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ORIGINAL RESEARCH ARTICLE

Biochemical and clinical effects of McKenzie therapy versus muscle endurance exercises in chronic low-back pain

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ABSTRACT

Background and objective: Apart from mechanical dysfunction, low back pain (LBP) is also associated with underlying inflammatory and muscle-related biochemical changes. An increase in certain biomarkers, such as IL-10, a key anti-inflammatory cytokine, provides a positive objective indicator of underlying physiological responses to interventions in LBP beyond subjective clinical measures. This study assessed the effects of McKenzie Extension Protocol (MEP), Static Back Extension Endurance (SBEE), and Dynamic Back Extension Endurance (DBEE) on selected clinical outcomes and biomarkers of muscle status [creatine kinase (CK)] and inflammation (IL-4 and IL-10) in LBP.

Methods: A randomized controlled trial involving 76 patients with chronic LBP who were randomly assigned to MEP, SBEE, or DBEE groups was conducted. MEP involved a specific sequence of lumbosacral repeated movements in extension. SBEE involved five different back extensor muscle endurance protocols of increasing difficulty level. DBEE was a dynamic replica of the SBEE. Pain, CK, IL-4, and IL-10 were the primary outcomes. Functional disability and health-related quality of life were the secondary outcomes. Assessments were conducted at baseline, 3rd, and 6th week of the study.

Results: MEP and SBEE caused significant effects in all clinical and biochemical variables ($p < 0.05$) except IL-4 and IL-10 ($p > 0.05$). DBEE yielded no significant effects on IL-4 and IL-10 ($p > 0.05$). MEP had a significantly higher effect on pain ($p < 0.05$). SBEE had a greater impact on IL-4 ($p < 0.05$) and IL-10 ($p < 0.05$) at week 3. SBEE led to a higher impact on IL-4 ($p < 0.05$) and IL-10 ($p < 0.05$) at week 6. All interventions had comparable effects on other clinical parameters at week 6 ($p > 0.05$).

Conclusion: MEP reduced pain more, while SBEE led to higher changes in IL-4 and IL-10 inflammatory biomarker levels. Serum CK levels rose in all groups without indicating muscle damage. The results suggest that these exercises show potential benefits in modulating inflammation and enhancing muscle status, potentially supporting tissue repair and reducing chronic LBP, and therefore should be incorporated as part of strategies targeting underlying inflammatory processes in the management of chronic LBP.

Keywords: Biomarkers, Creatine kinase, Endurance exercise, Interleukin, Low-back pain, McKenzie protocol

What is already known about this topic:

- *There is considerable stress on muscles during endurance exercise, and the biochemical changes during exercise are associated with clinical outcomes in musculoskeletal pain. However, data on the biochemical changes to endurance exercise in LBP is limited.*

What does the study add:

- *Endurance exercises in the form of McKenzie extension protocol (MEP) and static-and-dynamic back extension had beneficial clinical effects, did not cause muscle damage, and positively modulated inflammatory markers in chronic LBP.*

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Introduction

Low back pain (LBP) is a significant healthcare concern globally, causing more disability than any other medical condition (1,2). The management of LBP typically involves pharmacological and/or non-pharmacological means (3). The pharmacological approach is usually more suitable for acute LBP (4), while physiotherapy, as a non-pharmacological or conservative approach, is reported to be effective in chronic or long-term LBP (5). However, there are discrepancies in reports on the strength of evidence for various physiotherapy

interventions for LBP (6,7). Thus, there are numerous exercise programmes available for patients with chronic LBP (8-12), but there is still no consensus on the most effective and beneficial exercise programme (13).

One of the most common structured specific exercises for chronic LBP is the McKenzie protocol (14). Currently, clinicians and researchers continue to rely on reported clinical effects rather than side effects when implementing exercise-based treatments for LBP. However, gaining a deeper understanding of biomarkers represents a positive step toward comprehending the effects and potential side effects of these interventions (15). Biomarkers are becoming essential in physiotherapy to assess the safety and effectiveness of treatments for LBP. They offer objective measures of biological processes, allowing for precise monitoring of how patients respond to treatment. Additionally, biomarkers help predict patient outcomes, identify potential side effects, and guide the development of therapeutic interventions (15-20).

Endurance exercise imposes a significant toll on muscles, making them more susceptible to injuries. However, there is a lack of research on using biomarkers to measure treatment responses to endurance exercise in the context of LBP. Biomarkers can serve as indicators of disease progression, pathogenesis, and treatment response (21), providing insights into the biochemical changes and clinical outcomes, including pain intensity, fatigue, and quality of life following exercise (22,23). Pinto et al. (24) in a systematic review found a correlation between elevated levels of pro-inflammatory biomarkers (CRP, IL-6, TNF-α) and non-specific LBP while noting decreased levels of the anti-inflammatory biomarker IL-10. The review indicates that effective treatments reduce levels of pro-inflammatory biomarkers, while potentially increasing levels of the anti-inflammatory biomarker IL-10. Another review affirms a moderate correlation between the severity of LBP and elevated levels of CRP and IL-6 (25). However, the benefits and safety of McKenzie therapy and back extension endurance exercises for treating chronic LBP have not been studied at the molecular level, particularly regarding muscle status and changes in cytokine levels. Thus, this study aimed to assess the effects of MEP, Static Back Extension Endurance (SBEE), and Dynamic Back Extension Endurance (DBEE) on selected clinical outcomes (pain, functional disability, and general health status); and biomarkers of muscle status [creatine kinase (CK)] and inflammation [anti-inflammatory cytokines i.e. interleukin-4 (IL-4) and interleukin-10 (IL-10)] in patients with chronic LBP.

Materials and Methods

The Consolidated Standards of Reporting Trials (CONSORT) for reporting of RCTs was followed in this study. This study was retrospectively registered with the Pan African Clinical Trial Registry (PACTR202208757153267). The health research ethics committee of the Institute of Public Health, Obafemi Awolowo University, Ile-Ife, Nigeria, approved the study (HREC NO: IPH/OAU/12/1570). Patients with chronic LBP from Osun State University Teaching Hospital, and State Specialist Hospital, Osogbo, Nigeria were recruited for this study. Eligible participants were patients aged 18 and older who had been experiencing back pain for 12 weeks or more, with or without radiculopathy, and did not have any obvious physical deformities. Patients with LBP resulting from serious spinal conditions such as fractures, tumors, and inflammatory diseases were excluded from the study. Additionally, pregnant individuals, those who had undergone back surgery, those with a reported history of cardiovascular disease that contraindicated exercise or with high blood pressure (>140/90 mmHg), those with previous experience of the McKenzie therapy, and those who had a directional preference for flexion or no directional preference based on the McKenzie assessment were also excluded. Sample size estimation for this study was based on the sample size equation by Chan (26) – $M = c \times \pi1 (1 - \pi1) + \pi2 (1 - \pi2)/(\pi1 - \pi2)^2$, where c = 7.9 for 80% power, and π1 and π2 areproportion estimates derived from Chan's formula indicating the effect size (π1 = 0.25 and π2 = 0.65). Therefore, n = 7.9 * 0.25 (1 – 0.25) + 0.65 (1 – 0.65)/(0.25 – 0.65) = 20.49. Typically, adding 10-15% to the calculated sample size helps account for potential dropouts or non-responses during a study. This adjustment ensures that the study maintains sufficient power and statistical validity, even if some participants drop out without having underpowered results and conclusions. Using a 15% adjustment, 91 patients were assessed for eligibility, nine were excluded, and 28 patients were randomized into MEP, while 27 patients were randomized into SBEE and DBEE protocols, equalling 82 patients. However, only 76 completed the study. The number of participants lost to follow-up or discontinued intervention was three, two, and one in the MEP, SBEE, and DBEE protocols, respectively. Their data were removed from the final analysis. The baseline socio-demographic, clinical, and biochemical variables between the participants lost to follow-up and those who completed the study were comparable. The CONSORT flow diagram for this study is presented in Figure 1.

Instrument

The following instruments were used in this study:

(i) The quadruple visual analogue scale (QVAS): A 10-point numeric rating scale was used to measure pain intensity in patients with LBP. A Yoruba translation of the same questionnaire was administered to the Yoruba-speaking group among the participants (27). The Yoruba version of QVAS has adequate concurrent validity (r = 0.896) and good reliability (ICC = 0.622) in patients with LBP (27). In this study, pain intensity was considered a primary outcome while disability (activity limitation and participation restriction) and health-related quality of life were the secondary outcomes.

(ii) Oswestry Disability Index (ODI) for chronic LBP patients was used to measure work disabilities and other functional limitations associated with LBP. A Yoruba translation of the same questionnaire was administered to the Yoruba-speaking group among the participants (28). The psychometric properties of the ODI Yoruba version have been tested and found adequate (28). The Yoruba version of ODI showed excellent test-retest reliability (ICC = 0.89) and internal consistency (Cronbach's alpha = 0.81) (28).

(iii) Roland Morris's LBP disability questionnaire was used to assess functional disabilities. A Yoruba translation of the same questionnaire was administered to the Yoruba-speaking group among the participants (29). The Yoruba

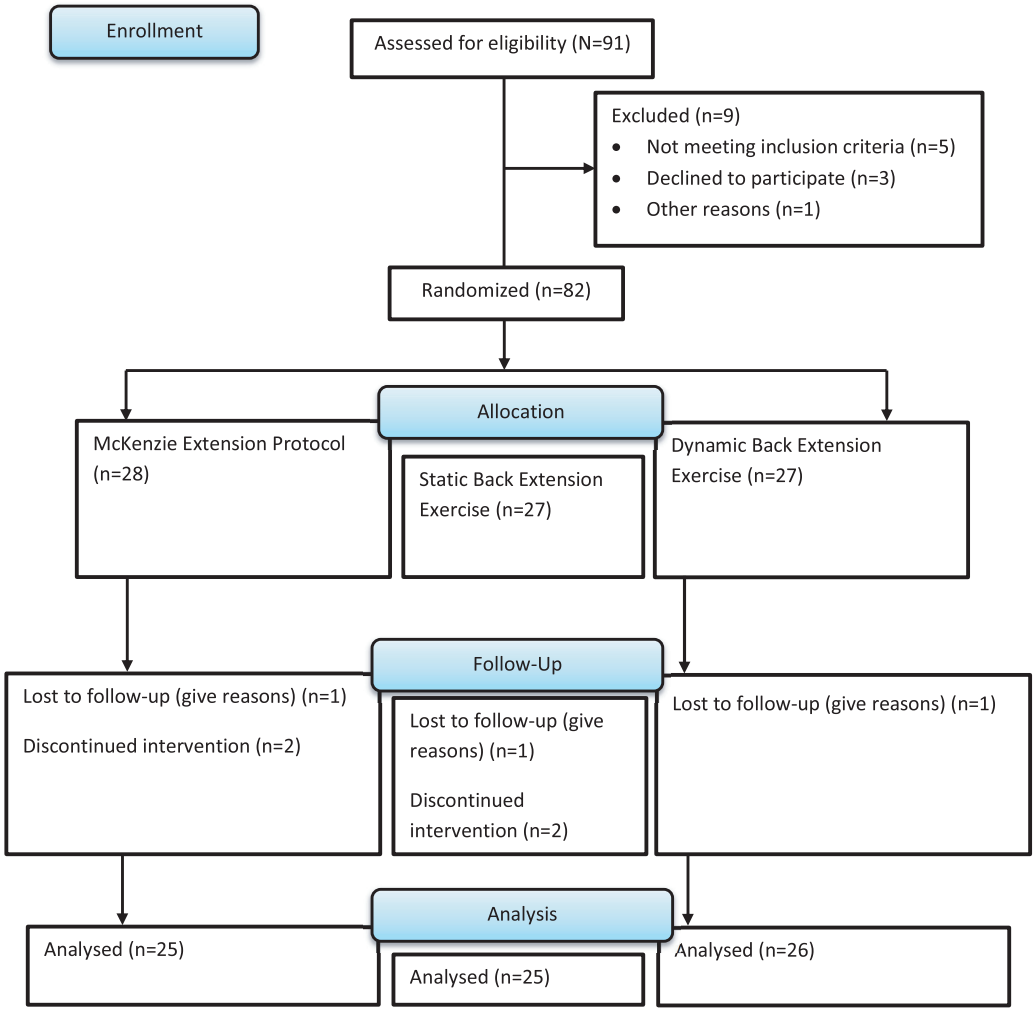

FIGURE 1 - CONSORT flow diagram for the study.

version has excellent reliability (ICC = 0.99) and validity (r = 0.82) among patients with LBP (29).

(iv) The SF-12 General Health Status Questionnaire was used to assess the general health status of the participants. A Yoruba translation of the same questionnaire was administered to the Yoruba-speaking group among the participants (30). Allscale and domain scores of the Yoruba version of SF-12 have acceptable concurrent validity (r = 0.879 – 0.938) and reliability (ICC = 0.775 – 0.949) (30).

In the present study, pain intensity was considered the primary clinical outcome, while functional disability (activity limitation and participation restriction) and general health status were the secondary clinical outcomes.

Procedure

The research team provided an explanation of the study to all participants who gave consent. To ensure inclusivity, language experts translated the informed consent form into Yoruba. Participants were recruited consecutively and then randomly assigned to one of three treatment groups. To maintain objectivity and minimize bias, a research assistant kept track of the number of participants invited to take part, the number who declined, and the number of screened patients who were ineligible, including the reasons for their ineligibility or refusal to participate. Volunteer participants who met the eligibility criteria were randomly placed in the McKenzie exercise protocol (MEP), SBEE, or DBEE exercise (DBEE) group by the same assistant who was not involved in assessing or treating the participants. Another assistant who was blinded to participant allocation was involved in the outcomes assessment. Random permuted blocks were used to ensure equal group sizes, following the method proposed by Pocock (31). A block size of six was chosen (i.e., MMDDSS, MMDSSD, MSDMSD, and other possible restricted permutations). The block permutations were computer-generated using a factorial equation formula: 6!6!, which is 1 × 2 × 3 × 4 × 5 × 6 = 7201 × 2 × 3 × 4 × 5 × 6 = 720. Some of the printout of 720 restricted computer-generated block permutations was sequentially numbered, cut, and placed in sealed envelopes. A block-permuted sequence was randomly drawn from the envelope, and accordingly, consecutive patients were assigned to either the M (MEP), S (SBEE), or D (DBEE) groups. The process of drawing block permuted sequences

and randomization was repeated as new participants were recruited. The physiotherapist, clinical outcomes assessor, and biochemical analysts were blinded to group allocation.

Pre-treatment Screening

All participants underwent an assessment to determine their eligibility for the study. The assessment used the McKenzie Institute's Lumbar Spine Assessment Algorithm (MILSAA), which is a defined method for classifying spinal-related disorders based on historical pain behaviour and the pain response to specific movements and activities. Participants were evaluated for their directional preference for certain movements, including those done while standing and lying down, in both front-to-back and side-to-side directions. This involved repeating each movement 5-10 times while observing their symptomatic and mechanical responses. After the movement testing, participants were asked standardized questions to assess the movements' effects on their pain (32,33). Those who did not respond well to certain movements or showed no response to repeated movements were excluded from the study. Only those who responded well to specific movements were considered eligible. Information regarding age, gender, education, occupation, marital status, onset and history of back pain, as well as previous interventions, was recorded for each participant. Blood samples were collected at baseline, 3, and 6 weeks to analyze biomarker patterns. Variations in biochemical profiles were compared with the exercise intensity throughout the study. Participants attended twelve treatment sessions, with two sessions per week. The clinic-based exercise interventions were supervised by a physiotherapist. Participants' adherence to the exercises was monitored through regular check-ins by the principal investigator (MIO) and logs in the diary, which were reviewed at sessions.

Laboratory Analysis

4 mL of whole blood was collected using BD Vacutainer™ tubes containing EDTA K2, in a vacuum puncture needle BD Eclipse™ about 10 minutes before starting each training session. CK was assayed using spectrophotometric methods with kits from Randox, while anti-inflammatory markers like interleukin-4 and -10 were assayed using Enzyme-Linked Immune Sorbent Assay (ELISA), with commercially prepared kits from DIAPRO Italy. CK, IL-4, and IL-10 were considered the primary biomarkers in this study. An experienced medical laboratory scientist conducted the biochemical analysis at the Medical Laboratory Complex of the Osun State University Teaching Hospital, Osogbo, Nigeria.

The McKenzie Protocol

The MEP is a classification-treatment-based method. Directional preference for extension was first assessed among the participants. This involved a course of specific lumbosacral repeated movements in extension that caused the symptoms to centralize, decrease, or abolish. The determination of the direction preference for extension was followed by the main MEP activities, including" Extension Lying Prone", "Extension In Prone", and" Extension In Standing". The details of the MEP are reported in an earlier publication (34).

Static Back Extensors Endurance Exercises

The static back extensors endurance exercises (SBEE) consisted of five different exercises that increased difficulty levels. During the exercises, participants adjusted the positions of their upper and lower limbs. The participants started the exercise training programme with the first exercise position and then progressed to the next exercises at their own pace once they could hold a given position for 10 seconds. After reaching the fifth progression, they continued with the fifth progression until the end of the exercise programme. The exercise period lasted from 30 to 45 minutes. The details of the SBEE are reported in an earlier publication (34).

Dynamic Back Extensors Endurance Exercise

The dynamic back extensors endurance exercise (DBEE) consisted of five different exercises. It closely resembled the static back extensors endurance exercise in terms of exercise positions, progressions, and duration. However, instead of maintaining a static posture in a prone lying position and holding the positions of the upper and lower limbs suspended in the air for 10 seconds during all five exercise progressions, the participant was asked to move the trunk and the suspended limbs 10 times. Each exercise was repeated 9 times. After 10 repetitions, the participants were instructed to rest for 30 seconds to 1 minute. The number of trunk movements in the exercise position gradually increased to 20 times to provide a more intense training stimulus. The details of the DBEE are reported in an earlier publication (34).

After the initial assessment, when all participants joined the study, two more assessments were conducted in the third and sixth weeks. During these reassessments, participants filled out questionnaires to measure the outcomes. Additionally, all participants were given a set of instructions on back care education, which included a 9-item guide on how to stand, sit, lift, and perform other daily activities. They were instructed to perform these exercises at home twice daily. The interventions were illustrated in Supplementary Material 1.

Data Analysis

Descriptive statistics of frequency, percentage, mean, and standard deviation were used to summarize data. Analysis of Variance (ANOVA) was used for across-group analysis. Within-group analysis was done using repeated-measured ANOVA (comparing baseline, third, and sixth weeks). Post Hoc Analysis (Least Significant Difference (LSD) was used to determine the trend of differences in the groups. Kruskal–Wallis test was used to compare physical functions across the three groups. Data were analyzed using the Statistical Program for Social Sciences for Windows version 20 (SPSS Inc., Chicago, Illinois, United States). Data was analysed using SPSS version 20.0. The alpha level was set at $p < 0.05$.

Results

The general characteristics and baseline parameters of the participants in each group are presented in Table 1. There was

no significant difference in age across the three groups ($p > 0.05$), but significant differences were found in height, weight, and BMI ($p < 0.05$) across groups. Among clinical variables, ODI, SF, VT, and CK scores were also comparable across groups ($p > 0.05$).

There were significant differences in the pain intensity ($F = 3.255$; $p = 0.044$; $\eta^2 = 0.12$), IL-4 ($F = 3.255$; $p = 0.044$; $\eta^2 = 0.08$), and IL-10 ($F = 5.664$; $p = 0.005$; $\eta^2 = 0.13$) across the groups at the third week of intervention (Table 2). However, there was no significant difference in other clinical parameters across the groups in the third week of intervention ($p > 0.05$). The LSD post hoc analysis showed that the pain intensity was significantly lower in DBEE compared to MEP ($p = 0.002$) and SBEE ($p = 0.011$). However, there was no significant decrease between MEP and SBEE groups ($p = 0.126$). In the third week of intervention, analysis of the biomarkers IL-4 and IL-10 showed significant differences between the treatment groups (MEP, SBEE, DBEE), with MEP showing significantly lower levels of IL-10 compared to SBEE and DBEE ($p < 0.05$ for both) (Table 2).

Table 3 presents comparisons of clinical parameters by treatment groups at the sixth week of intervention. There were significant differences in the serum levels of IL-4 ($F = 9.219$; $p = 0.001$; $\eta^2 = 0.20$) and IL-10 ($F = 7.851$; $p = 0.001$; $\eta^2 = 0.17$) across the groups. Similarly, the results of the LSD post hoc analysis showed that in the sixth week of intervention, analysis of the biomarkers IL-4 and IL-10 showed significant differences between the treatment groups (MEP, SBEE, DBEE), with MEP showing significantly lower levels of IL-10 compared to SBEE and DBEE ($p < 0.05$ for both).

The results of within-group comparisons of MEP, SBEE, and DBEE interventions on clinical parameters across the 3 time points of the study are presented in Tables 4, 5, and 6, respectively. The results showed that there were significant differences in pain severity ($F = 96.017$; $p = 0.001$; $\eta^2 = 0.92$) and CK ($F = 32.638$; $p = 0.001$; $\eta^2 = 0.57$) among patients in the MEP group across baseline, third, and sixth week of intervention (Table 4). Similarly, there were significant differences in pain severity ($F = 88.733$; $p = 0.001$; $\eta^2 = 0.78$) and CK ($F = 27.235$; $p = 0.001$; $\eta^2 = 0.53$) among patients in SBEE group (Table 5) and DBEE group (pain severity: [$F = 91.093$; $p = 0.001$; $\eta^2 = 0.78$]; CK: [$F = 26.790$; $p = 0.001$; $\eta^2 = 0.51$]) across baseline, third, and sixth week of intervention (Table 6).

TABLE 1 - One-way ANOVA comparison of general and baseline clinical characteristics across treatment groups

Variable	MEP (n = 25) x ± SD	SBEEE (n = 25) x ± SD	DBEEE (n = 26) x ± SD	F-ratio	p-value
General Characteristics					
Age (yrs)	50.0 ± 7.5	50.5 ± 7.8	50.0 ± 8.8	0.057	0.945
Height (m)	1.67 ± 0.04	1.64 ± 0.06	1.62 ± 0.06	7.615	0.001*
Weight (Kg)	68.9 ± 7.77	64.8 ± 9.36	58.3 ± 5.74	12.238	0.001*
BMI (Kg/m^2)	24.5 ± 2.32	23.9 ± 3.30	22.4 ± 2.89	3.443	0.037*
Clinical Characteristics					
ODI	24.8 ± 8.15	22.1 ± 7.22	20.0 ± 6.8	2.687	0.075
RMLDQ	15.0 ± 3.34^a	11.4 ± 3.33^b	10.8 ± 2.85^b	13.383	0.001*
QVAS	65.6 ± 13.9^a	54.8 ± 13.8^b	54.8 ± 13.9^b	5.012	0.009*
PF	24.7 ± 20.5^a	35.9 ± 27.7^b	42.9 ± 22.9^b	3.662	0.031*
RLP	90.2 ± 16.0^a	91.6 ± 15.3^b	79.6 ± 17.6^b	3.946	0.024*
RLE	87.4 ± 17.1^a	94.4 ± 13.1^b	80.2 ± 17.7^b	4.662	0.013*
BP	55.4 ± 18.4^a	92.2 ± 7.6^b	87.5 ± 5.7^b	69.170	0.001*
VT	54.4 ± 27.4	59.2 ± 21.2	65.0 ± 21.5	1.242	0.295
GH	38.2 ± 23.4^a	61.0 ± 24.2^b	72.8 ± 22.1^b	14.280	0.001*
SF	87.0 ± 12.8	89.0 ± 11.6	82.3 ± 11.6	1.893	0.158
MH	60.0 ± 13.9^a	37.3 ± 13.5^a	33.3 ± 12.1^b	29.407	0.001*
PHD	52.1 ± 10.5^a	70.1 ± 9.2^b	70.6 ± 7.1^b	33.709	0.001*
MHD	72.2 ± 8.6^a	69.9 ± 7.4^a	65.2 ± 6.9^b	5.177	0.008*
CK	69.2 ± 39.3	91.7 ± 55.4	70.4 ± 47.3	1.772	0.177
IL-4	55.9 ± 29.1^a	82.5 ± 37.6^b	70.8 ± 24.9^a	4.672	0.012*
IL-10	40.8 ± 15.7^a	54.0 ± 27.9^b	37.9 ± 24.9^c	3.346	0.041*

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; MEG = McKenzie Exercise Group; SBEEEG = Static back extension endurance exercise group; DBEEEG = Dynamic back extension endurance exercise group; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analogue scale; PF =Physical functioning; RLP = Role limitation physical; RLE = Role limitation emotion; BP=Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatinekinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts (^{a,b,c}).* For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

TABLE 2 - Comparisons of Clinical Parameters by Treatment Groups at the Third Week of Intervention

Variable	MEG (n = 25) x ± SD	SBEEEG (n = 25) x ± SD	DBEEEG (n = 26) x ± SD	F-ratio	p-value	η^2
ODI	14.6 ± 6.4	13.6 ± 6.1	12.9 ± 4.8	0.516	0.599	0.01
RMLDQ	5.2 ± 3.4	5.1 ± 2.7	4.7 ± 2.5	0.140	0.870	0.00
QVAS	38.8 ± 8.6[a]	35.2 ± 9.2[a]	31.8 ± 5.5[b]	5.045	0.009*	0.12
PF	50.7 ± 21.8	56.0 ± 19.2	56.3 ± 20.7	0.582	0.561	0.01
RLP	79.0 ± 17.5	72.0 ± 14.3	78.1 ± 17.3	1.343	0.268	0.03
RLE	70.6 ± 13.1	70.6 ± 13.1	67.9 ± 9.8	0.396	0.675	0.01
BP	74.4 ± 15.0	78.4 ± 13.4	74.7 ± 12.7	0.637	0.532	0.01
VT	72.8 ± 19.4	80.8 ± 22.7	85.8 ± 16.1	2.784	0.069	0.07
GH	61.0 ± 24.2	65.4 ± 18.3	66.4 ± 21.8	0.443	0.644	0.01
SF	81.0 ± 10.9	77.0 ± 6.9	76.0 ± 5.1	2.639	0.078	0.06
MH	68.8 ± 9.8	68.0 ± 7.5	69.2 ± 14.2	0.076	0.927	0.00
PHD	66.3 ± 10.7	67.9 ± 9.2	68.9 ± 9.5	0.473	0.625	0.01
MHD	73.3 ± 8.0	74.1 ± 7.8	74.7 ± 4.9	0.253	0.777	0.00
CK	134.2 ±40.7	153.6 ± 29.7	145.2 ± 38.2	1.864	0.162	0.04
IL-4	63.7 ± 29.1[a]	82.9 ± 19.8[b]	70.7 ± 30.2[b]	3.255	0.044*	0.08
IL-10	38.3 ± 14.4[a]	61.3 ± 34.8[b]	42.4 ± 24.3[b]	5.664	0.005*	0.13

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; MEG = McKenzie Exercise Group; SBEEEG = Static back extension endurance exercise group; DBEEEG = Dynamic back extension endurance exercise group; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analog scale; PF = Physical functioning; RLP = Role limitation physical; RLE = Role limitation emotion; BP = Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatine kinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts* (^{a,b,c}). For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

TABLE 3 - Comparisons of the participants' clinical parameters by treatment groups at the sixth week of the intervention

Variable	MEG (n = 25) x ± SD	SBEEEG (n = 25) x ± SD	DBEEEG (n = 26) x ± SD	F-ratio	p-value	η^2
ODI	8.7 ± 5.3	7.9 ± 4.0	10.4 ± 4.2	1.969	0.147	0.05
RMLDQ	3.6 ± 3.0	2.7 ± 1.3	3.8 ± 1.9	1.867	0.162	0.04
QVAS	25.8 ± 9.6	24.9 ± 6.2	26.1 ± 7.5	0.160	0.852	0.00
PF	70.6 ± 21.7	65.3 ± 20.4	77.1 ± 16.9	2.164	0.122	0.05
RLP	70.6 ± 13.1	73.4 ± 15.3	70.8 ± 13.3	0.309	0.735	0.00
RLE	70.6 ± 13.1	72.0 ± 14.2	67.9 ± 9.8	0.662	0.519	0.01
BP	82.8 ± 15.1	85.8 ± 8.4	83.8 ± 13.8	0.392	0.677	0.01
VT	81.6 ± 27.6	84.8 ± 26.0	91.7 ± 10.1	1.242	0.295	0.03
GH	72.8 ± 22.1	78.2 ± 14.7	76.4 ± 14.8	0.835	0.438	0.02
SF	80.0 ± 10.2	78.0 ± 8.2	77.1 ± 7.1	0.735	0.483	0.02
MH	69.6 ± 11.7	71.1 ± 6.4	71.4 ± 6.7	0.304	0.739	0.00
PHD	74.2. ± 10.9	75.7 ± 7.5	77.4 ± 8.4	0.761	0.471	0.02
MHD	75.5 ± 6.9	77.2 ± 7.1	77.0 ± 4.1	0.582	0.561	0.01
CK	133.8 ± 40.3	154.7 ± 21.7	140.7 ± 40.5	2.263	0.111	0.05
IL-4	58.8 ± 22.6[a]	84.2 ± 21.0[b]	64.1 ± 22.7[b]	9.219	0.001*	0.20
IL-10	38.0 ± 15.2[a]	60.7 ± 24.4[b]	42.5 ± 23.6[b]	7.851	0.001*	0.17

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; MEG = McKenzie Exercise Group; SBEEEG = Static back extension endurance exercise group; DBEEEG = Dynamic back extension endurance exercise group; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analogue scale; PF = Physical functioning; RLP = Role limitation physical; RLE = Role limitation emotion; BP = Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatine kinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts* (^{a,b,c}). For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

TABLE 4 - Within-group comparison of the effect of McKenzie exercise protocol across the three time points of the study (n = 25)

Variable	Baseline x ± SD	3rd week x ± SD	6th week x ± SD	F-ratio	p-value	η^2
ODI	24.8± 8.2[a]	14.6 ± 6.4[b]	8.8 ± 5.3[c]	53.206	0.001*	0.68
RMLDQ	15.0 ± 3.3[a]	5.2 ± 3.2[b]	3.6 ± 3.0[c]	144.25	0.001*	0.85
QVAS	65.6 ± 13.9[a]	38.8 ± 8.6[b]	25.8 ± 9.6[c]	96.017	0.001*	0.92
PF	24.7 ± 20.5[a]	50.7 ± 21.8[b]	70.7 ± 21.7[c]	36.151	0.001*	0.60
RLP	90.2 ± 16.0[a]	79.0 ± 17.5[b]	70.6 ± 13.0[c]	12.823	0.001*	0.34
RLE	87.4 ± 17.1[a]	70.6 ± 13.1[b]	70.6 ± 13.1[b]	14.961	0.001*	0.38
BP	55.4 ± 18.4[a]	74.4 ± 15.0[b]	82.8 ± 15.1[c]	16.894	0.001*	0.41
VT	54.4 ± 27.4[a]	72.8 ± 19.0[b]	81.6 ± 27.6[c]	9.864	0.001*	0.29
GH	38.2 ± 23.4[a]	61.2 ± 24.2[b]	72.8 ± 22.1[c]	20.937	0.001*	0.46
SF	87.0 ± 12.7[a]	81.0 ± 10.9[b]	80.0 ± 10.2[b]	4.016	0.040*	0.14
MH	60.0 ± 13.9[a]	68.8± 9.8[b]	69.6 ± 11.7[b]	4.972	0.013*	0.17
PHD	52.1 ± 10.5[a]	66.3 ± 10.7[b]	74.2 ± 10.9[c]	33.436	0.001*	0.58
MHD	72.2 ± 8.6	73.3 ± 8.0	75.5 ± 6.9	1.381	0.261	0.05
CK	69.2 ± 39.3[a]	134.1 ± 40.7[b]	133.8 ± 40.3[b]	32.638	0.001*	0.57
IL-4	55.9 ± 29.2	63.8 ± 29.1	58.8 ± 22.6	0.702	0.478	0.02
IL-10	40.8 ± 15.7	38.3 ± 14.4	38.0 ± 15.2	0.765	0.468	0.03

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analogue scale; PF = Physical functioning; RLP = Role limitation physical; RLE = Role limitation emotion; BP = Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatine kinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts ([a,b,c]).* For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

TABLE 5 - Within-group Comparison of the effect of SBEE exercise across the three time points of the study (n = 25)

Variable	Baseline x ± SD	3rd week x ± SD	6th week x ± SD	F-ratio	p-value	η^2
ODI	22.1± 7.2[a]	13.6 ± 6.1[b]	7.9 ± 4.0[c]	70.082	0.001*	0.74
RMLDQ	11.4 ± 3.3[a]	5.1 ± 2.7[b]	2.7 ± 1.3[c]	82.659	0.001*	0.77
QVAS	54.8 ± 13.8[a]	35.2 ± 8.6[b]	24.9 ± 6.2[c]	88.733	0.001*	0.78
PF	35.9 ± 27.7[a]	56.0 ± 19.2[b]	65.3 ± 20.4[c]	17.223	0.001*	0.41
RLP	91.6 ± 15.3[a]	72.0 ± 14.3[b]	73.4 ± 15.3[b]	13.855	0.001*	0.36
RLE	94.4 ± 13.1[a]	70.6 ± 13.1[b]	72.0 ± 14.3[b]	26.000	0.001*	0.52
BP	92.2 ± 7.6[a]	78.4 ± 13.4[b]	85.8 ± 8.4[c]	12.913	0.001*	0.35
VT	59.2 ± 21.2[a]	80.8 ± 22.7[b]	84.8 ± 26.0[c]	11.946	0.001*	0.33
GH	61.0 ± 24.2[a]	65.4 ± 18.3[a]	78.2 ± 13.4[b]	5.172	0.021*	0.17
SF	89.0 ± 12.7[a]	77.0 ± 6.9[b]	78.0 ± 8.3[b]	11.955	0.001*	0.33
MH	35.6 ± 10.3[a]	68.3± 7.4[b]	71.1 ± 6.4[c]	135.540	0.001*	0.85
PHD	70.2 ± 9.2[a]	67.9 ± 9.2[a]	75.7 ± 7.5[b]	6.915	0.003*	0.22
MHD	69.9 ± 7.5[a]	74.3 ± 7.9[b]	77.2 ± 7.2[c]	7.584	0.001*	0.24
CK	91.7 ± 55.4[a]	153.6 ±26.9[b]	154.7 ±21.7[b]	27.235	0.001*	0.53
IL-4	82.5 ± 37.6	82.9 ± 19.8	84.3 ± 21.0	0.032	0.926	0.00
IL-10	54.0 ± 27.9	61.3 ± 34.9	60.7 ± 24.4	0.816	0.424	0.03

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analogue scale; PF = Physical functioning; RLP = Role limitation physical; RLE=Role limitation emotion; BP=Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatine kinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts ([a,b,c]).* For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

TABLE 6 - Within-group comparison of the effect of DBEE exercise across the three time points of the study (n = 26)

Variable	Baseline x ± SD	3rd week x ± SD	6th week x ± SD	F-ratio	p-value	η^2
ODI	20.0 ± 6.8[a]	12.9 ± 4.8[b]	10.4 ± 4.2[c]	94.671	0.001*	0.79
RMLDQ	10.8 ± 2.8[a]	4.8 ± 2.5[b]	3.9 ± 1.9[b]	97.830	0.001*	0.79
QVAS	54.8 ± 13.9[a]	31.8 ± 5.6[b]	26.1 ± 6.7[c]	91.093	0.001*	0.78
PF	42.9 ± 22.9[a]	56.3 ± 20.7[b]	77.1 ± 16.9[c]	28.338	0.001*	0.55
RLP	79.6 ± 17.6	78.1 ± 17.3	70.8 ± 13.3	3.060	0.065	0.11
RLE	80.2 ± 17.7[a]	68.0 ± 10.1[b]	68.0 ± 10.1[b]	8.482	0.003*	0.27
BP	87.5 ± 5.7[a]	74.8 ± 12.7[b]	83.3 ± 13.9[c]	8.712	0.001*	0.27
VT	65.0 ± 21.5[a]	85.8 ± 16.2[b]	91.7 ± 10.1[c]	24.939	0.001*	0.52
GH	72.3 ± 22.4	66.7 ± 22.2	78.3 ± 14.8	3.235	0.054	0.12
SF	82.9 ± 11.6[a]	76.0 ± 5.1[b]	77.1 ± 7.1[b]	5.204	0.024*	0.18
MH	33.3 ± 12.1[a]	69.2 ± 14.2[b]	71.4 ± 6.6[c]	67.463	0.001*	0.74
PHD	70.6 ± 7.1[a]	68.9 ± 9.5[a]	77.4 ± 8.4[b]	8.421	0.001*	0.26
MHD	65.2 ± 6.9[a]	74.8 ± 5.0[b]	76.9 ± 4.2[c]	24.868	0.001*	0.53
CK	70.3 ± 47.4[a]	145.2 ±38.2[b]	140.7 ±40.5[c]	26.790	0.001*	0.51
IL-4	70.8 ± 24.9	70.7 ± 30.2	64.1 ± 22.6	1.023	0.367	0.03
IL-10	37.9 ± 24.9	42.4 ± 24.3	42.5 ± 23.6	0.656	0.511	0.02

Alpha level was set at $p < 0.05$; X = Mean; SD = Standard deviation; ODI = Oswestry Disability Index; RMLDQ = Roland Morris low back pain disability questionnaire; QVAS = Quadruple visual analogue scale; PF =Physical functioning; RLP = Role limitation physical; RLE=Role limitation emotion; BP = Bodily pain; VT = Vitality; GH = General health; SF = Social Functioning; MH = Mental health; MHD = Mental health domain; PHD = Physical health domain; CK = creatine kinase; IL-4 = Interleukin 4; IL-10 = Interleukin 10; *Superscripts ([a,b,c]).* For a particular variable, mean values with different superscripts are significantly ($p < 0.05$) different; * indicates significant difference.

Discussion

This study aimed to evaluate the impact of MEP, SBEE, and DBEE on various clinical outcomes (such as pain, functional disability, and general health status) as well as on biomarkers of muscle status (CK) and inflammation (anti-inflammatory cytokines, i.e., IL-4 and IL-10) in patients with chronic LBP. To our knowledge, this is the first study to provide empirical evidence of the biochemical effects of endurance exercises in the form of MEP and static-and-dynamic back extension in patients with chronic LBP. The average age of the patients in the study was 50.0 ± 7.5 years, falling within the 40-80 age brackets where LBP is commonly observed (2). The findings from within the study group indicated that MEP, SBEE, and DBEE had significant effects on pain intensity, activity limitation, participation restriction, and general health status. These results align with earlier studies showing evidence for the use of the McKenzie protocol (35-37) and back extensor exercises (34, 38, 39). Evidence has linked the therapeutic efficacy of the McKenzie protocol and back extension exercises in LBP to include lessening of pressure on sensitive tissue (40), reduction of load on the spinal disc (40, 41), increase in the height of the spine (42), and reduction in posterior protrusions in some intervertebral discs (43).

Regarding clinical outcomes, the study results showed that there were no significant differences in the effects of MEP, SBEE, and DBEE at the 3rd and 6th week of the study, except for pain intensity, which was significantly lower in DBEE compared to MEP and SBEE at the 3rd week. This indicates that all three interventions were equally effective and had similar effects on pain intensity, activity limitation, participation restriction, and general health status in patients with chronic LBP. The possible reason for this similar effect may be attributed to the mechanism of action of these exercise interventions, which are reported to be complementary. Although McKenzie's protocol works through centralization of pain by positively altering spinal mechanics, and back extension exercise works by improving the spinal muscle chain and spinal stability, both protocols involve spinal extension movements (44-46).

Similarly, there were no significant differences in the scores of IL-4 and IL-10 over time in patients receiving the SBEE and DBEE. The analysis of the biochemical effects of these interventions is an expanding area in physiotherapy research and could help improve patient care. The clinical outcomes align somewhat with expectations for similar interventions, but the results from blood samples are new. Biochemical markers have been explored as objective measures for risk assessment, diagnosis, or evaluation, as well as surrogate endpoints in chronic pain. Researchers have investigated biomarkers within pain pathways, such as inflammatory markers, molecular receptors detecting metabolites that influence pain, and neurotransmitters. These biomarkers are involved in the conduction, synaptic transmission, or modulation of pain response and are considered potential

therapeutic targets (47). Certain biochemical markers can provide diagnostic, prognostic, or intervention efficacy-related information (48). Additionally, they can indicate adaptation to regular training or changes occurring during or after exercise (48). However, there is a need to consolidate current studies assessing the effects of exercise on these biomarkers to evaluate their translational value in chronic pain. It is believed that the nature, volume, and intensity of exercise can produce varying effects on several biochemical markers (49).

Creatine kinase has been used as an indicator of training intensity and a diagnostic marker of overtraining. This suggests that the values fall within the normal range, indicating no harm to muscle status and no evidence of muscle damage (200-395 U/L for males and 200-207 U/L for females) (50). The findings on IL-4 and IL-10 support the argument submitted that training enhances the transcription of genes involved in the switch from a pro- to an anti-inflammatory macrophage phenotype (20). It is therefore expected to have more anti-inflammatory cytokines as a result of the training exercises. Anti-inflammatory cytokines are a series of immunoregulatory molecules that control the pro-inflammatory cytokine response. IL-4 and IL-10 are among the anti-inflammatory cytokines, but IL-10 is the most important anti-inflammatory cytokine found within the human immune system (51). Even while there is no significant rise in the cytokine levels, there is still some increase, which may be more at some points, showing some increase in the deposits of anti-inflammatory cytokines, therefore setting the stage for muscle recovery.

This is the first study to investigate the biochemical effect of MEP and endurance exercises in patients with chronic LBP. Hence, there is an apparent dearth of similar studies that directly compare findings. However, some emerging evidence indicates that non-pharmacologic interventions may positively modulate inflammatory mechanisms in chronic LBP (52). In their systematic review, Puerto Valencia et al. found that non-pharmacologic interventions such as yoga, acupressure, osteopathy, isokinetic training, neuro-emotional technique, etc., resulted in the decrease of pro-inflammatory markers (e.g., IL-6) and increase in the anti-inflammatory markers (e.g., IL-4) (52) in patients with chronic LBP. Biomarkers play a crucial role in monitoring patient responses, predicting outcomes, and guiding treatment decisions, which enhances the precision and effectiveness of interventions for patients with LBP (51). For instance, CK levels can indicate muscle damage, while cytokine profiles can help tailor anti-inflammatory treatments, leading to a more personalized and effective management approach for LBP (50,53,54). Additionally, IL-4 and IL-10 are important biomarkers as well. Elevated IL-10 levels suggest reduced inflammation and pain, whereas lower levels may indicate persistent inflammation (53, 54). Similarly, high IL-4 levels can signal a positive treatment response by promoting anti-inflammatory effects, while low IL-4 levels could suggest inadequate anti-inflammatory responses, leading to ongoing discomfort (53, 54).

As per earlier reports, this study found that the MEP and back extension endurance exercises are beneficial in managing lower back pain (LBP). Additionally, testing for serum biomarkers to assess muscle status, potential muscle damage, and inflammatory responses resulting from these interventions is an innovative approach. The study's results showed that while there was an increase in the level of serum CK following MEP, SBEE, and DBEE, the changes were not significant enough to indicate substantial muscle damage.

Clinical Implications of the Study

Creatine kinase is mainly a marker for muscle damage, while IL-4 can have both pro-inflammatory and anti-inflammatory effects, generally promoting anti-inflammatory responses by encouraging T helper type 2 (TH2) cell development and playing a crucial role in the immune response (55). IL-10 is predominantly anti-inflammatory, which is crucial for limiting inflammatory responses by inhibiting pro-inflammatory cytokine production (56). At weeks three and six, CK levels were elevated across all groups, indicating ongoing muscle activity or damage due to the exercise interventions, with no significant differences between groups. IL-4 and IL-10 levels were significantly higher in the SBEE group compared to the MEP group, suggesting that static exercise promotes a stronger and more effective anti-inflammatory response. Across all three exercise interventions (within-group comparison), CK levels significantly increased from baseline to week three and remained elevated at week six, indicating substantial muscle activity or potential damage. IL-4 and IL-10 levels remained relatively stable throughout the intervention periods, which may imply consistent anti-inflammatory responses for all exercise types. However, key differences include the slight increase in IL-4 levels at week three for the MEP group, which returned closer to baseline by week six, while IL-4 levels in the SBEE and DBEE groups remained stable. Additionally, IL-10 levels showed a slight increase at week three for the SBEE groups but remained stable, indicating similar anti-inflammatory responses across all interventions. This suggests that the interventions are effective and safe. Moreover, the minimal increase in IL-4 and IL-10 may indicate muscle healing. Therefore, understanding these biochemical processes can lead to more relevant treatment options and reduce the likelihood of failed treatments, providing significant benefits for biomarker development. Using serum biomarkers has the potential to identify more tailored treatments with improved efficacy in specific patient populations.

Limitations of the study

The clinical outcomes and biochemical changes of the different interventions were only assessed over a relatively short period of six weeks, which may be different at long-term follow-up. The non-blinding of therapist-to-treatment allocation may have also introduced performance bias. It must be stated that this potential bias was minimized by blinding the therapist to group allocation and the assessment of clinical and biochemical outcomes. The patients in this study had similar general characteristics and some baseline clinical parameters, including CK scores. Baseline characteristics are important indicators of how patients will respond to treatment in clinical trials for lower back pain (57). It is known that having comparable baseline measures in clinical

trials decreases the likelihood of factors other than the intervention affecting the outcomes. However, Friedman et al. (58) argued that for many measurements, baseline data may not accurately reflect the participant's true condition at the time of the baseline, as investigators typically perform the baseline assessment close to the time of the intervention. Therefore, the results obtained at different points in this study could have been largely influenced by the effects of the various treatment regimens. The lack of a placebo or control group in this study may also serve as a limitation. Also, the findings from this study are limited only to patients with chronic LBP who have a directional preference for extension. Finally, the significant differences in some baseline characteristics of the groups may have moderated the results, potentially influencing the observed outcomes.

Conclusion

MEP reduced pain more, while SBEE led to higher changes in IL-4 and IL-10 inflammatory biomarker levels. Serum CK levels rose in all groups without indicating muscle damage or significant inflammation. The significance of this study is that MEP showed a greater efficacy in reducing movement-evoked pain and central sensitization, while SBEE may offer broader anti-inflammatory benefits.

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