.05$ .





**Fig. 5.** CK response to different weight conditions over time. The data represented are mean (SD) of the change from baseline values. \*Significantly different from baseline,  $P < 0.05$ . §Significantly different between weight conditions at the same time point (2 h post: 11.3 kg vs. control; 24 h post: 11.3 kg vs. control and 11.3 kg vs. 2.3 kg),  $P < 0.05$ .

#### 4. Discussion

To our knowledge, this was the first study that investigated acute systemic inflammatory responses to specific biomechanical loadings of the low back in human subjects. Levels of IL-6, WBC, granulocytes, and CK all increased after both weight-lifting tasks, with the greatest changes observed with the higher tissue loadings generated during the heavier lifting task (11.3 kg). Similarly, plasma levels of IL-1 $\beta$  and TNF- $\alpha$  both increased following the heavier lifting task. These inflammatory responses were significantly correlated with specific spinal tissue loads.

Among the cytokines, IL-6 was the most responsive to the loading conditions. The control condition showed a 28% increase in IL-6 levels in the afternoon samples. This was consistent with the reported circadian change in IL-6 in young, healthy males (Vgontzas et al., 2005). The 2.3 kg and 11.3 kg loading conditions resulted in a 68% and 234% increase in IL-6, respectively. The trend of IL-6 concentration over time was consistent with previous running exercise studies (Langberg et al., 2002; Peake et al., 2005b). The magnitude of change was lower than that reported in the running studies, perhaps due to less stressful intensities of our experimental tasks. IL-1 $\beta$  and TNF- $\alpha$  are both pro-inflammatory cytokines that also showed increased plasma levels at the heavier lifting task. Taken together, the profile of cytokine up-regulations along with other biochemical responses support our original hypotheses that there was an acute inflammatory response to occupational tasks stressing the low back. These findings extend our understanding of the physiological responses to loading tasks incorporating the lumbar spine. We propose that when mechanical loads act on various tissues in the low back, micro- or small tissue injuries are produced. The tissue injury can initiate the release of inflammatory cytokines, such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  that in turn may act as inflammatory mediators and initiate pathways leading to low back pain.

The current study did not find statistically significant changes in plasma IL-8 and PGE<sub>2</sub> levels, perhaps due to the relatively low intensity of the tasks. In addition, we did not observe any differences for IL-10. Inconsistent results have been noted regarding IL-10 and its response to endurance exercise (Brenner et al., 1999; Peake et al., 2005a). Several reasons might account for our findings. First, the inflammatory response elicited in this study may not have been strong enough to initiate an increase in IL-10. Second, the up-regulation of IL-10 may occur after the pro-inflammatory response of IL-6, which would be after the 2 h post sampling time. Therefore, it is possible that an increase in IL-10 was missed by the current sampling protocol. Further study with additional data collection between the 2 h post and 24 h post time points is needed to elucidate this issue.

Our biomechanical model of the lumbar spine provided an opportunity to study the internal tissue loads in a more detailed and realistic fashion. Therefore, it is noteworthy that in the present study the A/P shear forces at various lumbar spine levels exceeded the reported 1000 N shear threshold (Cyron and Hutton, 1978; McGill, 1997), while the compressive forces were below the NIOSH recommended 3400 N limit (NIOSH, 1981, 1994). As seen in the correlation matrix, one biomechanical variable can have moderate correlations with multiple biochemical measures. And vice versa, one biochemical measure can be correlated with many biomechanical variables. One reason for this observation could be that some of the biomechanical variables are highly correlated, such as compression, A/P, and lateral shear loads with muscle forces. It could also be due to the fact that the experimental tasks involved multiple trunk muscles, which may all contribute to the biochemical responses. It is also possible for muscles from other parts of the body (shoulder, elbow, etc.) to respond to the physical work. We did not directly measure the exact sources of the up-regulated cytokines, as tissue biopsies were not practical in the current study. However, the discomfort data (not reported here) showed the back had the highest pain and discomfort rating. Previous study has found correlations between local muscle pain and significantly increased inflammatory mediators within the local tissues (Shah et al., 2005). We believe therefore that the spine muscles play a critical role in the cytokine responses observed in our subjects.

In order to further investigate the relationship between observed changes in cytokine levels and biomechanical factors, multiple regression models were developed using biomechanical variables and individual factors as independent variables and cytokine responses as dependent variables. The explanatory power of these models varied from R<sup>2</sup> values between 0.3 and 0.58. The multiple regression models included primarily muscle forces and individual factors. However, A/P shear forces were present in the strongest model and predicted IL-6 well. In addition, individual factors (anthropometric factors) entered the models and when combined with muscle forces, suggest individual biomechanical factors are important in defining cytokine responses.

Our current understanding of the causal pathways of LBD is based on epidemiological and biomechanical studies that rely on a mechanical load-tolerance model. This model lacks information on how mechanical loading may affect biological responses that can lead

**Table 2**

Mean and SD of the maximum spinal loads across all the levels of the lumbar spine and the maximum muscle forces for each experimental condition (unit: N).

		Compression (L5/S1 SUP)	A/P shear (L2/L3 SUP)	Lateral shear (T12/L1 SUP)	RLD	LLD	RES	LES	RRA	LRA	REO	LEO	RIO	LIO
Control	Mean	825.04	505.92	13.19	12.22	6.82	36.46	39.69	8.03	8.89	12.88	13.58	14.00	13.45
	SD	111.88	72.09	4.94	9.73	2.49	21.71	27.87	5.75	5.37	9.88	9.63	8.05	6.37
2.3 kg	Mean	2027.88	1061.64	205.81	64.74	57.81	541.66	488.42	16.41	17.73	52.20	43.26	93.55	100.72
	SD	453.22	273.44	64.17	41.91	30.72	174.98	147.12	14.00	17.18	71.28	41.55	50.18	41.98
11.3 kg	Mean	2833.01	1605.19	334.62	124.69	96.61	799.10	821.91	25.45	26.04	76.64	73.50	163.31	175.59
	SD	485.61	366.99	123.45	86.31	46.80	173.72	230.74	18.04	19.55	65.36	59.99	77.57	81.20

SD = standard deviation; SUP = superior endplate; RLD = right latissimus dorsi; LLD = left latissimus dorsi; RES = right erector spinae; LES = left erector spinae; RRA = right rectus abdominus; LRA = left rectus abdominus; REO = right external obliques; LEO = left external obliques; RIO = right internal obliques; LIO = left internal obliques.

**Table 3**  
Correlation matrix between the maximum tissue loads and the maximum biochemical responses.

	IL-1 $\beta$	IL-10	TNF- $\alpha$	IL-6	IL-8	PGE <sub>2</sub>	WBC	GRANp	GRANa	CK
LAT	0.285	0.008	0.196	<b>0.652</b>	0.104	0.114	0.310	<b>0.428</b>	<b>0.358</b>	<b>0.533</b>
COMP	0.327	0.015	0.206	<b>0.581</b>	0.092	0.064	<b>0.358</b>	<b>0.486</b>	<b>0.415</b>	<b>0.505</b>
A/P	0.259	0.056	0.271	<b>0.695</b>	0.216	−0.026	0.209	<b>0.367</b>	0.275	<b>0.491</b>
RLD	<b>0.455</b>	0.005	0.143	<b>0.587</b>	0.012	−0.033	0.033	0.166	0.085	<b>0.403</b>
LLD	<b>0.342</b>	0.079	0.144	<b>0.579</b>	0.000	0.072	<b>0.372</b>	<b>0.401</b>	<b>0.418</b>	<b>0.477</b>
RES	0.234	−0.010	0.222	<b>0.549</b>	0.046	0.075	<b>0.367</b>	<b>0.538</b>	<b>0.450</b>	<b>0.558</b>
LES	0.305	0.024	0.170	<b>0.562</b>	0.144	−0.010	<b>0.382</b>	<b>0.510</b>	<b>0.437</b>	<b>0.390</b>
RRA	0.299	<b>0.333</b>	0.126	<b>0.536</b>	0.027	0.303	<b>0.480</b>	0.323	<b>0.460</b>	<b>0.363</b>
LRA	0.291	0.179	0.179	<b>0.441</b>	0.087	<b>0.336</b>	<b>0.342</b>	0.206	0.314	<b>0.392</b>
REO	0.135	<b>0.518</b>	−0.033	<b>0.359</b>	0.130	−0.076	<b>0.625</b>	0.264	<b>0.561</b>	0.155
LEO	0.121	<b>0.512</b>	−0.012	<b>0.507</b>	0.153	−0.049	<b>0.574</b>	<b>0.342</b>	<b>0.543</b>	0.194
RIO	<b>0.364</b>	0.073	0.225	<b>0.592</b>	0.257	−0.262	0.143	<b>0.360</b>	0.217	0.321
LIO	<b>0.340</b>	0.077	0.147	<b>0.620</b>	0.191	−0.149	0.226	<b>0.435</b>	0.284	<b>0.419</b>

Values shown are Pearson correlation coefficients (*r*). Bold values indicate  $P < 0.05$ .

LAT = lateral shear; COMP = compression; A/P = anterior–posterior shear; RLD = right latissimus dorsi; LLD = left latissimus dorsi; RES = right erector spinae; LES = left erector spinae; RRA = right rectus abdominus; LRA = left rectus abdominus; REO = right external obliques; LEO = left external obliques; RIO = right internal obliques; LIO = left internal obliques.

to back pain development. The present study not only demonstrated that inflammatory cytokines were a key part of the biological responses, but also suggested that using biomechanical measures (e.g. compressive force) or focusing on one tissue in the lumbar spine (e.g. the endplate) is probably not sufficient to mitigate the risk of LBD. The A/P shear and muscle forces appear to contribute more to the inflammatory responses. Moreover, the study suggests that tissue inflammatory tolerances could be exceeded before structural damage occurs. This could change our view of LBD causality by shifting the focus from a purely biomechanical pathway to a systematic process that begins with a biomechanical stimulus that triggers a biochemical pathway. With this logic, the inflammatory tolerances could be much lower than the biomechanical thresholds. Therefore, assessment tools based on the inflammatory tolerances might be more protective than the ones based on the biomechanical thresholds.

There are several limitations of the current research that should be considered. First, the participants were all young, male subjects who had no experience with manual materials handling jobs. How their responses compare with subjects who perform these tasks on a regular basis is not predicted from this current study. Second, the current study only tested two loading conditions at one frequency and represents limited exposure conditions. More studies are needed to investigate the effect of frequency or the cumulative effect of weight and frequency. Third, the experimental tasks were two hours in duration and represent a much shorter workday than typically experienced by most workers. Because duration is positively related to systemic cytokine response, stronger responses would be expected if subjects were tested for an entire day. Fourth, there was a 20-min delay in obtaining the 0 h after task blood sample due to transportation of subjects. The biochemical responses may therefore have been reduced by this delay in venous blood sampling. No blood samples were collected between the 2 h and 24 h after task samples. Therefore, we were not able to characterize the nature of any responses between these time points. Fifth, our biomechanical model did not estimate forces on ligaments and facet joints yet both of these tissues may be quite important in terms of withstanding loads and producing inflammatory cytokines.

## 5. Conclusions

The current study indicates that there are acute inflammatory responses to biomechanical loading that involve various cytokines, especially IL-6, occurring after physical activities common to many working individuals. This study introduces a paradigm shift in the way we view LBD in that biomechanical forces acting upon the spine's tissues may serve as a stimulus for biochemical responses that could lead to low back pain. This process may occur at stimulus levels that

are far less than the levels typically associated with tissue damage. This may help explain why the vast majority of LBD cannot be identified using imaging technology (McNally et al., 2001; Savage et al., 1997). Moreover, identifying the sources of cytokine production may lead to novel treatment and prevention approaches.

## Conflict of interest statement

There is no commercial relationships or conflict of interest related to this work. No author has any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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## References

- Ahn, S.H., Cho, Y.W., Ahn, M.W., Jang, S.H., Sohn, Y.K., Kim, H.S., 2002. mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. *Spine* 27, 911–917.
- Andersson, G.B., 1981. Epidemiologic aspects on low-back pain in industry. *Spine* 6, 53–60.
- Barbe, M.F., Elliott, M.B., Abdelmagid, S.M., Amin, M., Popoff, S.N., Safadi, F.F., et al., 2008. Serum and tissue cytokines and chemokines increase with repetitive upper extremity tasks. *J. Orthop. Res.* 26, 1320–1326.
- Bass, E.C., Duncan, N.A., Hariharan, J.S., Dusick, J., Bueff, H.U., Lotz, J.C., 1997. Frozen storage affects the compressive creep behavior of the porcine intervertebral disc. *Spine* 22, 2867–2876.
- Brenner, I.K., Natale, V.M., Vasiliou, P., Moldoveanu, A.I., Shek, P.N., Shephard, R.J., 1999. Impact of three different types of exercise on components of the inflammatory response. *Eur. J. Appl. Physiol.* 80, 452–460.
- Bruunsgaard, H., Galbo, H., Halkjaer-Kristensen, J., Johansen, T.L., MacLean, D.A., Pedersen, B.K., 1997. Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage. *J. Physiol.* 499 (Pt 3), 833–841.
- Burke, J.G., Watson, R.W., McCormack, D., Dowling, F.E., Walsh, M.G., Fitzpatrick, J.M., 2002. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J. Bone Joint Surg. Br.* 84, 196–201.
- Chaffin, D.B., Park, K.S., 1973. A longitudinal study of low-back pain as associated with occupational weight lifting factors. *Am. Ind. Hyg. Assoc. J.* 34, 513–525.
- Cyron, B.M., Hutton, W.C., 1978. The fatigue strength of the lumbar neural arch in spondylosis. *J. Bone Joint Surg. Br.* 60-B, 234–238.
- Davis, K.G., Marras, W.S., Waters, T.R., 1998. Evaluation of spinal loading during lowering and lifting. *Clin. Biomech.* 13, 141–152.
- Deyo, R.A., Weinstein, J.N., 2001. Low back pain. *N. Engl. J. Med.* 344, 363–370.

- Dill, D.B., Costill, D.L., 1974. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J. Appl. Physiol.* 37, 247–248.
- Elliott, M.B., Barr, A.E., Clark, B.D., Amin, M., Amin, S., Barbe, M.F., 2009. High force reaching task induces widespread inflammation, increased spinal cord neurochemicals and neuropathic pain. *Neuroscience* 158, 922–931.
- Fathallah, F.A., Marras, W.S., Parnianpour, M., Granata, K.P., 1997. A method for measuring external spinal loads during unconstrained free-dynamic lifting. *J. Biomech.* 30, 975–978.
- Fielding, R.A., Manfredi, T.J., Ding, W., Fiatarone, M.A., Evans, W.J., Cannon, J.G., 1993. Acute phase response in exercise. III. Neutrophil and IL-1 beta accumulation in skeletal muscle. *Am. J. Physiol.* 265, R166–R172.
- Granata, K.P., Marras, W.S., 1993. An EMG-assisted model of loads on the lumbar spine during asymmetric trunk extensions. *J. Biomech.* 26, 1429–1438.
- Hoozemans, M.J., van der Beek, A.J., Fring-Dresen, M.H., van der Woude, L.H., van Dijk, F.J., 2002. Low-back and shoulder complaints among workers with pushing and pulling tasks. *Scand. J. Work Environ. Health* 28, 293–303.
- Igarashi, A., Kikuchi, S., Konno, S., Olmarker, K., 2004. Inflammatory cytokines released from the facet joint tissue in degenerative lumbar spinal disorders. *Spine* 29, 2091–2095.
- Kang, J.D., Georgescu, H.I., McIntyre-Larkin, L., Stefanovic-Racic, M., Donaldson 3rd, W.F., Evans, C.H., 1996. Herniated lumbar intervertebral discs spontaneously produce matrix metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2. *Spine* 21, 271–277.
- Keller, T.S., Holm, S.H., Hansson, T.H., Spengler, D.M., 1990. Volvo Award in experimental studies. The dependence of intervertebral disc mechanical properties on physiologic conditions. *Spine* 15, 751–761.
- King, K., Davidson, B., Zhou, B.H., Lu, Y., Solomonow, M., 2009. High magnitude cyclic load triggers inflammatory response in lumbar ligaments. *Clin. Biomech.* 24, 792–798.
- Knapiak, G.G., Marras, W.S., 2009. Spine loading at different lumbar levels during pushing and pulling. *Ergonomics* 52, 60–70.
- Langberg, H., Olesen, J.L., Gemmer, C., Kjaer, M., 2002. Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. *J. Physiol.* 542, 985–990.
- McIntyre, D.L., Reid, W.D., Lyster, D.M., McKenzie, D.C., 2000. Different effects of strenuous eccentric exercise on the accumulation of neutrophils in muscle in women and men. *Eur. J. Appl. Physiol.* 81, 47–53.
- Marras, W.S., 1990. Industrial electromyography. *Int. J. Ind. Ergon.* 6, 89–93.
- Marras, W.S., Granata, K.P., 1995. A biomechanical assessment and model of axial twisting in the thoracolumbar spine. *Spine* 20, 1440–1451.
- Marras, W.S., Granata, K.P., 1997a. The development of an EMG-assisted model to assess spine loading during whole-body free-dynamic lifting. *J. Electromyogr. Kinesiol.* 7, 259–268.
- Marras, W.S., Granata, K.P., 1997b. Spine loading during trunk lateral bending motions. *J. Biomech.* 30, 697–703.
- Marras, W.S., Lavender, S.A., Leurgans, S.E., Rajulu, S.L., Allread, W.G., Fathallah, F.A., et al., 1993. The role of dynamic three-dimensional trunk motion in occupationally-related low back disorders. The effects of workplace factors, trunk position, and trunk motion characteristics on risk of injury. *Spine* 18, 617–628.
- Marras, W.S., Lavender, S.A., Leurgans, S.E., Fathallah, F.A., Ferguson, S.A., Allread, W.G., et al., 1995. Biomechanical risk factors for occupationally related low back disorders. *Ergonomics* 38, 377–410.
- Marras, W.S., Parakkat, J., Chany, A.M., Yang, G., Burr, D., Lavender, S.A., 2006. Spine loading as a function of lift frequency, exposure duration, and work experience. *Clin. Biomech.* 21, 345–352.
- McGill, S.M., 1997. The biomechanics of low back injury: implications on current practice in industry and the clinic. *J. Biomech.* 30, 465–475.
- McNally, E.G., Wilson, D.J., Ostlere, S.J., 2001. Limited magnetic resonance imaging in low back pain instead of plain radiographs: experience with first 1000 cases. *Clin. Radiol.* 56, 922–925.
- Mirka, G.A., Marras, W.S., 1993. A stochastic model of trunk muscle coactivation during trunk bending. *Spine* 18, 1396–1409.
- Nieman, D.C., Davis, J.M., Henson, D.A., Walberg-Rankin, J., Shute, M., Dumke, C.L., et al., 2003. Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. *J. Appl. Physiol.* 94, 1917–1925.
- NIOSH, 1981. *Work Practices Guide for Manual Lifting*. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH.
- NIOSH, 1994. *Applications Manual for the Revised NIOSH Lifting Equation*. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH.
- NRC, 2001. *Musculoskeletal Disorders and the Workplace: Low Back and Upper Extremities*. National Academy of Sciences, National Research Council, National Academy Press, Washington, DC.
- Ohtori, S., Inoue, G., Ito, T., Koshi, T., Ozawa, T., Doya, H., et al., 2006. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and modic type 1 or type 2 changes on MRI. *Spine* 31, 1026–1031.
- Palmer, E.L., Lotz, J.C., 2004. The time dependent role of cytokines in mechanically induced intervertebral disc degeneration. *Transactions of the 50th Annual Meeting of the Orthopaedic Research Society*, San Francisco, CA, USA.
- Peake, J.M., Suzuki, K., Hordern, M., Wilson, G., Nosaka, K., Coombes, J.S., 2005a. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur. J. Appl. Physiol.* 95, 514–521.
- Peake, J.M., Suzuki, K., Wilson, G., Hordern, M., Nosaka, K., Mackinnon, L., et al., 2005b. Exercise-induced muscle damage, plasma cytokines, and markers of neutrophil activation. *Med. Sci. Sports Exerc.* 37, 737–745.
- Savage, R.A., Whitehouse, G.H., Roberts, N., 1997. The relationship between the magnetic resonance imaging appearance of the lumbar spine and low back pain, age and occupation in males. *Eur. Spine J.* 6, 106–114.
- Scholz, J., Woolf, C.J., 2002. Can we conquer pain? *Nat. Neurosci.* 5 (Suppl), 1062–1067.
- Shah, J.P., Phillips, T.M., Danoff, J.V., Gerber, L.H., 2005. An in vivo microanalytical technique for measuring the local biochemical milieu of human skeletal muscle. *J. Appl. Physiol.* 99, 1977–1984.
- Skutek, M., van Griensven, M., Zeichen, J., Brauer, N., Bosch, U., 2001. Cyclic mechanical stretching enhances secretion of interleukin 6 in human tendon fibroblasts. *Knee Surg. Sports Traumatol. Arthrosc.* 9, 322–326.
- 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, 218–224.
- Toumi, H., Best, T.M., 2003. The inflammatory response: friend or enemy for muscle injury? *Br. J. Sports Med.* 37, 284–286.
- Tsuzaki, M., Bynum, D., Almekinders, L., Yang, X., Faber, J., Banes, A.J., 2003. ATP modulates load-inducible IL-1beta, COX 2, and MMP-3 gene expression in human tendon cells. *J. Cell. Biochem.* 89, 556–562.
- Vgontzas, A.N., Bixler, E.O., Lin, H.M., Prolo, P., Trakada, G., Chrousos, G.P., 2005. IL-6 and its circadian secretion in humans. *Neuroimmunomodulation* 12, 131–140.
- Wang, D.L., Jiang, S.D., Dai, L.Y., 2007. Biologic response of the intervertebral disc to static and dynamic compression in vitro. *Spine* 32, 2521–2528.