

Immune responses following McKenzie lumbar spine exercise in individuals with acute low back pain: A preliminary study

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Introduction

Herniation of an intervertebral disc is implicated in 40% of acute low back pain (ALBP) (1). Mechanical pressure created by the escaped nucleus pulposus, and the inflammatory responses that follow, excite the nociceptive system, and trigger spinal pain and

Objective. This study explores the immune responses following 4 weeks of McKenzie lumbar spine exercise in individuals with acute low back pain (ALBP). **Patients and methods.** Fifteen patients with ALBP and 15 healthy individuals volunteered in this study. Ten ml of peripheral blood were obtained from each patient before and after exercise sessions, and from healthy individuals at the beginning of the study. Flow cytometric analysis was used to evaluate the frequencies of CD4+ T lymphocyte sub-populations and the intracellular cytokine expression within this cell population. Pain perceptions were obtained at baseline and following each week of exercise sessions. **Results.** In comparison with healthy subjects there was an elevated frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and a lower frequency of naïve/suppressor (CD4+CD45RA+) T cells at base line in back pain patients ($p < 0.05$). After 4 weeks of McKenzie exercise sessions, pain intensity significantly decreased ($p < 0.05$); however, there was no significant difference in the frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and naïve/suppressor (CD4+CD45RA+) T cells at base line relative to these cell populations after exercise sessions. The percentage of Pan (CD3+) T cells expressing IL-8 and TNF- α and the CD3+ T cells expressing the anti-inflammatory cytokine IL-4 increased significantly ($p < 0.05$) following exercise sessions in comparison with baseline and healthy references. The reduction in pain scores did not correlate with elevated anti-inflammatory cytokines. **Conclusion.** McKenzie exercise sessions induced an immune activation state and simultaneously up regulated anti-inflammatory IL-4 cytokines that boost pain relief.

Key words: McKenzie lumbar spine exercise, Inflammation, Lymphocytes, Intracellular cytokines.

dysfunction (2-4). McKenzie exercises are commonly used to relief pain and restore spine mobility (3, 5-9).

During the McKenzie assessment protocol, the therapist usually observes changes in pain intensity and location, known as the pain centralization phenomenon (3, 5,

6). Centralization of pain, observed only in discogenic pain, and is clinically defined as a shift in the pain from a distal to a more proximal location to the spine, in response to spinal loading by directional preference exercise or positions (3, 5, 6). The physical therapist then prescribes exercises that are performed in the direction that centralizes and/or abolishes the pain (3, 5, 6, 9-11). The positional change of the nucleus pulposus in response to these directional preference exercises is referred to as the dynamic disc model (3, 9). Conceptually, the disc dynamic model proposes that in a healthy disc with intact annulus fibers and hydrostatic mechanisms, the nucleus pulposus will move in the opposite direction to the spinal loading imposed by a specific body position or movements performed in a specific direction (3, 5-9, 12).

Accordingly, pain centralization and the associated pain relief have been exclusively explained on the basis of the disc dynamic model. However, biochemically pain arises from inflammation and inflammatory responses, regardless of its type or nature (1, 2). Biochemical mediators of pain include: cytokines, growth factors, neuropeptides and neurotransmitters (1, 2). The human intervertebral disc is avascular in nature, and the nucleus pulposus is immune-privileged. When a disc is herniated, the escaped nucleus pulposus is exposed to the immune system and triggers the release of pro-inflammatory cytokines, such as: interleukins, (IL)-1, IL-6, IL-8, prostaglandin E2, nitric oxide (1, 2 13-16) and IL-17 (17), as well as other regulatory cytokines including tumor necrosis factor alpha (TNF α), interferon gamma (IFN- γ) and IL-1 β . Normally, pro-inflammatory cytokines are counter-balanced by the release of anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1 α), IL-10, IL-4, IL-13, and transforming growth factor- β -1 (TGF- β 1) (1, 13), which maintain homeostasis (1, 13, 18).

There is evidence to suggest that exercise regulates immune responses (19-22). Studies show that changes in the plasma concen-

tration of cytokines depends on the type, intensity, and duration of physical exercise (18, 23-29). Moderately intense exercise boosts the immune system and reduces the risk of infection (27, 30-32), whereas intense and prolonged exercise induces pro-inflammatory cytokines and upper respiratory tract infections (28, 33).

Clinically suppressing pro-inflammatory cytokines by anti-inflammatory agents is usually considered the first-line treatment for patients with ALBP. In physical therapy, a non-invasive, non-chemical modality, such as therapeutic exercise, has been proven to be effective for pain relief. Whether therapeutic spinal exercise sessions trigger immune responses is worthy of investigation. We hypothesize that McKenzie exercises may have an immunoregulatory role that would rationalize pain relief.

Therefore, the aim of this study was to explore the immune responses following 4 weeks of intervention using McKenzie lumbar spine exercises in individuals with acute low back pain.

Methods

Patients

Initially, 65 patients (of Middle Eastern origin) with acute low back pain agreed to volunteer for the study. However, 21 were excluded because they were taking anti-inflammatory medications, 8 did not want to be treated only with McKenzie exercises, 6 did not return after the first visit, even though they demonstrated pain centralization, 15 patients did not demonstrate pain centralization (7 underwent lumbar microdiscectomy, and 8 received epidural injections). The final sample comprised of 15 patients who demonstrated pain centralization (9 males and 6 females; average age, 42.1 \pm 2.7 years). The blood of fifteen healthy individuals (8 males and 7 females; average age, 38.5 \pm 3.1 years) matched the basis of age, height and weight were used as refer-

ences for normal lymphocyte subpopulations and cytokines expression.

On their first visit to the physical therapy clinic each participant was screened for eligibility for participation in the study. Inclusion criteria were: ALBP lasting between 1 to < 7 days, extending between the 12th rib to the buttock with or without leg pain; with an established diagnosis of disc prolapse; referral for physiotherapy; acceptance to be treated by McKenzie exercises only, and not receiving worker's compensation. Exclusion criteria were: a spinal inflammatory and infectious disease; spinal fracture or dislocation; motor or sensory deficit; surgery within the past 6 months; concurrent inflammatory conditions; pregnancy; cardiopulmonary diseases; diabetes; cigarette smokers, utilization of pain medication (nonsteroidal anti-inflammatories drugs, steroids and analgesics), and psychotropic medications. Written consent was obtained from each participant and the study was approved by the institutional ethical committee.

Measurement of pain perception

Pain perception was measured by the visual analog scale (VAS), which is a 100-mm line used to reflect patient responses regarding pain intensity. The anchor terms on the VAS for overall pain and actual reported pain were: 0 mm for "no pain" and 100 mm for "maximum pain imaginable". Two types of pain perception were measured using two separate sheets of VAS; Overall pain (OP) measures pain throughout the day, and actual pain (AP) measures the intensity of pain at the time of the visit. High test-retest reliability has been found for the VAS, as well as high reliability when measuring multiple dimensions of pain, such as intensity, distress, and pain anticipation (34, 35). Pain measurements were obtained at the initial visit, prior to the McKenzie assessment, and at the end of each week.

Mackenzie assessment procedure

The McKenzie assessment protocol uses standardized questions soliciting information related to demographics, pain intensity, posture, nature of pain and general health. The objective information include: physical examination of posture, screening for spinal deformity, lumbar spine range of movement, and repeated spinal movement testing in a specific direction; in lying and standing postures with reference to pain and symptoms. Repeated spinal movements are: lumbar extension and flexion in standing and lying positions, lumbar side gliding when standing, and assessment of static end-range positions. Any change in the location of the pain was documented to determine occurrence of pain centralization. The procedure was repeated within 24–48 hours to confirm pain centralization (3, 5, 6, and 11). Pain centralization was based on the operational definition given by Werneke et al. (5, 6), and changes in pain location on body diagrams.

Treatment

Treatments were individually designed following the Robin McKenzie treatment techniques (3). The treatments included: use of sustained end-range positions, repeated directional preference exercises, vertebral mobilizations, and the use of passive lumbar supports. Exercises and manual techniques were implemented according to the McKenzie objective lumbar spine examinations. Movement(s) associated with pain centralization determined the direction of exercise, while movement(s) associated with peripheralization were avoided (3, 5, 9). Home exercises were selected from the directional preference exercises that enhance pain centralization and each patient was instructed to repeat the prescribed home exercises every 2 hours. Standardized instructions and advice regarding posture correction and the

use of passive lumbar supports were given to all participants (3). Treatment visits were scheduled within 24–48 hours of the initial assessment, with a minimum of 2 visits per week and a maximum of seven sessions over 4 weeks. Werneke et al. (5, 6) concluded that further reductions in lumbar pain are not to be expected if favorable changes in pain location are not evident by the 7th visit.

Satisfaction with treatment was based on the McKenzie criteria of recovery that included: reduction or total abolition of pain, recovery of full spinal movement previously avoided, and the ability to maintain good posture (3). In this study reduction in VAS >50% of base line scores of both the actual and the overall pain was considered satisfactory. In one study reduction of VAS of low back pain, correlated with reliable scales of the Short-Form 36 (SF-36), in particular the body-related dimension ($r=0.52$ and 0.70 , $p<0.001$) (35). No restrictions were placed on healthy individuals in terms of routine daily activities, sports or diet.

Phlebotomy and analysis of lymphocyte subpopulations

On the initial visit, and prior to McKenzie assessment and treatment, a 10 ml of venous blood was drawn from the right arm of each participant. Blood was drawn into tubes containing EDTA and the different lymphocyte subpopulations analyzed. In brief, 50 μ l of blood was added to 5 μ l of fluorescein-isothiocyanate (FITC) or phycoerythrin (RD1)-conjugated monoclonal antibodies against the surface markers of interest, and incubated for 30 min at room temperature. Blood cells were then treated with Q-prep (Coulter Corporation, Hialeah, FL, USA). A two-color fluorescence analysis was performed using an automated flow cytometer (Coulter FC 500). Monoclonal antibodies (Coulter Corporation, Hialeah, FL, USA), specific for human T-lymphocytes (CD3,

CD4), natural killer (NK) T cells (CD16/CD56) and indicators of lymphocyte activation (CD29, CD45RA, CD45RO) were used in the study. The blood was collected from all patients at baseline and immediately following 4 weeks of McKenzie exercise sessions. The participants in the healthy group donated 10 ml of blood at the beginning of the study, which was used as a reference for normal lymphocyte subpopulations and cytokine expression.

Cell cultures and intracellular cytokine analysis

Peripheral blood mononuclear cells (PBMC) were separated by Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient centrifugation. Cells were washed and suspended in RPMI 1640 medium (Gibco BRL, Gaithersburg, MD) at density of 1×10^6 cells/ml. PBMC were cultured in 96-well plates (200 μ l/well) and incubated for 24 hours at 37 °C. The cells were stimulated with 50 ng/ml of phorbol 12-myristate 13-acetate (PMA) 1 mg/ml of ionomycin and 2 mM monensin (Sigma, St. Louis, MO), and intracellular cytokine levels (IL1- β , IL-6, IL-8, TNF- α , IFN- γ , IL-4 and IL-13) were assessed by flow cytometry after three-color immunofluorescence staining.

Statistical analysis

Mean and standard deviation were reported for all variables. The Wilcoxon signed ranks test was used to compare differences between lymphocyte subpopulation frequencies in peripheral blood, cytokine expression of stimulated cells, and pain intensities at baseline and following every week of McKenzie intervention. For all variables, the patients were compared with the reference levels using the Kruskal-Wallis test, and if significant, the Mann-Whitney U-test was applied. Spearman rank correlation was

used to correlate between pain scores and lymphocyte subpopulations and cytokines levels before or after intervention. Data were analyzed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

Table 1 shows the demographic data for the ALBP patients. Table 2 displays a significant reduction in both pain scores after 4 weeks of McKenzie exercise sessions, more after

the 4th week of intervention relative to the baseline ($p < 0.01$).

Figure 1 displays the flow cytometric analysis of the blood samples, showing

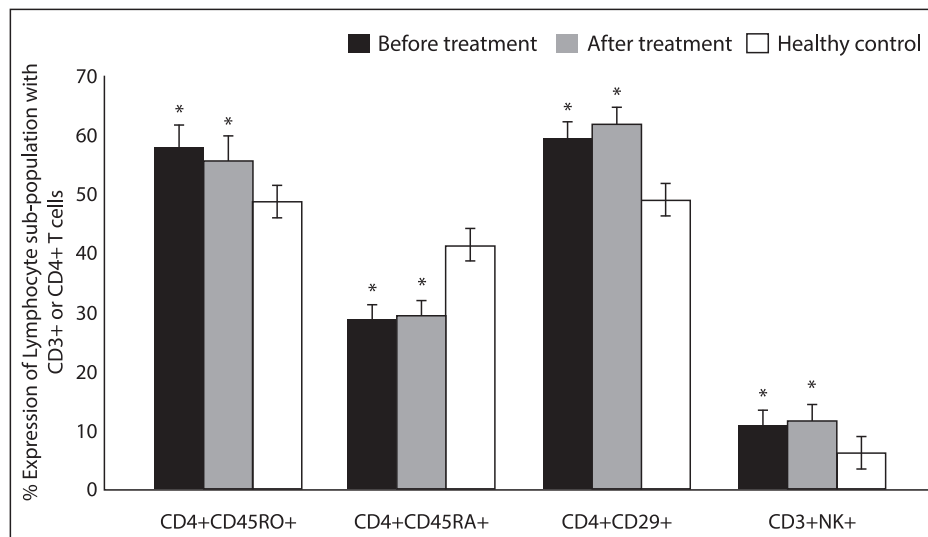
Table 1 Demographic data of patients with acute low back pain

Demographic data	$\bar{x} \pm SD$
Age (years)	42.0 \pm 7.9
Height (cm)	172.9 \pm 3.8
Weight (kg)	69.3 \pm 5.2
Body mass index (kg/m ²)	23.2 \pm 2.1
Pain duration (months)	4.6 \pm 1.4

Table 2 Measurements of pain at baseline and following McKenzie interventions

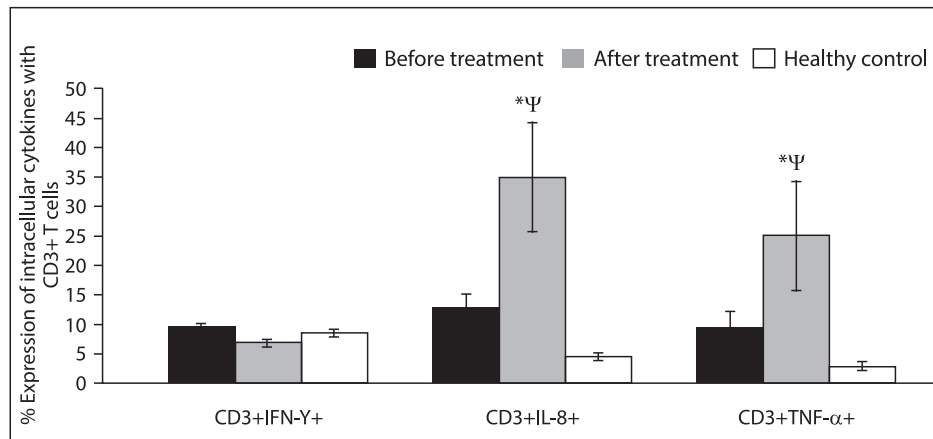
Pain characteristics	Baseline	Week 2	Week3	Week4
Overall pain ($\bar{x} \pm SD$; Range) mm	88.8 \pm 0.87; 78-94	72.1 \pm 2.6*; 62-86	58.2 \pm 2.3*; 48-70	38.8 \pm 2.6**; 20-49
Actual reported pain ($\bar{x} \pm SD$; Range) mm	89.0 \pm 2.1; 79-98	52.9 \pm 4.4*; 41-79	26.6 \pm 2.7*; 11-42	6.9 \pm 3.0**; 10-32

*Compared to baseline ($p < 0.05$); **Compared to baseline ($p < 0.01$).



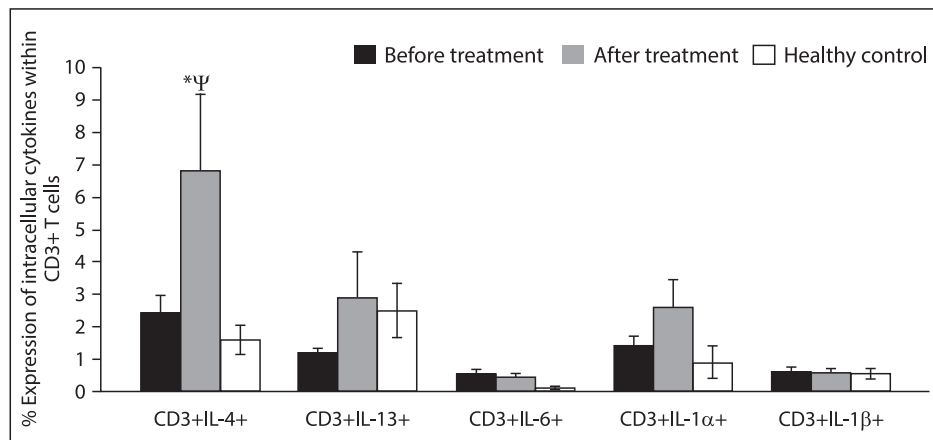
Mean \pm SE of % expression of lymphocyte subpopulations within CD3+ or CD4+ T cells. No significant change in expression of lymphocyte subpopulations was observed after McKenzie exercises relative to baseline. * $p < 0.05$ versus healthy references.

Figure 1 Lymphocyte sub-populations before and after 4 weeks of McKenzie exercises in patients with acute low back pain.



Mean \pm SD of % expression of intracellular cytokines within CD3+ T cells. McKenzie exercise induced a significant increase in CD3+IL-8+ and CD3+TNF- α + T cells. * $p < 0.05$ versus before treatment, $\Psi p < 0.05$ versus healthy references.

Figure 2 Intracellular cytokine expression before and after 4 weeks of McKenzie exercises in patients with acute low back pain.



Mean \pm SD of % expression of intracellular cytokines within CD3+ T cells. McKenzie exercises induced a significant increase in CD3+IL-8+ and CD3+TNF- α + T cells. * $p < 0.05$ versus before treatment, $\Psi p < 0.05$ versus healthy references.

Figure 3 Intracellular cytokine expression before and after 4 weeks of McKenzie exercises in patients with acute low back pain.

ing no significant differences in the frequency of memory (CD4+CD45RO+) T cells, helper inducer (CD4+CD29+) T cells, CD3+CD16+CD56+ T cells and Naive (CD4+CD45RA+) T cells after 4 weeks of McKenzie exercises relative to the baseline. The percentage representation of Pan (CD3+) T cells expressing the inflammatory cytokines IL-8 and TNF- α and the CD3+ T cells expressing the anti-inflammatory cy-

tokine IL-4 increased significantly ($p < 0.05$) following exercise relative to the baseline and healthy subjects (Figure 2 and 3). The percentage expression of CD3+IL-13+ T cells were increased, but not to a significant level (Figure 3). No correlation was found between pain scores (OP and AP) and lymphocyte subpopulations or the percentage expression of cytokines within CD3+ T cells.

Discussion

The effectiveness of McKenzie directional preference exercises for ALBP has been reported by several studies.(4, 6-8, 10). The pain centralization phenomenon that occurs when performing the directional preference exercises has been reported to decrease or abolish the pain and associated symptoms, increase spinal range of motion, leading to fast recovery, and return to work, whereas delayed recovery, chronic pain and poor outcomes are associated with absence of pain centralization.(4, 6-8, 10).

McKenzie exercises did not induce expansion in the cell surface activation markers; our preliminary results showed no significant change in the frequencies of CD4+CD45RO+ T cells, CD4+CD29+ T cells, CD3+NK+ T cells and CD4+CD45RA+ T cells in the blood samples from our ALBP patients after McKenzie exercises, relative to the baseline (Figure 1). These cell species are major mediators of inflammation.

There is evidence that the CD4+CD29+ T cells (a helper/inducer subset) increase in the peripheral blood of patients with a T-cell mediated disease, such as Guillain–Barre syndrome (36), and T cells with NK surface markers express humoral factors that regulate inflammatory responses in a wide range of immune conditions, including: infections, anti-tumor responses, allograft rejection, graft-versus-host disease (37-39), and autoimmunity (40-42). However, the increased level of these activated lymphocyte subsets at baseline and following intervention observed in the present study may be due to the ongoing inflammatory status caused by the deranged intervertebral disc.

McKenzie lumbar spine exercises are considered to be of light intensity (43, 44) and, when performed with a frequency of 10 repetitions every 2 hours throughout the day, may provide an ongoing stimulus that up regulates the immune response. One

study reported that 12 weeks of light intensity tai chi exercises enhanced regulatory T cell function and anti-inflammatory cytokine production (45). Another study showed that progressive, moderate intensity exercise has a beneficial effect on natural killer T cell numbers, up-regulates T-helper cell mediated immune functions, and reduces the risk of infection and autoimmune disease in elderly people (46).

Our major observation in this study is that following McKenzie exercises there was a significant increase in the production of pro-inflammatory cytokines (IL-8 and TNF- α) ($p < 0.05$) (Figure 2). Numerous studies report overexpression of TNF- α , IL-1 α , and/or IL-1 β , IFN- γ and IL-6 in patients with protruded, extruded, or sequestered intervertebral disc tissues (14, 15, 47-50). Animal studies also confirm the role of these cytokines in mediating pain (51-54).

Our study reported intercellular cytokine results that demonstrated increased levels (CD3+IL-8+ and CD3+TNF- α + T cells; $p < 0.05$), even following McKenzie exercises, in contrast to lower pain scores reported by all patients. The absence of a relationship between pain scores and intercellular pro-inflammatory cytokines level in this study was statistically insignificant, possibly due to the small sample size. However, in their study Kraychete et al. did not find any correlation between blood serum levels of TNF- α or IL-6 and pain intensity, or the duration of pain among patients with low back pain (55). In contrast, Koch et al. reported that the serum level of proinflammatory cytokine (IL-1- β , IL-2, IL-6, IFN- γ and TNF α) correlated significantly with increased pain intensity in patients experiencing chronic pain (56).

Following McKenzie exercises, the percentage of CD3+ cells expressing IL-1 β and IL-6 was not significantly altered; these pro-inflammatory cytokines mediate pain. However, it is worth mentioning that IL-6

has both pro-inflammatory and anti-inflammatory properties (13). IL-1 β excites the nociceptive dorsal root ganglia (57), increases the production of substance P and prostaglandin E2 by neuronal and glial cells (58, 59), and causes hyperalgesia.

There was a slight, insignificant elevation in the percentage of CD3+IL-13+ T cells following McKenzie exercises (Figure 3). IL-13 is an anti-inflammatory cytokine that down-regulates the production of TNF, IL-1, IL-8, and macrophage inflammatory protein (MIP-1 α) by monocytes and, therefore, the inflammatory source of pain (60, 61). It was interesting to observe that the level of the anti-inflammatory cytokine, IL-4, increased significantly after 4 weeks of McKenzie exercises ($p < 0.05$) compared to the baseline. IL-4 has a strong inhibitory effect on the expression and release of pro-inflammatory cytokines. The release of IL-4 suppresses monocyte-derived pro-inflammatory cytokines, including IL-1, TNF- α , IL-6, IL-8, as well as the production of MIP and macrophage-derived nitric oxide (13). IL-4 also enhances the synthesis of the cytokine inhibitor IL-1 α , which, in turn, blocks the action of IL-1 α and IL-1 β (13). Again, the increase in anti-inflammatory cytokines IL-4 observed in the present study did not correlate with a reduced pain score.

It is difficult, from these preliminary results, to attribute all the immune regulation to the mechanical effect of the McKenzie directional preference exercises. The increased level of both pro-inflammatory IL-8 and anti-inflammatory IL-4 cytokines following exercise may also reflect the natural human immunoregulatory responses to re-establish the homeostasis between pro-inflammatory and anti-inflammatory cytokines (1, 2). However, it is possible that the significant increment in IL-8 following exercise may be caused by the ongoing inflammatory status of the deranged intervertebral disc, caused by muscle spasm and excessive postural and

mechanical stresses throughout the day. The increment of anti-inflammatory IL-4 cytokines following intervention may possibly suggest that McKenzie exercises accelerate the up regulating of the anti-inflammatory cytokines.

Further, recent studies have demonstrated that low intensity exercise, such as walking 10,000 steps/day 3/week may enhance phenotypic switching of the macrophage (M1 to M2) (62-64). This may suggest that low intensity exercise, such as McKenzie exercises, may boost the M2 polarization, and thus constitute a novel exercise anti-inflammatory effect (64). Furthermore, M2a macrophage phenotypes are specifically involved in the resolution of inflammation and tissue repair process. Therefore, our preliminary results may suggest a possible long-term effect on systemic responses, which is driving the repair process in the patients undergoing McKenzie exercises in the long term. It is worth saying that the phenotype polarization of M1 to M2a macrophages occurs after exposure to IL-4 or IL-13 (65). Our preliminary results also demonstrate a systemic change in lymphocyte subsets, which may suggest a strong immune-regulatory shift following McKenzie exercises.

On the basis of our preliminary findings, we suggest that McKenzie directional preference exercises may relieve pain by two different consecutive mechanisms. First, pain may be diminished initially by mechanical mechanisms, as explained by the concept of the disc dynamic model, i.e. relocation of the nucleus pulposus material in response to the precise McKenzie directional preference exercises (3, 5-9, 12). This would initially eliminate the pressure on the richly innervated nociceptive structures, including the outer annular fibers, posterior longitudinal ligament, dorsal root ganglia, and nerve root dural sleeves. Secondly, McKenzie exercises may help in stimulating and up regulating the anti-inflammatory cytokines, such as

IL-4 and IL-13, and therefore relieve pain in the long term.

Our results however, must be interpreted in the light of several limitations, including: the small sample size, the possible confounding effect of other anti-inflammatory biomarkers not explored in this study, patients' compliance with the study protocol, i.e. whether or not they took any pain medication, and whether they complied with the frequency of the prescribed home exercises. Another limitation is the absence of a control group. as we find it unethical to withhold treatment from patients with acute pain for a period of 4 weeks, or accepting patients as a control group receiving simple non-steroidal anti-inflammatory drugs which affect the immune-regulatory process and confound the results. Accordingly, further studies are needed to shed light on the therapeutic role of specific exercises used in physical therapy to treat low back pain, such as the McKenzie exercises, and to determine their role in stimulating favorable anti-inflammatory cytokine responses.

Conclusions

Four weeks of McKenzie exercise interventions significantly relieved back pain in patients with acute low back pain, induced an immune activation state with increase in pro-inflammatory cytokines, IL8 and TNF α , with a consequent increase in the anti-inflammatory cytokine, IL4, which may enhance and maintain pain relief in the long term.

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Conflict of interest: The authors declare that they have no conflict of interest.

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