

Muscle as an Endocrine Organ in Stroke Rehabilitation: Aerobic Exercise–Driven Myokine Responses and Functional Gains

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Article

Keywords: Ischemic stroke, myokine, irisin, myonectin, BDNF, IL-15, aerobic exercise

Posted Date: June 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9368487/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

In recent years, the role of myokines released from muscles in response to exercise in supporting neuroplasticity and recovery has attracted increasing attention within the scientific community. Among these, irisin, myonectin, brain-derived neurotrophic factor (BDNF) and interleukin-15 (IL-15) are particularly associated with neuromuscular health, energy metabolism and neurogenesis. This study aimed to investigate the effects of a structured aerobic exercise programme on serum levels of selected myokines and functional recovery in post-stroke patients.

Methods

Patients with ischaemic stroke were prospectively allocated according to rehabilitation modality into two comparative exercise settings over a 6-week period: a supervised bicycle-based aerobic exercise programme (n = 41) and a self-directed home exercise programme (n = 40). In biochemical assessments, serum irisin, myonectin, BDNF and IL-15 levels were measured using the ELISA method. Physical assessment tools included the Fatigue Severity Scale Test (FSS Test), the 30-Second Sit-to-Stand Test (30s-STs), the 6-minute walk test (6MWT) and the Borg perceived exertion scale (RPE).

Results

The aerobic exercise group demonstrated statistically significant changes ($p < 0.001$) in serum myonectin, BDNF, irisin and IL-15 levels following the intervention. These changes were accompanied by marked improvements in balance and walking capacity. In contrast, the home exercise group showed only marginal or non-significant changes in both biochemical and functional outcomes.

Conclusion

Aerobic exercise influences serum myokine profiles in post-stroke patients, and these changes are associated with improvements in physical function. This study demonstrates that integrating exercise programmes conducted under professional supervision into stroke rehabilitation may provide significant benefits at both the molecular and functional levels.

1. Introduction

Stroke is one of the leading causes of long-term disability worldwide and represents a major public health burden due to its high prevalence, morbidity, and functional consequences. Impairments following stroke commonly include motor dysfunction, muscle weakness, reduced aerobic capacity, impaired

balance, and decreased functional independence, all of which significantly affect quality of life and increase healthcare costs ^{1,2}.

Skeletal muscle dysfunction after stroke is not limited to neural impairment but also involves profound structural, metabolic, and endocrine alterations, including muscle atrophy, fiber type transformation, mitochondrial dysfunction, and increased intramuscular adipose tissue (3,4). These changes contribute to reduced functional recovery and increased risk of secondary metabolic and cardiovascular complications ^{3–5}.

In recent years, skeletal muscle has been recognized not only as a contractile organ but also as an endocrine organ that secretes biologically active molecules known as myokines. These molecules are released into circulation during muscle contraction and exert autocrine, paracrine, and endocrine effects on distant organs, including the brain, adipose tissue, liver, and immune system ^{6,7}. Myokines play critical roles in regulating muscle metabolism, neuroplasticity, inflammation, and tissue regeneration, and they are considered key mediators of exercise-induced systemic adaptations ⁸.

Among these myokines, irisin, brain-derived neurotrophic factor (BDNF), interleukin-15 (IL-15), and myonectin have received increasing attention due to their roles in neuromuscular and metabolic regulation. Irisin, a cleavage product of fibronectin type III domain-containing protein 5 (FNDC5), is involved in energy metabolism, mitochondrial biogenesis, and muscle-adipose tissue crosstalk, and may contribute to exercise-induced metabolic adaptations ⁹. BDNF is a neurotrophic factor that plays a critical role in neuronal survival, synaptic plasticity, neurogenesis, and motor learning, and has been shown to contribute to neuroplasticity and functional recovery after stroke ^{10,11}. IL-15 is involved in muscle hypertrophy, muscle-fat interaction, and anti-inflammatory processes, and is associated with improved muscle function and metabolic health ¹². Myonectin, also known as CTRP15, regulates lipid metabolism and enhances fatty acid uptake in peripheral tissues, contributing to improved metabolic homeostasis ¹³.

Aerobic exercise is a well-established intervention in stroke rehabilitation and has been shown to improve cardiovascular fitness, muscle strength, walking ability, balance, and overall functional capacity ^{14,15}. In addition to its functional benefits, aerobic exercise may promote recovery through molecular and cellular mechanisms, including increased neuroplasticity, enhanced angiogenesis, improved mitochondrial function, and modulation of inflammatory pathways ^{16–19}. Importantly, exercise-induced myokine secretion has been proposed as a key mechanism linking muscle activity to neural recovery and systemic adaptations after stroke ^{20,21}.

Previous studies have demonstrated that exercise can modulate circulating myokine levels in both healthy individuals and patients with neurological and metabolic disorders ²¹. Exercise-induced increases in irisin, BDNF and IL-15 have been associated with improved neuroplasticity, muscle function,

and functional recovery^{22,23}. Similarly myonectin have been implicated in metabolic regulation and muscle adaptation in response to exercise^{9,13}.

Understanding the molecular mechanisms underlying exercise-induced recovery is essential for optimizing rehabilitation strategies in stroke patients. In particular, identifying changes in myokine profiles in response to aerobic exercise may provide valuable insights into the endocrine function of skeletal muscle and its contribution to neurofunctional recovery²⁴.

Although evidence regarding the role of myokines in exercise physiology is growing, there are few studies investigating the effects of structured aerobic exercise on myokine responses in stroke patients, and the relationship between myokine modulation and functional recovery remains poorly understood. Therefore, the aim of this study was to investigate the effects of structured aerobic exercise on circulating myokine levels, including irisin, myonectin, BDNF, and IL-15, and to evaluate their association with functional recovery in stroke patients. We hypothesized that structured aerobic exercise would significantly modulate myokine levels and contribute to improved functional outcomes compared with a home-based exercise program.

2. Materials and methods

2.1 Identifying the participants in the study

All procedures carried out in this study were conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki. Approval for the experimental procedures was granted by the Ethics Committee for Non-Interventional Clinical Research at Etlik City Hospital. Because the present study was designed as a comparative rehabilitation observation rather than a formal registered therapeutic clinical trial, external clinical trial registry registration was not applicable. After providing detailed written and verbal explanations regarding the potential risks and benefits of the study protocol, written informed consent was obtained from each participant. This study was conducted as a prospective non-randomized comparative rehabilitation study evaluating the biochemical and functional effects of two different routinely implemented exercise modalities in post-stroke patients. Participants were assessed at the Department of Physiotherapy and Rehabilitation at Etlik City Hospital.

2.1.1 Inclusion Criteria

A diagnosis of ischaemic stroke confirmed by clinical and imaging methods, being medically stable, being able to mobilise with minimal support, the absence of cardiac or orthopaedic contraindications that would prevent participation in the exercise programme, and a Mini Mental State Examination score at a level sufficient to comply with the study (test score of 24 or above).

2.1.2 Exclusion Criteria:

History of haemorrhagic stroke, severe cardiac disease or uncontrolled hypertension, active infection, malignancy or inflammatory disease, severe musculoskeletal problems that would prevent participation in exercise, failure to adhere to the exercise programme during the study period.

2.3 Grouping of participants and exercise protocol

Participants were comparatively evaluated in two rehabilitation settings: the Aerobic Exercise Group (n = 41) and the Home-Based Exercise Group (n = 40).

Aerobic Exercise Group

Aerobic exercise was performed on a bicycle ergometer (Ergoline) in the rehabilitation unit using the Opticare software. Prior to exercise, the patient's case number and date of birth were recorded in the system. Blood pressure, heart rate and oxygen saturation values were recorded during exercise. The exercise intensity was moderate and was determined using the Karvonen formula, calculated based on maximum heart rate ($220 - \text{age}$) and resting heart rate. The patients' perceived exertion was assessed using the Borg scale. The maximum load that could be applied using 6 DYT was calculated prior to the programme, and a load of 60–80% of the calculated maximum load (W_{max}) was applied throughout the exercise. In the three-stage exercise programme, during the warm-up phase, 50% of the initially determined load was applied to the patients for 5 minutes.

During the exercise phase, a 20-minute exercise programme was administered to the patient, with the full prescribed load applied for 20 seconds and one-fifth of the prescribed load for 40 seconds every minute. The exercise programme was concluded with one-fifth of the prescribed load applied for a further 5 minutes during the cool-down phase. Finally, at the end of the exercise programme, the exercise intensity perceived by the patient during that session was calculated using the Borg scale; this value was then used to determine the difficulty level of the next session. Patients were assessed a total of twice by the same clinician: at the start of treatment and at the end of treatment (week 6). Participants in the aerobic exercise group underwent a structured aerobic exercise programme three days a week for six weeks, with each session lasting approximately 45 minutes. All sessions were conducted under the supervision of a physiotherapist in a controlled environment.

Home-Based Exercise Group

Participants in this group were provided with a home-based exercise programme to be carried out over the same duration and frequency as the aerobic exercise group. This programme included lower limb strengthening, joint range of motion, and low-intensity endurance exercises. Participants performed the exercises independently at home, and compliance with the exercise regimen was monitored verbally at regular intervals.

Venous blood samples were collected from participants at 08:00 via the antecubital vein, whilst they were fasting, at the start and end of the 6-week treatment programme and following a 24-hour rest

period. The blood samples were centrifuged at 3000 rpm for 15 minutes to separate the serum. The samples were stored at – 80°C until analysis.

Myokine levels were measured using blood samples taken before treatment and after the 6-week programme. Serum irisin (Elabscience, Wuhan, China), myonectin (BT LAB, Shanghai, China), BDNF (Elabscience, Wuhan, China) and IL-15 (Elabscience, Wuhan, China) levels were measured using the ELISA method in accordance with the test protocol, employing commercial kits. Physical functional assessments were conducted using the 6-minute walk test (6MWT), Berg Balance Scale (BBS), 30-Second Sit-to-Stand Test (30s-STs), Borg rating of perceived exertion scale (RPE) and Fatigue Severity Scale Test (FSS).

2.4 Functional Assessments

The participants' functional status was assessed prior to the exercise programme and following the six-week intervention. The assessments utilised standardised measurement tools with established validity and reliability to evaluate post-stroke functional capacity, balance, walking performance, functional movements related to muscle strength, and fatigue levels.

2.4.1 Berg Balance Scale: Balance performance was assessed using the Berg Balance Scale (BBS). The test consists of 14 items covering sitting, standing, turning and transfer activities; each item is scored on a scale of 0–4, and the total score ranges from 0 to 56. Higher scores indicate better balance performance. The Berg Balance Scale is a widely used measurement tool for assessing balance in individuals who have suffered a stroke, possessing high validity and reliability.

2.4.2 6-minute walk test: Walking capacity and functional endurance were assessed using the 6-minute walk test (6MWT). In this test, participants were asked to walk the greatest possible distance on a flat surface for six minutes. The total distance covered was recorded in metres at the end of the test. The 6-minute walk test is a reliable method for assessing walking endurance and aerobic capacity in stroke patients.

2.4.3 30-Second Sit-to-Stand Test: Lower extremity functional endurance, neuromuscular performance, and dynamic balance were assessed using the 30-Second Sit-to-Stand Test (30s-STs). Participants were seated on a standard armless chair with a height of 43 cm, maintaining an upright posture with both feet in contact with the floor. Upon the “start” command, participants were instructed to rise to a full standing position and return to sitting as many times as possible within 30 seconds. The total number of completed sit-to-stand repetitions was recorded. Higher repetition counts indicate better lower extremity functional performance.

2.4.4 Fatigue Severity Scale Test (FSS): The perceived level of fatigue was assessed using the Fatigue Severity Scale. The scale consists of nine items that assess the impact of fatigue on daily living activities, with each item scored on a scale of 1–7. Higher scores indicate a more severe level of fatigue. The Fatigue Severity Scale is a valid and reliable measure for assessing fatigue following a stroke.

2.4.5 Borg Rating of Perceived Exertion Scale: The level of perceived exertion during exercise was assessed using the Borg Rating of Perceived Exertion Scale (RPE). The scale allows the individual to numerically express the level of difficulty felt during exercise and was used to adjust the exercise intensity to suit the individual.

2.5 Statistical analysis

The statistical analysis of the data obtained in the study was carried out using SPSS (Statistical Package for the Social Sciences) version 26.0. The normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. Parametric tests were used for variables that met the assumption of normal distribution, whilst non-parametric tests were used for those that did not.

When comparing the demographic characteristics of the groups, the independent samples t-test was applied for continuous variables such as age and body mass index where the normality assumption was met, and the Mann–Whitney U test was applied where it was not. Categorical variables such as alcohol consumption, smoking status and educational level were analysed using the chi-square test.

In comparing groups in terms of functional assessment results (6MWT, BBS, 30s-STST Test, RPE and FSS) and biochemical parameters (irisin and myonectin levels), an independent samples t-test or the Mann–Whitney U test was used depending on the distribution characteristics of the data.

Intra-group temporal changes were assessed between pre-intervention (T0) and post-intervention (T1) measurements; a paired t-test was applied for variables meeting the assumption of normality, and the Wilcoxon Signed-Rank test was applied for those that did not. Linear relationships between the biochemical and functional parameters included in the study were examined using correlation analysis. Pearson correlation analysis was used for variables showing a normal distribution, whilst Spearman correlation analysis was used for those not showing a normal distribution. The correlation coefficient (r) was reported to indicate the direction and strength of the relationship between variables. A significance level of $p < 0.05$ was adopted for all statistical analyses. Data are presented as mean $\pm$ standard deviation (SD) for normally distributed variables and as minimum–maximum values for non-normally distributed variables.

3. Results

3.1 Assessment of demographic and clinical characteristics in the groups

A total of 81 individuals were included in the study, 41 of whom were in the aerobic exercise group and 40 in the home exercise programme group. The mean age of the participants was found to be 56.86 ± 7.33 years. The mean age of the aerobic exercise group was 57.60 ± 7.08 years, whilst that of the home exercise programme group was 56.12 ± 7.60 years; no statistically significant difference in age was found between the groups. No significant difference was observed between the groups in terms of Body

Mass Index (BMI) either ($p = 0.63$). The mean BMI in the aerobic exercise group was $23.30 \pm 2.0 \text{ kg/m}^2$, whilst that of the home exercise programme group was $23.50 \pm 1.62 \text{ kg/m}^2$. These differences were assessed using an independent samples t-test. No significant differences were found in the comparison of comorbidities and clinical characteristics between the groups, except for hypertension. The number of participants with hypertension in the aerobic exercise group was significantly higher than in the home-based exercise group ($P = 0.002$).

3.2 Assessment of functional status in the groups

In the BBS Test, a significant increase was observed in the aerobic exercise group compared to the home exercise programme group ($p = 0.02$). Aerobic exercise group: 29.5 ± 10.2 . Home exercise programme group: 34.6 ± 7.2 . In the within-group analysis, a significant improvement in balance performance was observed in the aerobic exercise group following treatment ($p = 0.001$). No significant change was found in the home exercise programme group ($p = 0.694$).

A significant increase was observed in the aerobic exercise group compared to the home exercise group in the 30s-STS test ($p < 0.001$). Aerobic exercise group: 8.9 ± 3.2 . Home exercise programme group: 7.1 ± 3.1 . In the within-group analysis, a significant increase in lower limb strength was observed in the aerobic exercise group ($p < 0.001$). A significant decrease in lower limb strength was found in the home exercise programme group ($p = 0.001$).

On the FSS Fatigue Severity Scale, a significant reduction was found in the aerobic exercise group compared to the home exercise programme group ($p = 0.001$). Aerobic exercise group: 3.3 ± 1.7 . Home exercise programme group: 3.4 ± 1.1 . In the within-group analysis, fatigue severity decreased significantly in the aerobic exercise group ($p < 0.001$). No significant change in fatigue levels was found in the home exercise programme group ($p = 0.665$).

In the 6MWT test, a significant increase was observed in the aerobic exercise group compared to the home exercise programme group ($p < 0.001$). Aerobic exercise group: 264.9 ± 106.4 metres. Home exercise programme group: 315.2 ± 95.6 metres. Within-group analysis showed that cardiovascular endurance in the aerobic exercise group increased significantly following treatment compared to pre-treatment 6MWT results ($p < 0.001$). In the home exercise programme group, a significant decrease in endurance was observed following treatment compared to pre-treatment 6MWT results.

3.3 Assessment of myokine levels in the groups

A significant decrease in irisin levels was observed in the aerobic exercise group following treatment compared to pre-treatment levels ($p < 0.001$). No significant change in irisin levels was observed in the home exercise programme group following treatment ($p = 0.294$).

In the aerobic exercise group, a significant increase in myonectin levels was observed post-treatment compared to pre-treatment ($p < 0.001$). This increase suggests that aerobic exercise accelerates muscle recovery and metabolic processes. In the home exercise programme group, a significant increase in

myonectin levels was observed post-treatment ($p < 0.001$). Low-intensity home exercise also demonstrated effects supportive of muscle metabolism.

In the aerobic exercise group, a significant increase in IL-15 levels was observed post-treatment compared to pre-treatment ($p < 0.001$). This indicates that exercise supports muscle recovery by regulating inflammation. In the home exercise programme group, however, no significant change in IL-15 levels was observed post-treatment ($p = 0.898$). This suggests that low-intensity exercise is not effective in regulating inflammation.

In the aerobic exercise group, a significant increase in BDNF levels was observed post-treatment compared to pre-treatment ($p < 0.001$). This increase has been associated with nervous system recovery, neuroplasticity and neuroprotective effects. In the home exercise programme group, there was no significant change in BDNF levels post-treatment ($p = 0.801$). This result indicates that the home exercise programme has a limited effect on the nervous system.

3.4 Correlation Analysis

Aerobic Exercise Group:

Positive correlation between the 30s-STS test and irisin: The significant positive relationship between increased duration in the 30s-STS test and elevated irisin levels suggests that aerobic exercise may influence muscle metabolism and that physical performance is linked to metabolic processes.

Positive correlation between the 6MWT test and IL-15: The increase in physical performance alongside rising IL-15 levels highlights the regulatory effect of aerobic exercise on inflammation and its role in accelerating muscle recovery. The rise in IL-15 levels with increased walking distance provides important insights into muscle and metabolic health.

Home Exercise Programme Group:

Positive correlation between BSS and IL-15: The positive correlation observed between the balance test and IL-15 in the home exercise group suggests that the home programme's effect on balance functions may be related to inflammation. This indicates that inflammation may be regulated as balance performance improves.

4. Discussion

This study clearly demonstrates that structured and supervised aerobic exercise significantly modulates both the myokine response and functional recovery in post-stroke patients. In particular, the observation that increases in BDNF, IL-15 and myonectin levels coincide with improvements in balance, muscle strength and walking capacity strongly supports the pivotal role of skeletal muscle-derived signalling mechanisms in the rehabilitation process. Conversely, the limited effects of the home-based exercise

programme indicate that it is not merely the implementation of exercise that matters, but also its dosage, intensity and supervision.

One of the most striking findings of this study is the significant increase in BDNF levels observed following aerobic exercise. It is well established that BDNF plays a central role in neuronal survival, synaptic plasticity and learning processes²⁵. Furthermore, it has been demonstrated that aerobic exercise increases BDNF levels and that this increase is associated with neuroplasticity^{26–29}. Furthermore, it has been established that exercise increases BDNF expression via the PGC-1 α /FNDC5 pathway and exerts its effects via the muscle-brain axis³⁰. In this context, the increase in BDNF observed in our study can be interpreted not merely as a biochemical change, but also as a reflection of exercise-induced neuroplastic adaptations.

A significant increase in IL-15 levels is also one of the study's key findings. It has been experimentally demonstrated that IL-15 supports muscle hypertrophy and exhibits protective effects against muscle loss^{31,32}. Furthermore, it has been reported that IL-15 has exercise-related immunomodulatory and metabolic effects¹². In this study, the positive association between IL-15 and walking performance suggests that IL-15 is not merely a biochemical marker but may also be directly related to functional capacity. This finding suggests that IL-15 could be a potential target and biomarker in the rehabilitation process.

The increase in myonectin levels represents another important indicator of the metabolic effects of exercise. Myonectin has been shown to regulate lipid metabolism and enhance fatty acid uptake in peripheral tissues^{33,34}. Previous studies have demonstrated that myonectin may improve skeletal muscle dysfunction and represent a potential therapeutic target for muscle atrophy³⁵. These properties of myonectin indicate that it contributes to the optimization of energy utilization, while also supporting exercise performance and functional recovery. In our study, the observed increase in myonectin levels in both the aerobic and home-based exercise groups suggests that even low-intensity exercise can elicit a metabolic response; however, it is evident that supervised exercise markedly amplifies this effect.

The decrease in irisin levels observed in our study represents a noteworthy finding when compared with the existing literature. Irisin has been identified as a myokine induced by exercise that promotes the browning of white adipose tissue³⁶. However, it is well established that irisin responses in clinical populations are heterogeneous and may vary depending on exercise parameters^{24,37,38}. Therefore, the reduction in irisin levels observed in the aerobic exercise group in our study may be interpreted as an adaptive regulation of metabolic stress or a homeostatic response to chronic exercise. This finding suggests that the biology of irisin is more complex, particularly under pathological conditions.

From a functional perspective, the improvements observed in the aerobic exercise group are in strong agreement with the existing literature. Aerobic exercise has been extensively demonstrated to enhance physical capacity and functional independence in patients with stroke^{14,15}. Moreover, the mechanisms through which exercise supports neuroplasticity include processes such as the upregulation of growth

factors and the modulation of inflammation^{16,17}. This study contributes significantly to the literature by demonstrating that these mechanisms are reflected at the systemic level through myokines.

Another important contribution of this study is the clear delineation of the differences between supervised exercise and home-based exercise. More pronounced improvements in both biochemical and functional parameters were observed in the supervised exercise group. This finding indicates that the effectiveness of exercise depends not only on its presence but also on the manner in which it is implemented. Indeed, meta-analyses of randomized controlled trials have demonstrated that structured rehabilitation programs are more effective in promoting motor recovery. Previous rehabilitation studies and meta-analyses have demonstrated that supervised rehabilitation programs are more effective in promoting motor recovery and functional improvement after stroke³⁹.

Correlation analyses further support the biological relationship between myokines and functional performance. In particular, the association between IL-15 and walking capacity reflects the interaction between muscle function and inflammation. These findings are consistent with studies demonstrating that skeletal muscle functions not only as a mechanical organ but also as an endocrine organ, with myokines released during exercise orchestrating systemic adaptations^{6,8}.

Nevertheless, this study has several limitations. The relatively small sample size and short intervention duration may limit the generalizability of the findings. In addition, the evaluation of only selected myokines may have restricted the comprehensive assessment of exercise-induced biological responses. Future studies should incorporate broader biomarker panels and longer follow-up periods to better elucidate these mechanisms.

5. Conclusion

This study demonstrates that structured and supervised aerobic exercise induces significant alterations in circulating myokine profiles and promotes functional recovery in post-stroke patients. The observed increases in BDNF, IL-15, and myonectin levels, together with improvements in balance, muscle strength, and walking capacity, highlight the critical role of muscle-derived signaling pathways in neurorehabilitation.

Importantly, the superiority of supervised exercise over home-based programs underscores the necessity of controlled intensity, adherence, and professional guidance to achieve optimal rehabilitation outcomes. These findings support the concept of muscle–brain crosstalk as a key mechanism underlying exercise-induced recovery.

From a clinical perspective, myokines such as BDNF and IL-15 may serve as promising biomarkers for monitoring rehabilitation progress and optimizing individualized therapeutic strategies. Future studies with larger cohorts and longer follow-up periods are warranted to further elucidate the mechanistic pathways and long-term clinical implications of myokine modulation in stroke recovery.

Study Design Clarification

The present investigation represents a prospective non-randomized comparative rehabilitation study comparing two routinely prescribed exercise modalities in post-stroke patients. The objective was to evaluate comparative biochemical and functional responses during standard rehabilitation follow-up.

Declarations

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

This study was supported by Yozgat Bozok University Scientific Research Projects Unit under project number TYL-2024-1376.

Author Contribution

Ş.T.A. and M.Ç. developed the study into a project and designed it. M.Ç. wrote the article. Ş.T.A. implemented the exercise programme with the patients and collected patient data. I.A.K. performed the ELISA analyses. Ö.Z.K., E.A.Ö. and E.A. examined the patients and prepared the treatment programme. Ş.T.A. and M.Ç. analysed the data.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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