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Effects of Single-Bout Endurance Exercise Intensity on Peripheral Neurotrophic Factors in Patients With Ischemic Stroke During the Subacute Phase of Rehabilitation

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Strong evidence suggests that a single session of aerobic exercise can alter serum neurotrophin concentrations and induce neural adaptations. This study aimed to analyze the effects of exercise intensity during a single exercise session on serum neurotrophin concentrations in patients after a first ischemic stroke.

Material/Methods: Thirty participants (mean age: 65.64±9.34 years) were randomly assigned to either the low-intensity continuous exercise group (n=15) or the moderate-intensity continuous exercise group (n=15). Serum neurotrophin concentrations were measured using an enzyme-linked immunosorbent assay. Cognitive function was assessed with the Addenbrooke's Cognitive Examination III; functional ability with the Rivermead Motor Assessment; depressive symptoms with the Beck Depression Inventory; and exercise intensity with the Graded Cycling Test with the Talk Test.

Results: Descriptively, a single session of aerobic exercise in the moderate-intensity continuous exercise group was associated with a substantial increase in serum brain-derived neurotrophic factor concentration (median change=1.9 ng/mL, 95% bootstrap confidence interval [0.7, 2.8]) and a decrease in serum irisin concentration (median change=-257.4 ng/mL, 95% bootstrap confidence interval [-490.1, -206.8]). Mean-based inferential analyses using 2-way repeated-measures analysis of variance revealed no significant Group×Time interactions for serum neurotrophins, except for lactate concentration.

Conclusions: A single session of aerobic exercise in patients after ischemic stroke was associated with changes in circulating lactate concentrations. Descriptive median-based analyses indicated exercise-related shifts in selected biomarkers, whereas mean-based analyses suggested broadly similar neurotrophin responses across exercise intensities.

Keywords: Stroke Rehabilitation • Exercise • Patients

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Introduction

There is growing recognition in the rehabilitation field that incorporation of aerobic exercise sessions into post-stroke rehabilitation during the subacute recovery phase may enhance neuroplasticity. During post-ischemic stroke rehabilitation, there is a limited subacute recovery window characterized by heightened neuroplastic potential. Increasing evidence suggests that implementation of aerobic exercise during this period may enhance neuroplasticity and reinforce therapeutic effects [1]. This regenerative-compensatory period of neural plasticity typically occurs within the first weeks to 3 months after a stroke [2]. Motor rehabilitation initiated during the early post-stroke weeks appears to restore impaired functions most effectively [3].

Aerobic exercise stimulates serum neurotrophic factors; thus, it may support neuronal health and recovery. Consequently, this intervention has been explored as a potential strategy to mitigate neurodegeneration [4]. Moderate-intensity aerobic exercise has also been associated with enhanced structural and functional brain connectivity, supporting the recruitment of multiple neural pathways in patients recovering from ischemic stroke [5]. Animal studies and clinical trials have shown that endurance exercise, through rhythmic skeletal muscle contractions, increases levels of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) [6], glial cell-derived neurotrophic factor (GDNF), insulin-like growth factor 1 (IGF-1) [7], irisin, and vascular endothelial growth factor A (VEGF-A) [8], among others. These proteins mediate neural plasticity and promote energy metabolism within the central nervous system after stroke [8].

Previous meta-analyses investigating the effects of a single session of moderate-intensity aerobic exercise in patients with chronic post-stroke rehabilitation have reported mixed findings regarding serum BDNF concentrations [6,9]. One analysis detected a nonsignificant decrease in serum BDNF levels favoring no exercise [10]. However, the findings were limited to patients in the chronic stage of rehabilitation. Thus, further studies and meta-analyses are needed to evaluate the effects of aerobic exercise on additional neurotrophic factors in patients during the subacute rehabilitation stage.

Moreover, aerobic exercise increases peripheral lactate concentrations; lactate serves as an energy substrate for the brain after ischemic stroke [11]. Elevated serum lactate levels following aerobic exercise may reflect increased metabolic demand for neuronal activation and could help to mitigate neurodegenerative dysfunction [12].

Considering this background, we investigated whether a single session of aerobic exercise performed at different intensities during the regenerative-compensatory phase of post-stroke neurorehabilitation affects serum neurotrophin concentrations. We also examined correlations of serum neurotrophin concentrations with motor and cognitive function.

Material and Methods

Ethical Considerations

This study was approved by the Bioethics Committee of the Karol Marcinkowski Medical University of Poznań, Poland (Decision No. 126/21). The study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. Additionally, the study protocol was registered at ClinicalTrials.gov (NCT06824116).

Inclusion and Exclusion Criteria

Participants were eligible if they were 21 to 75 years of age, had experienced a first ischemic stroke, were in the subacute phase after stroke, were clinically stable, were able to stand independently, and could walk at least 4 m. Participants were excluded if they had unstable cardiac status, lower extremity claudication or amputation, hip and/or knee joint endoprostheses, weight-bearing pain greater than 4/10, lower extremity spasticity (ie, Ashworth score >2), or other concomitant neurological diseases and/or malignancies.

Study Procedures

Participants were recruited and underwent the training procedure and data collection between June and November 2021. All participants were recruited from the Department of Neurological Rehabilitation at the District Hospital in Śrem, Greater Poland Voivodeship, Poland.

Figure 1 illustrates participant flow throughout the study. In total, 80 participants were screened; of these, 34 met the inclusion criteria and provided written informed consent. Participants were randomly assigned at a 1: 1 ratio to either of 2 groups: the study group participated in moderate-intensity continuous exercise (MICE) on a bicycle ergometer (n=17), and the control group participated in low-intensity continuous exercise (LICE) on a bicycle ergometer (n=17). The randomization sequence was generated via simple random allocation using a computerized random sequence at random.com. Participant identifiers were provided to a research staff member with no further involvement in the study, who performed the randomization in a blinded manner. Two participants in each group did not complete the single exercise session. Therefore, 15 participants in each group were included in the analyses.

On the first day of the study, participants were randomly assigned to groups. They completed the Rivermead Motor Assessment

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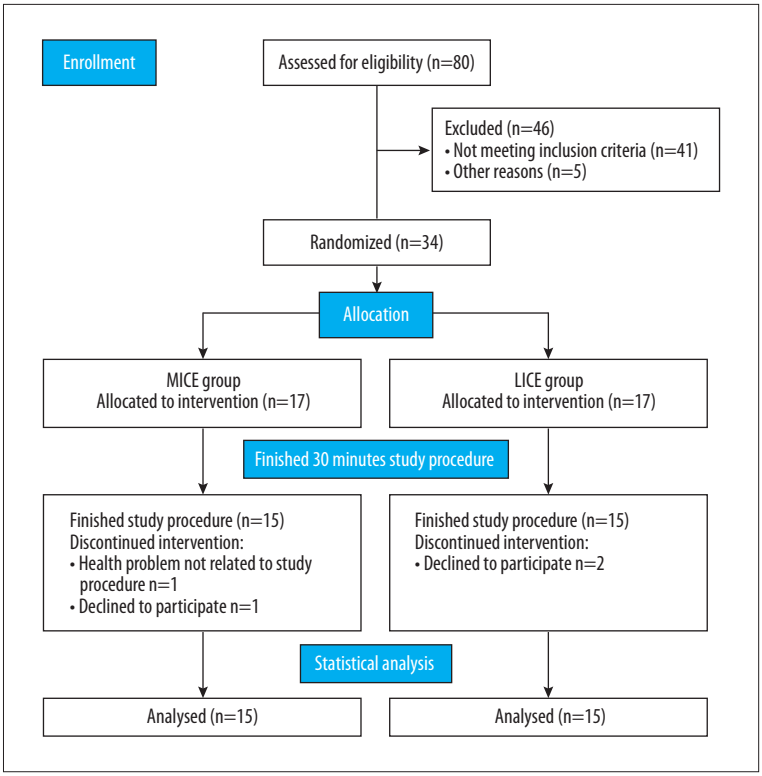

Figure 1. Flow of participants through the trial. Abbreviations: LICE, low-intensity continuous exercise; MICE, moderate-intensity continuous exercise.

(RMA), Addenbrooke's Cognitive Examination III (ACE-III), Beck Depression Inventory (BDI), and Graded Cycling Test with the Talk Test (GCT-TT). On the following day, participants completed a single session of aerobic exercise (ie, MICE or LICE). Exercise intensity was individualized based on GCT-TT results (see below).

Exercise Intervention Protocol

Aerobic exercise sessions were conducted in the morning, at least 2 hours after a meal, in the exercise room of the Neurological Rehabilitation Ward at the District Hospital in Śrem. Each aerobic exercise session began with a 5- to 10-minute warm-up period and concluded with a 5- to 10-minute cool-down period. Exercise was performed on a cycle ergometer (928E-G3, Monark Exercise, Vansbro, Sweden) for 30 minutes at a cadence of 60 rotations per minute (rpm). Exercise intensity was set at 50% to 60% of maximal oxygen consumption (VO_{2max}) for the LICE group and 70% to 80% of VO_{2max} for the MICE group. VO_{2max} was estimated from Talk Test thresholds obtained during the graded exercise test to determine individualized aerobic training intensity.

Outcome Measures

GCT-TT

The GCT-TT assesses submaximal exercise intensity and determines an individual's power output. The Talk Test is utilized to evaluate aerobic capacity during endurance exercise. Participants performed the test on a stationary bicycle (928E-G3, Monark Exercise, Vansbro, Sweden). The protocol began with a 5-minute warm-up at 25 watts using a comfortable cadence selected by each participant. The initial workload consisted of 3 minutes at 25 watts and a cadence of 60 rpm. The workload was subsequently increased by 25 watts every 3 minutes while maintaining a constant cadence of 60 rpm. During the final 10 to 15 seconds of each stage, participants were asked to repeat a fragment of text. The test was terminated when the participant could no longer speak comfortably [13]. The GCT-TT was used to determine individualized power output. The highest workload at which the participant could speak comfortably without accelerated breathing was classified as low intensity. Comfortable speech indicated that exercise intensity remained within a safe and sustainable range. In contrast, the first workload at which the participant demonstrated accelerated breathing while speaking was classified as moderate intensity. Increasing difficulty in speaking suggested that exercise intensity was approaching the physiological threshold.

RMA

The RMA assesses functional mobility in patients after stroke. It consists of 38 motor tasks divided into 3 categories: gross function (RMA-gf), leg and trunk function (RMA-lt), and arm function (RMA-a). The total RMA score ranges from 0 to 38 points, with higher scores indicating greater functional mobility [14].

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ACE-III

The ACE-III was used to assess participants' cognitive function. It comprises 5 domains: attention (ACE-III A; range, 0-18 points), memory (ACE-III M; range, 0-26 points), verbal fluency (ACE-III F; range, 0-14 points), language (ACE-III L; range, 0-26 points), and visuospatial ability (ACE-III V; range, 0-16 points). The total score ranges from 0 to 100, with higher scores indicating better cognitive function [15].

BDI

The BDI was used to assess the severity of depressive symptoms. This instrument consists of 21 items, each with 4 response options. The total score ranges from 0 to 63, with higher scores indicating more severe depressive symptoms [16].

Blood Sampling

Blood samples (4 mL) were collected from the antecubital vein into tubes without anticoagulant before and 5 minutes after the aerobic exercise session. After collection, samples were incubated at room temperature for 30 minutes, then centrifuged. The serum was separated, aliquoted (100 µL), and stored at -80°C until analysis. Commercially available enzyme-linked immunosorbent assay kits were used to measure serum concentrations of BDNF, GDNF, IGF-1, irisin, and VEGF-A. Measurements were performed using a Synergy 2 SIAFRT multi-mode plate reader (BioTek, Winooski, VT, USA).

To measure lactate concentration, blood samples were collected via fingertip puncture before and 45 seconds after exercise using a handheld analyzer (The Edge™, ApexBio, Taiwan).

Statistical Analysis

R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and Statistica 13.3 (StatSoft, Kraków, Poland) were used for statistical analyses. Group differences are presented as medians with 95% confidence intervals (CIs) calculated using bootstrap methods with 10 000 resamples and highest density intervals. Spearman rank correlation coefficients were calculated to evaluate relationships between serum neurotrophin concentrations and functional outcomes; 95% CIs were derived using bootstrap methods (10 000 resamples). Two-way repeated-measures analysis of variance (ANOVA) was used to analyze differences in serum neurotrophin concentrations before and after aerobic exercise between groups. No covariates were included in the ANOVA models. ANOVA was considered appropriate given the balanced repeated-measures design (n=15 per group) and its robustness to moderate violations of normality assumptions. Concerning ANOVA results, Group×Time interaction effects were examined first; when significant, simple effects were interpreted. Descriptive summaries (medians with bootstrap 95% CIs) are presented for illustrative purposes only and should not be interpreted as inferential findings. All statistical conclusions were exclusively based on 2-way repeated-measures ANOVA testing of Group×Time interactions. When interactions were not significant, directional language (eg, "increase" or "decrease") was avoided and main effects were examined. Eta-squared (η^2) was calculated as a measure of effect size.

Results

Shapiro-Wilk tests showed that 6 of 12 neurotrophic variables followed a normal distribution (P>0.05). Given the mixed distributional properties and small sample size, descriptive statistics are presented as medians; inferential analyses were conducted using methods appropriate to their respective estimands, as described below.

Table 1 presents the sociodemographic, anthropometric, and clinical characteristics of the study participants. The mean±standard deviation age of the 30 participants was 65.64±9.34 years. In the MICE group, a single session of aerobic exercise was associated with a higher median serum BDNF concentration (median change=1.9, 95% bootstrap CI [0.7, 2.8]; **Figure 2A**). In the LICE group, the median change in BDNF concentration was smaller, and the bootstrap CI included zero (median change=1.6, 95% CI [-0.7, 2.3]). For GDNF, the LICE group showed a negative median change after a single exercise session (median change=-0.5, 95% CI [-0.6, -0.3]), whereas the MICE group showed a smaller change (median change=-0.2, 95% CI [-0.5, 0.0]; **Figure 2B**). Median VEGF-A concentrations were lower after exercise in both groups, with a larger median change observed in the LICE group (median change=-9.3, 95% CI [-11.9, -7.0]) than in the MICE group (median change=-7.0, 95% CI [-12.0, -4.3]; **Figure 2C**). Median changes in serum IGF-1 concentrations were close to zero in both groups and accompanied by wide bootstrap CIs (LICE: median change=-12.5, 95% CI [-37.5, 25.1]; MICE: median change=-1.1, 95% CI [-27.3, 20.1]; **Figure 2D**). Serum irisin concentrations also showed lower median values after exercise in both groups (LICE: median change=-342.3, 95% CI [-585.0, -179.8]; MICE: median change=-257.4, 95% CI [-490.1, -206.8]; **Figure 2E**). These median-based summaries are provided to describe the typical direction and magnitude of change; they should not be interpreted as formal hypothesis tests.

Two-way repeated-measures ANOVA was used to test mean differences in serum neurotrophin concentrations across Time (pre vs post) and Group (LICE vs MICE). For BDNF ($F(1, 28)=0.48$, $P=0.496$; $\eta^2=0.046$), GDNF ($F(1, 28)=0.98$, $P=0.332$; $\eta^2=0.083$), VEGF-A ($F(1, 28)=1.78$, $P=0.193$; $\eta^2=0.025$), IGF-1 ($F(1, 28)=0.00$,

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Table 1. Demographic, anthropometric, and clinical characteristics of the participants.

Group	LICE	MICE
Number	15	15
Age (years)	65.79±9.56	65.48±9.44
Male sex,%	9 (60.0)	8 (53.3)
Post-stroke time (weeks)	2.80±1.29	3.40±1.74
Body mass (kg)	79.44±18.94	79.67±22.30
Height (m)	1.69±0.09	1.71±0.08
Body mass index (kg/m^2)	27.70±5.70	27.09±6.44
Addenbrooke's Cognitive Examination III score (points)	53.67±26.59	63.80±27.73
Rivermead Motor Assessment score (points)	22.93±11.19	20.67±11.08
Beck Depression Index score (points)	10.67±8.16	14.20±11.32

Abbreviations: LICE, low-intensity continuous exercise; MICE, moderate-intensity continuous exercise. Data are shown as mean±standard deviation or number (%).

P=0.991; η^2=0.001), and irisin (F(1, 28)=0.30, *P*=0.588; η^2=0.006), the Group×Time interactions were not significant, indicating similar response patterns across groups. Descriptively, post-exercise median BDNF values were higher in the MICE group; however, the Group×Time interaction was not significant, and thus no differential effect of exercise intensity on BDNF was presumed. The median changes presented above are descriptive only and were not tested inferentially; ANOVA interaction effects for these biomarkers were nonsignificant.

In contrast, peripheral lactate concentration showed a significant Group×Time interaction (F(1, 28)=51.01, *P*<0.001; η^2=0.267), indicating that mean changes in lactate concentration substantially differed between exercise modalities. Given this significant interaction, simple effects were examined. Mean-based analyses indicated higher post-exercise lactate concentrations in both groups; the increase was greater in the MICE group.

To aid interpretation, median changes are also reported descriptively. Median increases in lactate concentration were 4.9 (95% bootstrap CI [3.6, 6.9]) in the MICE group and 0.8 (95% CI [0.6, 1.0]) in the LICE group (**Figure 2F**), corresponding to an approximately 6-fold greater typical increase in the MICE group.

Associations between serum neurotrophin concentrations and functional or clinical variables were examined using Spearman rank correlation coefficients. In the LICE group, a positive correlation was observed between VEGF-A concentration and RMA score (rs=0.59, 95% CI [0.23, 0.84]). In the pooled pre-exercise data, significant positive correlations were detected between RMA score and GDNF (rs=0.37, 95% CI [0.05, 0.64]), age and lactate concentration (rs=0.50, 95% CI [0.20, 0.73]), and body mass index and VEGF-A concentration (rs=0.54, 95% CI [0.22, 0.81]; a negative correlation was noted between BDI score and VEGF-A concentration (rs=-0.44, 95% CI [-0.72, -0.13]; **Table 2**). In the MICE group, positive correlations were observed between age and post-exercise BDNF concentration (rs=0.79, 95% CI [0.51, 0.95]), as well as BDI score and post-exercise lactate concentration (rs=0.52, 95% CI [0.05, 0.90]; **Table 3**). In the LICE group, a positive correlation (rs=0.53) was noted between post-exercise IGF-1 concentration and post-exercise BDNF concentration (**Figure 3**).

Discussion

Among patients in the subacute phase of rehabilitation after ischemic stroke, the present study showed that a single session of aerobic exercise in the MICE group was associated with higher peripheral BDNF and lactate concentrations but not with changes in peripheral GDNF or IGF-1 concentrations. The results also indicated lower serum VEGF-A concentrations following a single exercise session. Further research is needed to determine the optimal timing of changes in VEGF-A levels in the bloodstream among patients with stroke who are undergoing aerobic training. King et al [7] observed that among 35 patients at 31.5 ± 26.7 months after stroke, peripheral IGF-1 concentrations substantially decreased following incremental maximal aerobic testing. Another clinical trial involving 16 participants in the chronic phase after stroke (mean duration: 6.5 ± 4.1 years post-stroke) reported a nonsignificant increase in serum IGF-1 during a single graded exercise test and moderate continuous walking at a mean intensity of 45% ± 5%

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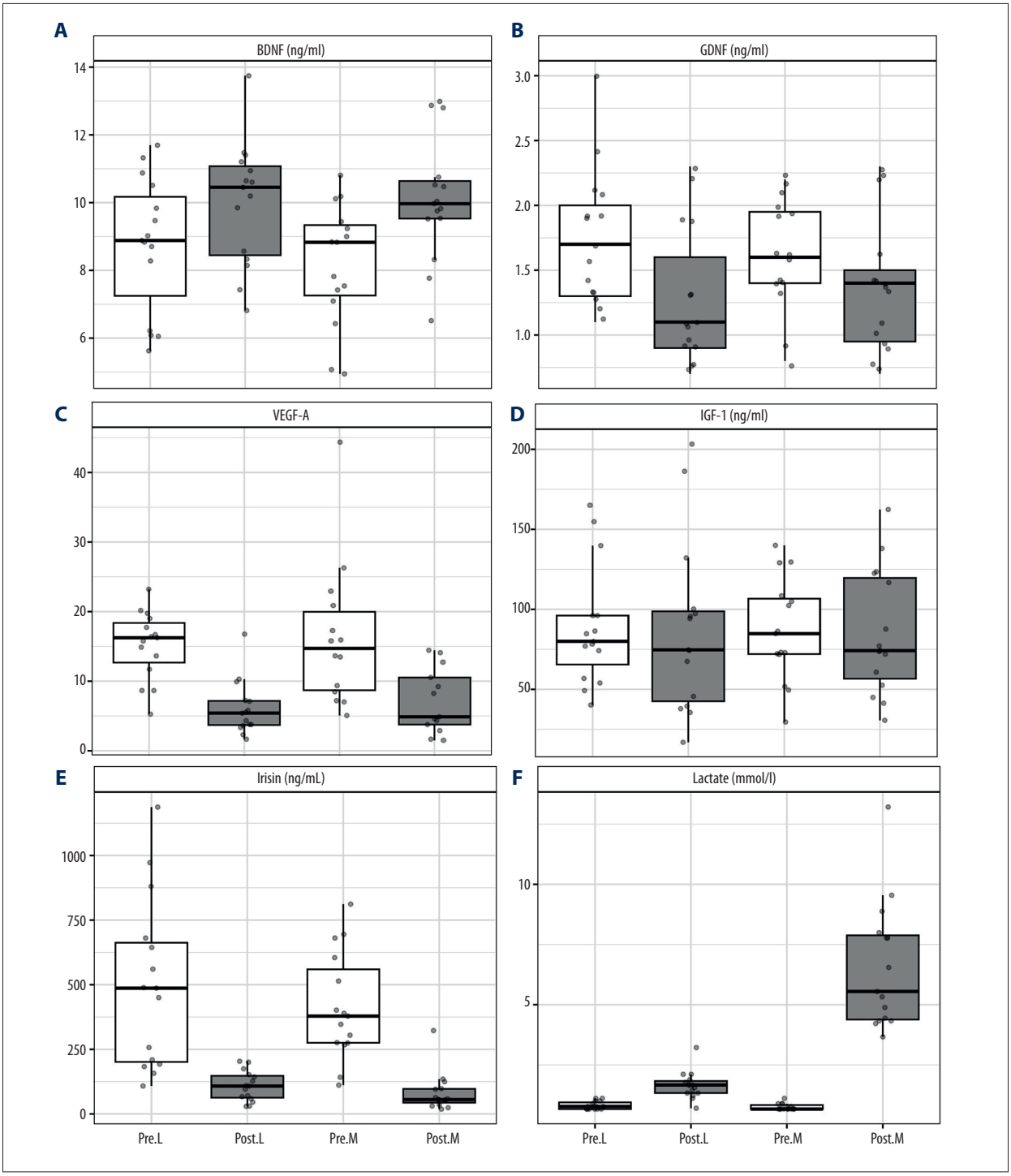

Figure 2. Effects of a single exercise session on serum brain-derived neurotrophic factor (BDNF) (**A**), glial cell-derived neurotrophic factor (GDNF) (**B**), vascular endothelial growth factor A (VEGF-A) (**C**), insulin-like growth factor 1 (IGF-1) (**D**), irisin (**E**), and peripheral lactate concentration (**F**). Boxplots show median values, interquartile ranges (boxes), and ranges (whiskers), with individual data points overlaid for pre-exercise (white) and post-exercise (gray) concentrations in the low-intensity continuous exercise (LICE) and moderate-intensity continuous exercise (MICE) groups. Boxplots depict raw data with medians and interquartile ranges for descriptive purposes only. Inferential conclusions were derived exclusively from 2-way repeated-measures analysis of variance tests of Group×Time interactions. Abbreviations: Pre.L, pre-exercise LICE group; Post.L, post-exercise LICE group; Pre.M, pre-exercise MICE group; Post.M, post-exercise MICE group.

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Table 2. Correlations between pre-exercise serum neurotrophic factor concentrations (ng/mL), peripheral lactate concentration (mmol/L), and physical performance, cognitive status, and psychological function before exercise in participants (n=30).

Parameter	BDNF	GDNF	VEGF-A	IGF-1	Irisin	Lactate
Age (years)	-0.11 (-0.45, 0.26)	-0.17 (-0.51, 0.2)	0.06 (-0.34, 0.44)	0.19 (-0.2, 0.57)	-0.13 (-0.54, 0.29)	**0.5 (0.2, 0.73)***
BMI (kg/m^2)	-0.15 (-0.54, 0.25)	0.29 (-0.05, 0.6)	**0.54 (0.22, 0.81)***	-0.01 (-0.36, 0.35)	0 (-0.39, 0.37)	0.1 (-0.26, 0.48)
ACE-III (points)	0.04 (-0.35, 0.4)	0.07 (-0.32, 0.46)	0.05 (-0.34, 0.45)	-0.18 (-0.52, 0.16)	-0.04 (-0.37, 0.33)	-0.31 (-0.61, 0.01)
RMA (points)	0.04 (-0.3, 0.39)	**0.37 (0.05, 0.64)***	0.17 (-0.17, 0.46)	-0.12 (-0.43, 0.23)	-0.24 (-0.57, 0.13)	-0.21 (-0.55, 0.15)
BDI (points)	0.12 (-0.27, 0.47)	0.03 (-0.33, 0.39)	**-0.44 (-0.72, -0.13)***	-0.01 (-0.39, 0.38)	0.1 (-0.25, 0.45)	0.07 (-0.36, 0.44)

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BMI, body mass index; GDNF, glial cell-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; RMA, Rivermead Motor Assessment; VEGF-A, vascular endothelial growth factor A. Data are shown as rs (95% confidence interval). * P<0.05.

Table 3. Correlations between pre-exercise physical performance, cognitive status, and psychological function and post-exercise peripheral neurotrophic factor (ng/mL) and lactate (mmol/L) concentrations.

Parameter Group	BDNF		GDNF		VEGF-A		IGF 1		Irisin		Lactate	
	M	L	M	L	M	L	M	L	M	L	M	L
Age (years)	**0.79***	**-0.52#**	-0.13	-0.34	-0.03	0.10	0.08	-0.39	-0.12	0.34	-0.26	-0.10
BMI (kg/m^2)	0.02	0	0.34	0.24	0.24	0.05	-0.17	-0.09	-0.23	0.11	-0.34	-0.36
ACE-III (points)	-0.34	0.25	-0.08	0.03	-0.03	0.15	-0.11	-0.16	0.24	0.21	-0.07	-0.15
RMA (points)	0.14	-0.03	-0.21	-0.07	-0.16	**0.59***	-0.02	-0.32	0.11	0.25	-0.36	0.24
BDI (points)	-0.12	0.03	0.40	0.27	-0.01	-0.06	0.11	-0.04	0.03	0.31	**0.52***	0.16

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BMI, body mass index; GDNF, glial cell-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; L, low-intensity continuous exercise; M, moderate-intensity continuous exercise; RMA, Rivermead Motor Assessment; VEGF-A, vascular endothelial growth factor A. * P<0.05, # P<0.10.

heart rate reserve [9]. Similarly, our study showed no significant changes in serum IGF-1 concentrations following a single session of aerobic exercise in either the LICE or MICE group.

Findings regarding irisin have also been inconsistent. In a recent randomized crossover trial involving 25 adolescents, a single 35-minute cycle ergometer session did not significantly alter plasma irisin concentrations; no differences were observed before and after exercise [17]. Furthermore, in a clinical trial involving adults who completed a maximal cycle ergometer test with progressively increasing intensity, a significant increase in irisin concentration was recorded from baseline (7.6±1.6 ng/mL) to 15 minutes post-exercise (8.7±1.5 ng/mL) [18]. In contrast to these studies conducted in healthy individuals, our analysis of patients after stroke showed lower serum irisin concentrations immediately following exercise. This reduction may be related to increased uptake or altered transport mechanisms across the blood-brain barrier. Irisin regulates thermogenesis, glucose metabolism, and lipid metabolism in skeletal muscle during contraction, among other physiological processes [19]. One possible explanation for the reduction in irisin after a single session of aerobic cycling exercise may involve exercise-induced regulation of energy metabolism.

Another study enrolled 12 patients with a mean age of 61±13 years and an average duration of 3 years and 11 months post-stroke; participants completed a single 30-minute treadmill walking session at moderate to high intensity [20]. The authors reported enhanced sensorimotor adaptation after the treadmill intervention, accompanied by significantly increased

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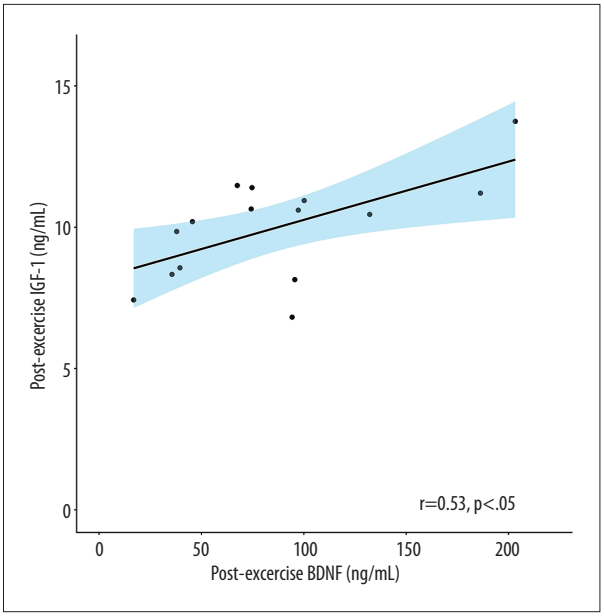

Figure 3. Spearman rank correlations between post-exercise serum brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1) concentrations in the low-intensity continuous exercise (LICE) group.

serum BDNF concentrations. Similarly, a study involving 36 healthy young men revealed that a single session of interval sprint cycling significantly increased peripheral BDNF, IGF-1, and VEGF concentrations [21]. These changes were associated with increased peripheral lactate concentrations and enhanced cognitive function. Other studies have suggested that cognitive benefits after acute exercise are most frequently observed with cycling-based aerobic exercise relative to other exercise modalities [22]. Moreover, moderate-intensity acute exercise may provide the greatest benefits for executive cognitive processes; low-intensity aerobic exercise appears to exert limited effects on cognitive function [23]. One proposed mechanism by which moderate-intensity acute exercise may enhance these cognitive processes is increased cerebral blood flow [24]. The authors of the interval sprint cycling study concluded that elevations in neurotrophic factors may reflect a neuroprotective response [21].

A recent study indicated that increased lactate levels during aerobic exercise might contribute to enhanced motor learning and motor cortical plasticity [25]. Lactate influences several brain functions, including neuronal metabolism and endogenous neuroprotective pathways. Additionally, there is evidence that lactate modulates inflammatory mediator release and may facilitate neural repair and motor recovery. Studies have also shown that lactate can meet the increased energy demands of neurons during post-stroke neuroplasticity processes [26,27]. The present study revealed higher lactate concentrations in the MICE group after exercise. Further research investigating changes in lactate concentrations across exercise intensities is needed to clarify its role in improving post-stroke motor function.

In the MICE group, we observed a significant positive correlation between post-exercise serum BDNF concentration and participant age (rs=0.79, $P<0.05$). This finding implies that a single session of moderate-intensity cycling exercise during the early subacute stage of post-stroke recovery could represent a beneficial rehabilitation strategy associated with higher BDNF concentrations. Consistent with this observation, a previous study indicated that physical activity performed at an appropriate intensity and duration can counteract declines associated with aging and nervous system damage [28].

Pedroso et al [29] reported a negative correlation between post-stroke depression severity and GDNF concentrations. In contrast, we identified a positive correlation between motor function and baseline serum GDNF concentrations. Notably, previous research has suggested that reduced GDNF levels are associated with major depressive disorder, whereas physical activity may increase GDNF concentrations [30].

In the present study, Group×Time interactions for neurotrophins (BDNF, GDNF, VEGF-A, IGF-1, and irisin) were not significant. Thus, we found no evidence that moderate-intensity exercise produced distinct neurotrophin responses relative to low-intensity exercise. Any descriptive within-group shifts should be considered exploratory and non-inferential. Although median values suggested higher post-exercise BDNF concentrations in the MICE group, the nonsignificant interaction effect precludes attributing these findings to a differential effect of exercise intensity; such observations should be regarded as exploratory. Future longitudinal studies are warranted to determine the extent to which these neurotrophins mediate the effects of moderate-intensity exercise on post-stroke rehabilitation outcomes.

There were some limitations in this study. First, we included a relatively small number of participants, and therefore the study may have been underpowered. Second, evaluation of additional neurotrophic factors could provide a more comprehensive understanding of exercise-related effects. Investigations of neurotrophin polymorphisms may improve the broader understanding of how aerobic exercise influences psychomotor function and contributes to beneficial neurorehabilitation outcomes. Future studies should also determine the optimal timing of peak peripheral biomarker release. Third, systematic investigation of the most effective exercise protocols, including exercise duration and intensity, is needed, along with evaluation of the effects of long-term exercise interventions on rehabilitation outcomes after ischemic stroke.

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Conclusions

Our findings suggest that endurance exercise intensity does not differentially affect peripheral neurotrophic factor levels during the regenerative-compensatory phase of post-stroke rehabilitation. Additional studies investigating other endothelial biomarkers are needed to clarify the broader effects of aerobic exercise and expand the overall understanding of how endurance exercise supports neuroplasticity during post-stroke rehabilitation.

Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Patient Consent

All patients provided written informed consent to participate in this study.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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