Immediate Effects of Core Stabilization Exercise on β-Endorphin and Cortisol Levels Among Patients With Chronic Nonspecific Low Back Pain: A Randomized Crossover Design

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Abstract

Objective: The main objective of the study was to measure the levels of plasma β-endorphin (PB) and plasma cortisol (PC) under lumbar core stabilization exercise (LCSE), placebo and control conditions in patients with chronic nonspecific low back pain.

Methods: Twenty-four participants with chronic nonspecific low back pain participated in a randomized, placebo-controlled, crossover design study. There were 3 experimental exercise conditions: control condition (positioning in crook lying and rest), placebo condition (passive cycling in crook lying using automatic cycler), and LCSE on a Pilates device tested with a 48-hour interval between sessions by concealed randomization. A blood sample was collected before and after the exercise conditions. Plasma β-endorphin and PC were measured through enzyme-linked immunosorbent assay and electrochemiluminescence in a Cobas E411 auto analyzer.

Results: A significant difference in PB level was identified before and after the LCSE condition ($P < .05$), whereas no significant differences were noted in control and placebo exercise conditions. Also, the trend of elevation of PB under the LCSE was significantly different compared with the placebo and control conditions ($P < .01$). In contrast, the PC level remained unchanged in all 3 conditions.

Conclusion: The findings of this study indicate that LCSE could possibly influence PB but not PC level among patients with chronic nonspecific low back pain. The mechanism of action of the pain-relieving effect of LCSE might be related to an endogenous opioid mechanism as part of its effects and might not be involved with a stress-induced analgesia mechanism. (J Manipulative Physiol Ther 2018;41:181-188)

Key Indexing Terms: *Back Pain; Exercise; Beta-endorphin; Cortisol; Rehabilitation*

Introduction

Lumbopelvic core stability exercise (LCSE) training is a common therapeutic management in day-to-day practice for patients with low back pain. The LCSEs recruit and train certain specific muscles, such as transverses abdominis and multifidus, to provide spinal stabilization.[1] Evidence from the systematic reviews suggests that LCSE is an effective treatment for patients with low back pain because it reduces pain and improves function.[2] The mechanical and neurophysiological effects of LCSE, such as improved contractility of core muscle, enhanced feed forward mechanism, and improved lumbopelvic stability, are accounted as established effects for pain reduction among patients with chronic low back pain (CLBP).[3-6] Although the mechanical effects of LCSE are well documented, the biochemical effects of the LCSEs behind pain relief are yet to be fully understood. Exercise can cause endogenous induced analgesia through release of endogenous opioids.[7] However, it is not clear whether the LCSE can release the endogenous opioids that may be behind the mechanism of pain relief among patients with CLBP.

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Endogenous opioids have been found to have analgesic effects in a variety of chronic pain syndromes, including CLBP.[8] β-Endorphin (BE) is one such peptide released with adrenocorticotropic hormone from the anterior pituitary gland as a result of exercise stress.[9] The release of BE works on the endogenous opioid receptors and acts on the descending inhibitory system that modulates pain at the spinal cord level.[10] An appropriate metabolic and thermal stress is required in any exercise for the release of BE.[11] Moreover, it is suggested that exercise intensity and BE release are correlated in producing the opioid-induced analgesic effect in human beings after exercises.[12] However, it is not clear whether the LCSE has enough physical stress to induce BE release and to increase plasma BE (PB) in patients with CLBP.

Evidence suggests that functional somatic symptoms like CLBP are often associated with physical and mental stress.[13,14] Cortisol is a primary peripheral hormone from hypothalamic-pituitary-adrenocortical activity that reflects the coping mechanism of the body for stress response and pain adaptation.[13,14] The cortisol is released by the adrenal cortex by stimulation of adrenocorticotropic hormone at the anterior pituitary and corticotropin-releasing factor from the paraventricular nucleus of the hypothalamus.[15] The mental and physical stress associated with acute pain and anxiety causes an increased hypothalamus-pituitary-adrenal (HPA) axis activation.[13] Furthermore, the altered activity of the HPA axis contributes to evolution of stressful characteristics of a clinical problem into chronic pain disorder.[13] An increased concentration of plasma cortisol (PC) has been postulated to cause attenuation of pain perception in acute stress conditions.[16] Also, the cortisol regulates sympathetic and opioid mechanisms related with central pain processing.[15] If altered levels of the stress hormone cortisol influence stress-somatic complaints in functional somatic syndromes, such theories may apply in conditions like CLBP.[17] Therefore, in a common stressful condition like back pain or a physical stressor like exercise, it may be possible that both BE and cortisol are released as responses from the body to exhibit endogenous opioid–induced analgesia and stress-induced analgesia, respectively.

Although clinical studies have focused on the roles of BE and cortisol in health, the biochemical changes on PB and PC levels after LCSE have not been studied previously. Moreover, a recent systematic review concluded that there was limited evidence to determine whether or not the exercise therapy induces pain-modulating substances, and therefore, it warrants further investigation to explore the effects of LCSE on PB and PC.[18] In addition, stress-induced analgesia and placebo-induced analgesia are 2 of several other clinical reasoning mechanisms proposed to affect patients with low back pain.[19,20] Thus, it is appropriate to use deductive reasoning to differentiate and investigate the real effects of LCSE on PB and PC compared with placebo and controlled intervention.

Therefore, the main aim of the present study was to investigate the effects of 3 groups of exercise interventions—LSCE training, placebo (automated passive cycling training), and control (rest)—on the levels of PB and PC in patients with CLBP. The present study hypothesized that the LCSE might increase PB and reduce PC compared with the placebo and control interventions among patients with CLBP. Information from this study may help clinicians to understand the potential biochemical effects of LCSE compared with other exercise regimens. Such knowledge may assist clinicians to design appropriate exercise prescriptions for low back pain rehabilitation.

Methods

Participants

A total of 24 participants (7 men, 17 women; aged 33.76 ± 14.51 years) with CLBP residing in a community and university area participated in the study. An advertisement about the research study was placed around the community and in university locations, and the participants were recruited through predefined inclusion and exclusion criteria. Participants aged 20 to 35 years with mild to moderate back pain, with a visual analog scale pain score between 2 and 7 cm and presence of pain for more than 3 months with location of pain in the area between the lowest (12th) rib and the gluteal folds, participated in the study. Any participants with referred pain or neurologic involvement in the lower limbs, with a history of past surgery, with a history of smoking, or with a history of injury in the last 3 months were not recruited for the study. In addition, pregnant women and women who reported menstruation 3 days before or 3 days after the study period were not included. Also, any participants who performed any forms of physical exercises regularly were not considered for the study because routine exercises might have influenced the physiological levels of BE. None of the participants took stimulants, medications, or alcohol or was involved in heavy physical activities at least 12 hours before the test. All participants gave written informed consent to join the study, and the whole research project was conducted in an outpatient physiotherapy department of a university teaching hospital. A university ethical committee approved the human ethics for the study according to the standards of the Declaration of Helsinki, Finland.

Study Design

The effects of the 3 different groups of intervention—LCSE training, placebo (automated passive cycling training), and control (rest)—on the levels of PB and PC were investigated through a randomized, placebo-controlled crossover trial. An envelope-based concealment of random assignment and allocation of the participants was used in the study. Two independent physiotherapists who were not the part of the study assisted the process of random

assignment and allocation. All 3 interventions were numerically coded in an opaque sealed envelope and placed in a closed box by 1 of the independent physiotherapy staff before the screening of the participants. A second staff member, who was not aware of the coded allocation sequence for intervention, assisted with the screening of the participants for the study and collected the written consent. Then each of the participants was asked by the other staff to choose any 1 envelope during the first visit and allocated to the corresponding intervention group accordingly. During the second visit, the same procedure was repeated and the second allocation was carried out for the second intervention. The participants were allocated to the third intervention based on the last envelope left inside the box. Thus, the participants crossed over from one intervention to the other intervention during the course of the trial. The crossover design was employed in this study to avoid variations in the physical, physiological, and psychosocial characteristics among the study participants.

Experimental Exercise Training Conditions

The 3 types of exercise interventions—LCSE, placebo (automated passive cycling training), and control (rest)—for this study were implemented as per the previously established protocols.[3,4,6] All participants performed each type of exercise in a controlled-environment room with a temperature of 24.5 ± 0.5°C, relative humidity of 60 ± 5%, for approximately 15 minutes randomly with 48 hours between sessions to minimize any possible carryover effect. The participants performed all the exercises under the supervision of a qualified physiotherapist who had postgraduate clinical training in musculoskeletal physiotherapy. The position of the participants for all types of exercise interventions was supine crook lying. All participants received 1 familiarization trial for each exercise on the day of the corresponding exercise intervention. The familiarization trial was strictly maintained to a single attempt to prevent any learning effects. The therapist instructed all the participants to report any incidence of increased intensity of pain during the course of the interventions. Any participant who reported increased intensity of pain during the intervention was stopped from further participation in the trial for safety and ethical reasons as per the study protocol. The exercises were monitored and corrected by the therapist if necessary to adhere to the exercise protocols.

A Pilates power gym transformer device (Thane Fitness, United Kingdom) and air pressure biofeedback unit were used to perform the LCSE. For the LCSE intervention, the participants lay down on the Pilates exercise training device with hip and knee flexed to 70° and 90°, respectively. The core muscle activation was facilitated by encouraging abdominal hollowing and co-contraction of trunk muscles. The core muscle contractility and the progression of the exercises were monitored by an air pressure biofeedback unit that was also placed beneath the lumbar spine from L2 to S1 and inflated to 40 mm Hg. All participants performed core muscle exercise with a resistance of approximately 10% of their body weight using a weight pulley system on the device incorporating the limb movements in the following progressive order: core with alternate hip abduction, core with alternate leg raise, core with both arms adduction, core with both arms extension, core with alternate arm lift, core with alternate leg lift, core with alternate leg and arm.[3] Figure 1 shows one of the exercise description of the core stability training. The progression of the exercises was stopped when the participant could not maintain the registered air pressure at 40 ± 10 mm Hg. Every stage of exercise was repeated 10 times. The placebo (automated passive cycling) intervention was administered by using an automatic bicycle (Reck MOTOmed Viva, RECK Technik, Betzenweiler, Germany). In supine crook lying position, the participants performed alternate leg movements passively at the speed of 30 revolutions per minute (rpm) with their feet attached to the pedals of the automatic bicycle. For the control (rest) intervention, the participants were made to relax completely on the Pilates power gym in the similar supine crook lying position. In addition, both knees were supported by pillows with hip flexion of 70° and knee flexion of 90° to ensure complete rest and relaxation.

Measurements

Procedures. A qualified biomedical person who was independent to the study protocol was employed to collect the blood samples from the participants. Ten milliliters of blood were drawn from each participant through a venipuncture at the cubital vein. The blood samples from the participants were collected at 2 points, such as 1 minute before the exercise intervention and 1 minute after the exercise intervention. All blood samples were collected during the late morning period between 9:00 and 11:00 to standardize the circadian rhythm effects on the blood markers. The samples of blood were collected in vacutainer plastic tubes and stored on an iced container and moved for the centrifugation process at the university hospital.

Plasma BE. The PB was collected per an established protocol.[21] Five hundred microliters of plasma were acidified with 500 μL of 1% trifluoracetic acid (TFA) and mixed, then centrifuged at 17000 × g for 20 minutes at 4°C. A Sep column containing 200 mg of C18 was equilibrated by washing with 60% acetonitrile in 1% TFA (1 mL, once) followed by 1% TFA (3 mL, 3 times). Acidified plasma solution was loaded onto the pretreated C-18 Sep column. The column was slowly washed with 1% TFA (3 mL, twice). The peptide was eluted slowly with 60% acetonitrile (3 mL, once). The eluant was collected in a polypropylene tube and evaporated to dry in a centrifugal concentrator. The dried sample was kept at –20°C. Fifty microliters of sample or standard, 25 μL of primary antiserum, and 25 μL

Fig 1. *A depiction of one of the core stabilization exercises with alternate leg lifting on the Pilates power gym device.*

of biotinylated BE were added into an enzyme-linked immunosorbent assay well plate and incubated for 2 hours at room temperature. The plate was washed 6 times with assay buffer and dried by inverting the plate on an absorbent material. One hundred microliters of diluted streptavidin horseradish peroxidase solution was added into each well, except for the blank, and incubated for 1 hour at room temperature. The plate was washed again 3 times and dried. Finally, 100 μL of 3,3′, 5,5-tetramethylbenzidine solution was added to each well and incubated for 1 hour at room temperature. The reaction was stopped with 2N hydrochloric acid and absorbance was read at 450 nm. The concentration of BE was calculated with the standard curve of standard BE (0.01-1000 ng/mL).

Plasma Cortisol. The PC levels were detected using Elecsys Cortisol (Roche, Indianapolis, Indiana) in a Cobas E411 auto analyzer using the electrochemiluminescence immune assay method. The sample was incubated with a cortisol-specific biotinylated antibody, a ruthenylated cortisol derivative and releasing agent. The antibody binding sites were occupied either by cortisol or the ruthenylated derivative, with the proportion of each depending on the concentration of cortisol in the sample. Streptavidin-coated microparticles were added to the reaction mixture and the immune complexes bound to the solid phase via biotin streptavidin interactions. The reaction mixture was transferred to a measuring cell and the microparticles were magnetically captured onto the surface of an electrode; unbound sample was washed away before a chemiluminescent reaction was induced by applying a voltage to the electrode. The detection limit was 0.5 nmol/L and measuring range was 0.5 to 1750 nmol/L.

Data Analysis. The sample size for the present study was established in previous studies using the G*Power statistical program.[3,6] A significant α level of .05 and power analysis of 0.80 with an estimated moderate effect size of 0.54 resulted in a sample size of approximately 24 participants for this study. The Shapiro-Wilk test was used for examination of the data normality. The percentage change (%change) of the PB and PC levels was also estimated by the difference between pre- and post-changes divided by 100. Because the data were not normally distributed, the nonparametric statistics, Friedman rank test, and post hoc analysis by Wilcoxon signed rank test were used to analyze the changes in PB and PC levels after 3 types of exercise interventions. SPSS for Windows Version 20.0 (IBM Corp., Armonk, New York) was used to analyze the data.

Results

All of the participants had low back pain with reported pain intensity of 4.28 ± 1.82 cm on the pain visual analog scale, and the mean duration of the low back pain was 41.54 ± 35.81 months. The mean weight and height of the participants were 59.02 ± 9.38 kg and 162.42 ± 10.89 cm, respectively. None of the participants reported any increase in the pain intensity during the course of the interventions.

Table 1 shows the PB and PC levels in all 3 exercise interventions. The PB and PC levels among the 3 groups of exercise interventions had no significant difference at baseline measurements. The percentage change in the level of PB was approximately 142.30%, which suggested a trend of elevation in the release of PB before and after the LCSE intervention ($P < .05$). On the other hand, the level of PB dropped with total percentage change of –40.59% and –44.18% after the placebo intervention ($P < .001$) and control (rest) interventions ($P < .001$), respectively. The results indicated that there was a significant difference

Table 1. *Data on β-Endorphin and Cortisol Levels, Which Are Shown as Mean (Standard Deviation) and Overall %Ch Values Across All 3 Experimental Conditions (ie, Core Exercise, Placebo, Control)*

	Conditions								
	Core Exercise			Placebo			Control		
Outcomes	Pre	Post	%Ch	Pre	Post	%Ch	Pre	Post	%Ch
β-endorphin, ng/mL	6.24 (17.10)	15.11 [a] (32.95)	142.30% [b,c]	6.02 (11.30)	3.58 (9.57)	–40.59% [d]	10.75 (19.20)	6.00 (16.06)	–44.18% [e]
Plasma cortisol, ng/mL	8.91 (4.61)	7.50 (4.95)	–15.83%	10.48 (6.97)	6.95 (3.79)	–33.70%	8.81 (4.76)	6.24 (4.31)	–29.19%

No significant differences in the baseline data among 3 conditions ($P > .05$). *%Ch*, percent change.

[a] Significant differences between pre-post under core stability exercise group ($P < .01$).

[b] Significant differences between placebo ($P < .01$).

[c] Significant differences between control ($P < .01$).

[d] Significant differences between pre-post under placebo exercise group ($P < .001$).

[e] Significant differences between pre-post under control group ($P < .001$).

between the 3 groups in the total percentage change of the PB after the exercise interventions ($P < .01$). The results from the levels of PC analysis indicated that there was no significant difference in the percentage change of PC compared among the 3 groups of exercise interventions—the LCSE intervention (–15.83%), placebo (automated passive cycling training) (–33.70%), and control (rest) intervention (–29.19%).

Discussion

The present study investigated the effects of LCSE on the levels of PB and PC compared with placebo (automated passive cycling) and control (rest) interventions. The PB and PC are related substances because both are generated by HPA axis activation in chronic painful conditions such as CLBP or as a result of the presence of any stressors, such as physical exercise. Also, both these substances are reported to modulate pain through descending inhibitory system in chronic pain conditions. Therefore, it is important for clinicians to understand the regulating mechanism of these substances after LCSE among patients with low back pain. The effects of general exercises on the endogenous opioids are well established in literature.[9] However, very limited understanding exists on the effects of LCSE on the biochemical substances.[18] In our opinion, the present study might be the first to investigate the changes in the PB in combination with PC after administration of the LCSE intervention. The knowledge of biochemical changes in PB and PC after LCSE may help clinicians to understand the mechanism behind the analgesic effect of LCSE among patients with low back pain. Thus, the present study findings are important to understand the changes in the levels of PB and PC after LCSE prescription in patients with CLBP. However, the present study did not focus on the correlation between the identified changes in the levels of PB and the pain intensity reported among the patients. Therefore, further studies are warranted in this field particularly to report on the levels of PB and PC with regard to changes in the pain intensity among CLBP patients in LCSE training because such knowledge may further strengthen the evidence for the use of LCSE in clinical practice.

The results indicated trend of increase in the average PB level from 6 ng/mL at baseline to 15 ng/mL immediately after the LCSE intervention. The result suggested that LCSE could influence circulating PB levels in the bloodstream, which might explain one of the possible facets of pain suppression mechanisms based on the endogenous pain-relieving peptides in CLBP. Past evidence that supports an increase in the plasma concentration of serotonin after application of lumbar stabilization exercises among patients with low back pain may reinforce the rationale that the LCSE increased the levels of PB among the participants in the present study.[22,23] Exercise intensity in relation to the release of PB has been discussed in the literature.[24-26] A critical intensity of exercise is a prerequisite for elevation of PB levels in the bloodstream. An exercise intensity exceeding 60% to 80% VO_2 max was reported to increase the blood BE levels in most individuals.[25] It is possible that LCSE may provide an adequate stimulus to trigger the release of pain-relieving peptides. Because none of the participants reported any increase in pain intensity during the course of interventions, it could be suggested that the identified elevation in levels of PB are directly related to the LCSE and not as a result of increased pain while performing the intervention. On the other hand, no elevated levels of PB were identified in the placebo (passive automated cycle) and control (rest) interventions. It could be explained that these 2 forms of interventions did not have adequate physical stimulants to release PB compared with LCSE among patients with CLBP.

The results indicated that there was no significant change in the levels of PC between the 3 types of exercise intervention groups. Cortisol is released by the adrenal

cortex after physiological and psychological stress.[11] The range of PC levels in this study was within the normal range.[27] Excessive release of cortisol has a negative effect on muscle, immune cell function, and metabolism.[28] Also, when cortisol is released higher than the normal range, it is counterproductive to optimal tissue repair and remodeling.[28] Exercise is a primary stimulant for the release of PC, which depends on exercise protocols where intensive anaerobic demands increase PC, whereas moderate aerobic exercise is reported not to elicit any response.[29] The results of the present study might explain that LCSE intervention possibly should be characterized as moderate intensity, which was evidenced by the fact that the percentage change in PC levels was not elevated. In our opinion, the relationship between the levels of PC and PB and the intensity of LCSE using tools such as perceived exertion scale needs to be ascertained in future trials because it may help clinicians to understand the dosage and intensity required for LCSE to achieve the desired therapeutic effects from endogenous opioids. It could be suggested that although the LCSE might contribute to endogenous induced analgesic response as supported by elevated PB levels, the participants were not stressed because of LCSE or the laboratory environment during the study. Absence of a significant difference in the percentage change of PC levels between the 3 exercise intervention groups hinted that the LCSE could be considered as a safe therapeutic exercise with possibly endogenous opioid–induced analgesic effects as part of its actions.

There is a huge paucity of knowledge in evidence-based practice regarding the effects of LCSE on PB and PC in patients with CLBP. Therefore, further research is recommended in this field on topics such as establishing a dosage and response among LCSE, PB, and PC; understanding the pain modulating effects of PB and PC after LCSE; and alterations in the autonomic nervous system. Any spinal therapies such as spinal mobilization and spinal manipulation have been reported to have an effect on the autonomic nervous system and cardiovascular system.[30-32] It is suggested that stimulation of spinal joints through manipulative therapy decreases heart rate and blood pressure through the autonomic system activity.[33] Furthermore, aberrant stimulation of the spinal or paraspinal structures was reported to cause segmentally organized reflex responses of the autonomic system and visceral function.[32] Also, the endogenous opioid system is activated by various stimuli such as hypoglycemia, severe hypotension, acute myocardial ischemia, and congestive cardia failure.[34] Because LCSE is believed to act on the segmental stability of the lumbar spine, it may be relevant to investigate the effects of LCSE on PB and PC in the context of autonomic nervous system activity, visceral function, and the cardiovascular system. Therefore, future studies may investigate the mechanism of interaction among PB, PC, the autonomic nervous system, visceral function, and the cardiovascular system during LCSE in patients with CLBP. The present study contributes to some important clinical implications for clinicians regarding rehabilitation of CLBP. Neuroendocrine and neuroimmune effects are 2 important output mechanisms hypothesized in the clinical reasoning of CLBP. The present study might facilitate an understanding of the levels of PB and PC among patients with low back pain as indicators of neuroendocrine and neuroimmune mechanisms. Such knowledge may help clinicians to strengthen the hypotheses of pain and tissue-healing mechanisms in management of CLBP. Also, the study might provide an explanation of the analgesic mechanism reported in LCSE by documenting the biochemical changes in levels of PB. Additionally, the present study might help clinicians to differentiate endogenous opioid– vs stress-related analgesia in low back pain conditions.

Limitations

The present study did not directly investigate the changes in pain intensity in relationship to changes in the levels of PB and PC during LCSE. Therefore, it was not possible to comment on the direct pain inhibition effects by the levels of PB and PC identified during the study after the LCSE. The smaller sample size could be considered as another limitation. Nevertheless, the present study was the first to report on the effects of LCSE on PB and PC; therefore, it might be useful for other researchers to calculate an adequate sample size in further studies on this topic. Various substages (acute vs subacute) and subpopulations of low back pain were not taken into account during sample recruitment. Therefore, the study findings may differ in different subpopulations of low back pain and hence they require further investigations in future studies. The outcome of the study did not consider long-term follow-up of PB and PC levels. However, the present study design was not appropriate to evaluate long-term follow-up because several confounding factors, such as neuroticism, positive and negative emotions, sleep deprivation, and socioeconomic and psychosocial variables, might influence the PB and PC levels in a longitudinal design. Therefore, clinicians may consider all of these limitations before translating the study findings. Further studies are advocated to confirm and translate the study findings to a wider clinical practice.

Conclusion

The findings of this study indicate that LCSE could possibly influence PB but not PC levels among CLBP patients. The mechanism of action of the pain-relieving effect of LCSE might be related to an endogenous opioid mechanism as part of its effects and might not be involved with a stress-induced analgesia mechanism.

The LCSE intervention potentially increased the PB levels compared with placebo and control interventions in CLBP. In addition, the percentage change of PC levels remained the same after LCSE intervention.

Funding Sources and Conflicts of Interest

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Contributorship Information

Concept development (provided idea for the research): A.P., L.H.J., K.P., P.S., U.P., S.U.
Design (planned the methods to generate the results): A.P., L.H.J., K.P., P.S., U.P., S.U.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): A.P., L.H.J., K.P., P.S., U.P., S.U.
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Writing (responsible for writing a substantive part of the manuscript): A.P., L.H.J., K.P., P.S., U.P., S.U.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): A.P., L.H.J., K.P., P.S., U.P., S.U.

Practical Applications

- Core stabilization exercise potentially increased PB levels.
- Increase in plasma β-endorphin level under core stabilizing exercise was significantly higher than in the placebo and control exercise conditions.
- The percentage change of PC levels remained the same after LCSE intervention.

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