Research Article

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Neuroprotective and metabotropic effect of aerobic exercise training in female patients with type 2 diabetes mellitus

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Abstract

Objectives: We aimed to evaluate the effects of acute and chronic aerobic exercise on cognitive function and depression levels in patients with Type 2 Diabetes Mellitus (T2DM) and the changes in related neurotrophic and metabotropic factors.

Methods: Sixteen female patients (age=57.5 ± 7.3) diagnosed with T2DM were included. A and B sections of the Trail Making Test (TMT) and Beck Depression Inventory (BDI) were used to assess executive function and depression states. Brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), irisin, total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), fasting plasma glucose, hemoglobin A1c, and high-density lipoprotein (HDL) cholesterol were analyzed in blood. Aerobic exercise intensity was applied at 50–70% of the maximal heart rate for 40 min/day, three days weekly on the treadmill. All evaluations were repeated after one exercise session, a 12-week exercise program, and after one year for follow-up.

Results: TMT-A (p=0.001) and TMT-B (p=0.002) values were increased following both acute and chronic exercise. BDI scores were decreased after long-term exercise (p=0.031). Measurement of metabolic parameters revealed positive changes in HDL cholesterol (p=0.044), TAS (p=0.005), and OSI (p=0.009) values after chronic period exercise. No significant difference was found in BDNF (p=0.271), NGF (p=0.230), and irisin (p=0.101) values after acute or chronic exercise, on the other hand.

Conclusions: Although aerobic exercise training had a positive effect on metabolic and cognitive outcomes, this effect was independent of neurotrophic and metabotropic factors. Regular and long-term aerobic exercise training has protective and regulatory functions in T2DM.

Keywords: aerobic exercise; cognition; depression; inflammation; neurotrophin; type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia resulting from impaired insulin secretion, increased hepatic glucose production, and decreased peripheral glucose utilization [1]. In T2DM, hyperglycemia predisposes to chronic low-grade inflammation, and accordingly, increased oxidative stress may occur. Conversely, increased oxidative stress and chronic low-grade inflammation also trigger impaired insulin secretion. These conditions also pave the way for the formation of complications related to diabetes. In addition to metabolic results, cognitive impairment, decreased memory, increased incidence of Alzheimer's disease (AD), and secondary neuronal disorders due to hyperglycemia accompany the picture and adversely affect the treatment process [2–5]. Also, subcortical ischemic changes and brain atrophy can be observed, and the risk of major depression increases twice in T2DM patients compared to the general population [6, 7].

The development of cognitive dysfunction or depression is associated with other disorders secondary to T2DM such as dysglycemia, hyperglycemia, hypoglycemia, insulin

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resistance, hyperinsulinemia, systemic inflammation, and cerebrovascular diseases [7, 8]. The concept of neuroprotection refers to preventing neuronal cell death by interfering with and inhibiting the pathogenetic processes that cause cellular dysfunction and death. Thus, new interventions that can help preserve brain tissue and improve overall outcomes have recently gained attention. Modifiable lifestyle factors such as physical activity and diet modulate widespread neurogenesis, neurotrophic signaling, stress, and antioxidant defense responses in the brain. Thus, they constitute alternative non-drug treatment options for neurodegenerative processes such as possible dementia and AD. Epidemiological studies have shown that physical activity reduces the risk of AD and dementia by 45 and 28%, respectively [9, 10]. Neurotrophins such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), nerve growth factor 3 (NG-3), and nerve growth factor 4 (NG-4) provide neuroprotection and also are affected by physical activity. Studies have shown that tropomyosin receptor kinase B (TrkB), the receptor on which neurotrophins act, is also found in non-nerve cells such as myocardial and pancreatic alpha cells. For this reason, neurotrophins, especially NGF and BDNF, have begun to be referred to as neurotrophic factors and metabotropic factors. Among its metabotropic effects, TrkB was reported to improve glucose, lipid, and antioxidant metabolisms [1, 11–13]. In addition to these neurotrophins, Fibronectin Type III Domain Containing 5 (FNDC5)/irisin, the proteolytic product of the exercise-induced transmembrane protein fibronectin Type III domain 5, is also mentioned to have neuroprotective and metabotropic effects, such as protection of cognitive function and prevention of neurodegeneration [14–16]. It has been shown that irisin also increases thermogenesis, improves glucose homeostasis and obesity, as well as contributes to BDNF expression, neuroprotection, reduction of neuronal damage, and neuropathic pain [17, 18].

Although current anti-diabetic pharmacological agents are effective on both primary and secondary outcomes of T2DM, they cause some clinical disorders due to their accompanying side effects. For this reason, in recent years, the metabotropic and neuroprotective positive effects of lifestyle modifications such as increasing the level of physical activity and regulating nutrition in individuals with T2DM are mentioned [8, 19, 20]. However, the literature on this subject is still limited. Based on this, we examined the effect of supervised exercise training on cognitive functions, depression states, glycemic control and blood lipids in patients with T2DM and its relationship with neurotrophic and metabotropic factors. Thus, we predict that if individuals with T2DM follow a regular exercise program, their consumption of pharmacological agents and hospitalizations may decrease.

Materials and methods

Study design and participants

The study was conducted in Fatih Sultan Mehmet Training and Research Hospital Diabetes and Obesity Treatment Center and Demiroglu Bilim University Multidisciplinary Laboratory between September 2019 and March 2020. Permission for the study was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (09.2019.484). Female patients diagnosed with T2DM between the last 5–20 years, aged 40–65, whose blood glucose was controlled by oral pharmacological agents or diet, and who did not do regular physical activity were included in the study. We chose this age range and female subjects in our research to show that the parameters we will evaluate are affected by these parameters in the literature [21]. For this reason, we worked in a more local group. Patients who use insulin, have advanced cardiac problems, use beta-blockers, and have any contraindications (kidney, liver, cardiovascular, etc.) to participate in the exercise program were excluded from the study. We conducted the study with 16 female patients who met the inclusion criteria and agreed to sign the 'Voluntary Consent Form' (Figure 1).

Sociodemographic information of the patients was obtained, cognitive functions and depression status were evaluated, and BDNF, NGF, irisin, total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), fasting plasma glucose, hemoglobin A1c (HbA_{1c}) and high-density lipoprotein (HDL) cholesterol values were measured in blood samples. A and B sections of Trail Making Test (TMT), which tests executive function, was used to evaluate cognitive functions, and Beck Depression Inventory (BDI) was used to measure depression states [22, 23]. Approximately 30 min after satiety, 5 mL blood samples were taken from the patients before exercise between 08:00 and noon into gel biochemistry tubes for serum collection.

After the blood samples were taken at the Diabetes and Obesity Treatment Center of Fatih Sultan Mehmet Training and Research Hospital, they were delivered to Demiroglu Science University Multidisciplinary Laboratory under cold chain conditions between 2 and 6 °C. The collected blood was centrifuged with a Rotina 380R (Hettich, Tuttlingen, Germany) refrigerated centrifuge device at 1,500 $g \times 10$ min, and serums were obtained and aliquoted (divided into three parts), then stored at −80 °C (Sanyo, Tokyo, Japan) until the day of the experiment. After the blood samples were dissolved at room temperature on the day of the experiment, they were vortexed (IKA labortechnik, Staufen, Germany). Human irisin (Abbkine KTE62744, Wuhan, China), Human NGF (NGF; Abbkine KTE63089, Wuhan, China), and Human BDNF (BDNF; Abbkine KTE62780, Wuhan, China) ELISA kits were used. These kits have similar assay procedures (two-side sandwich ELISA). Standard and samples are added to the ready irisin, NGF, or BDNF antibody-coated plates and incubated for 45 min at 37 °C. After incubation, the plates are washed, and HRP-conjugate is added to each well and incubated for 30 min at 37 °C. After incubation, the plate is washed, Chromogen solutions A and B are added. It was then incubated for an additional 15 min at

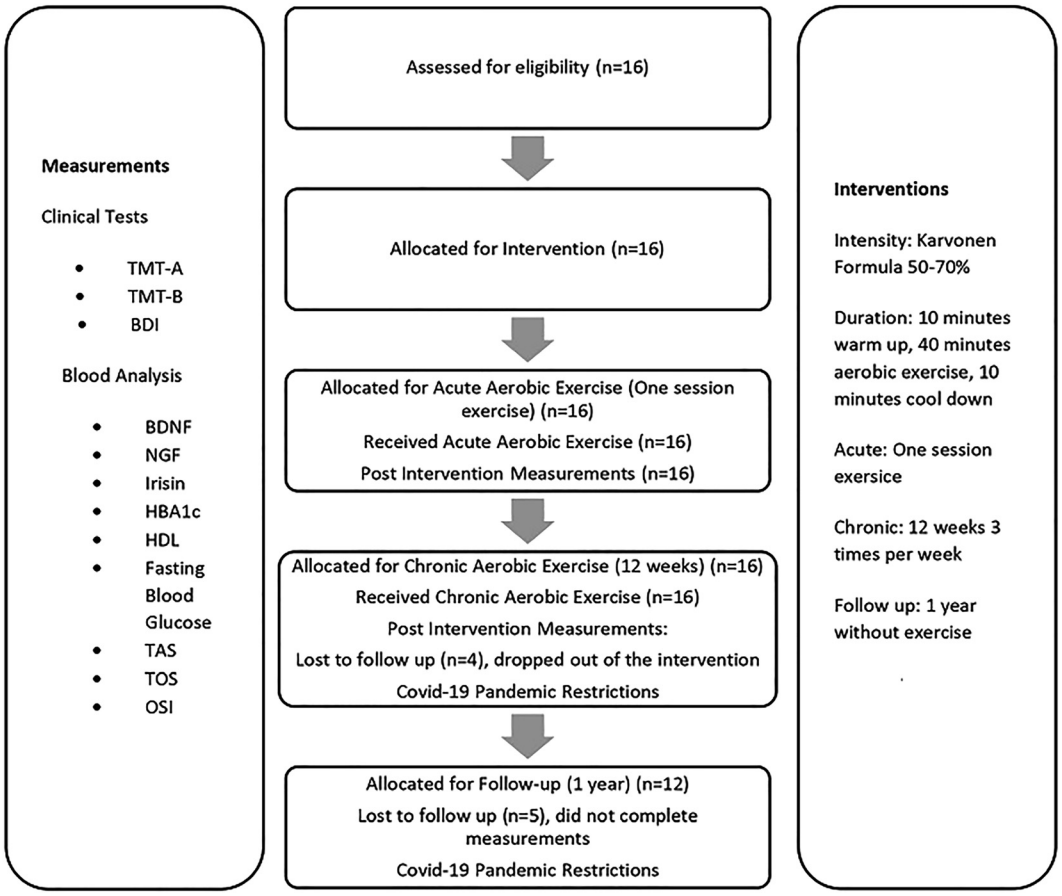

Figure 1: The description of the logistics of the study.
TMT, trail making test; BDI, Beck depression inventory; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

37 °C in the dark. Finally, a stop solution is added to each well, and the ELISA plate is read at 450 nm with an ELISA reader (Biotek, Vermont, USA). Human irisin, NGF, and BDNF results were expressed as pg/mL, ng/L, and µg/L, respectively. Human irisin ELISA kit detection range from 15 to 240 pg/mL. The minimum detectable dose (MDD) of Human irisin is typically less than 1.0 pg/mL. Human NGF kit detection range from 1 to 16 ng/L. MDD of Human NGF is typically less than 0.1 ng/L. BDNF ELISA kit detection range is 0.625–10 µg/L. MDD of Human BDNF is typically less than 0.05 µg/L. ELISA kits, four samples of know concentration were tested in 20 separate assays to assess intra-assay precision. The imprecisions were less than 9%. Linear regression analysis of samples vs. the expected concentration yielded a correlation coefficient of 0.99.

Total oxidant status (TOS; Rel Assay Diagnostics RL0024, Gaziantep, Turkey) and Total antioxidant status (TAS; Rel Assay Diagnostics RL0017, Gaziantep, Turkey) of serum samples were measured with the appropriate commercial kits. The TOS test principle is based on the process of oxidized forms in cells forming a complex of ferric iron (Fe^{+3}) and ferrous (Fe^{+2}) ion-o-dianicide. Ferric ion produces xylenol orange complex in an acidic environment. The color intensity measured spectrophotometrically (530 nm) is directly proportional to the sample's total amount of oxidant molecules. Results were expressed as µmol H_2O_2 Equiv/L. The TAS test principle is based on reducing colored 3-ethylbenzothiazoline-6-sulfonate (ABTS) to the colorless ABTS form by antioxidants and spectrophotometric absorbance (660 nm) measurement of the reduced form. Results were expressed as mmol H_2O_2 Equiv/L. OSI that shows the degree of oxidative stress was calculated according to the following equation: OSI (arbitrary unit)=TOS (µmol H_2O_2 Equiv/L)/TAS (mmol Trolox Equiv/L). TOS samples containing 0.2–80 µmol H_2O_2 Equiv/L can be assayed without further dilution or concentration. Inter-and intra-assay coefficients of variation were 3.2 and 3.9%, respectively. TAS samples containing 0.1–3.5 mmol H_2O_2 Trolox Equiv/L can be assayed without further dilution or concentration. Inter-and intra-assay coefficients of variation were 2.8 and 3.3%, respectively.

Fasting plasma glucose and HDL levels were analyzed by the spectrophotometric method in serum on a Roche Cobas 8000 c502 auto analyzer (Roche Modular Systems, Mannheim, Germany) by using commercial Roche kits. HbA_{1c} test was performed by high-performance liquid chromatography technique (HPLC-boronate affinity method) on a Premier Hb9210 analyzer (Trinity Biotech Plc. IDA Business Park, Bray, Co.Wicklow, Ireland).

After one exercise session, these evaluations were repeated to look at the acute effects of exercise, after a 12-week exercise program to look at the chronic effects, and after a one-year follow-up for long-term effects.

Interventions

The Karvonen formula was used to determine the target heart rate at aerobic exercise loading intensity. According to the Karvonen formula, the maximal heart rate was determined by the calculation of '220-age'. The intensity of the individual's loading was found by taking the difference between the maximum heart rate and resting heart rate as the percentage desired to be loaded and adding it to the resting heart rate [24].

Target heart rate=load intensity × (maximum heart rate – resting heart rate) + resting heart rate

The patients applied aerobic exercises on the treadmill for 12 weeks, three days a week, 40 min/day at 50–70% loading intensity according to their maximal heart rate. Heart rate and saturation were monitored with pulse oximetry throughout the exercise. Pulse oximetry is a valid and reliable method for monitoring heart rate, as shown in the literature [25]. During aerobic exercise on the treadmill, pulse oximetry was used to ensure that the patient's age and resting heart rate worked at the determined target heart rate. It aimed for the patients to exercise at a safe oxygen level by monitoring their heart rate and saturation. The saturation values of all our patients remained within the normal range throughout the exercise. Lower and upper extremity active exercises were applied to warm up for 10 min before the aerobic exercise and cool down for 10 min afterward. The same evaluations were made before the exercise, at the end of the one exercise session for the acute effect of aerobic exercise, after a 12-week exercise program for the chronic effect of aerobic exercise, and after one-year follow-up. Patients continued a moderate-intensity aerobic exercise program for 12 weeks. They did not exercise until the next one year.

Outcome measures

The primary outcome measure of our study was BDNF. Secondary objective outcome measures are NGF, irisin, TAS, TOS, OSI, HbA_{1c}, fasting plasma glucose, and HDL cholesterol. The cognitive outcome measure is TMT, and the depression outcome measure is BDI.

Statistical analyses

The IBM SPSS Statistics software version 25.0 software was used for statistical analysis. Descriptive statistics were used to characterize the participants. Multiple imputations (five imputations) were used to adjust the loss to follow-up. Repeated-measures analysis of variance (ANOVA) was used to analyze the effect of time on the outcomes. The outcome measures were TMT, BDI, BDNF, NGF, TOS, TAS, OSI, HbA_{1c}, fasting plasma glucose, and HDL cholesterol. A p-value less than 5% was considered statistically significant in all statistical analyses.

Results

Sixteen female patients diagnosed with T2DM were included in the study. At the end of the one-year follow-up, seven patients completed the study. The basic characteristics of the patients are presented in Table 1. The mean age was 57.5 ± 7.3, and the mean body mass index (BMI) was 32.7 ± 6.08. T2DM disease duration mean of the patients was 11.3 ± 5.04 years.

Table 1: Baseline characteristics of participants.

	Mean (95% CI)	SD
Age, year	57.5 (53.6–60.4)	7.4
Weight, kg	83.4 (76.1–89.9)	14.7
BMI, kg/m^2	32.7 (29.1–34.9)	6.0
Year of diagnosis	11.3 (8.8–13.8)	5.04

BMI, body mass index; SD, standard deviation; CI, confidence interval.

The results of clinical tests and blood values are given in Tables 2 and 3. The results of the TMT A and B sections increased statistically significantly at the end of the one exercise session and 12-week exercise program (p=0.001, 0.002 respectively). BDI scores decreased with a 12-week exercise program, and this change was maintained at one-year follow-up (p=0.044).

HbA_{1c} values of the cases decreased with 12 weeks of exercise training (p=0.074) but increased above the baseline value (p=0.113) one year after the exercise was stopped. HDL cholesterol values; increased from 50.4 to 60.8 mg/dL with long-term exercise follow-up (p=0.044). There was no difference in BDNF (p=0.271), NGF (p=0.230), and irisin (p=0.101) values after acute and chronic exercise. TAS values were determined to be increased with one exercise session and decreased with a 12-week exercise program (p=0.005). On the other hand, OSI values decreased with one exercise session but increased with a 12-week exercise program (p=0.009).

Discussion

In our study, we investigated the effects of moderate-intensity aerobic exercise. According to our results, it was found that both acute and chronic moderate-intensity aerobic exercise practices significantly increased TMT scores (p=0.001), HDL cholesterol (p=0.044), and BDI (p=0.031), which evaluated depression. While the TAS value associated with oxidative stress increased in acute exercise, it decreased in chronic exercise (p=0.005), while the OSI value decreased with acute exercise and increased with chronic exercise (p=0.009). There were no significant changes in BDNF (p=0.271), NGF (p=0.230) and irisin (p=0.101) values.

A study conducted on T2DM cases found that even sedentary time exceeding 15 min affected the BDNF level [26]. It has been emphasized that moderate-intensity exercises can positively affect BDNF density and, therefore,

Table 2: Results of cognitive and depression state tests and blood measurements.

	Before exercise Mean ± SD	After one exercise session Mean ± SD	After 12-week exercise program Mean ± SD	One-year follow-up Mean ± SD	p-Value
TMT-A time, sn	56.9 ± 18.3	48.0 ± 17.9	41.2 ± 13.6	34.2 ± 5.6	0.001
TMT-B time, sn	121.1 ± 44.1	96.5 ± 43.6	81.8 ± 30.9	67.4 ± 10.5	0.002
BDI	15.8 ± 7.7	–	12.0 ± 4.6	10.2 ± 3.5	0.031
HbA_{1c}, %	6.8 ± 1.1	–	6.5 ± 0.7	6.9 ± 1.3	0.177
Fasting blood glucose, mg/dL	132.8 ± 35.0	–	130.7 ± 33.4	134.1 ± 26.7	0.907
HDL cholesterol, mg/dL	50.4 ± 13.3	–	55.5 ± 12.7	60.8 ± 26.6	0.044
TAS, mmol trolox equiv/L	1.6 ± 0.2	2.0 ± 0.4	1.5 ± 0.1	1.4 ± 0.3	0.005
TOS, μmol H_2O_2 equiv/L	31.8 ± 16.8	24.7 ± 9.8	28.2 ± 11.3	30 ± 11.7	0.254
OSI, arbitrary unit	19.1 ± 8.7	12.5 ± 5.5	18.9 ± 8	20.2 ± 8.1	0.009
BDNF, μg/L	0.6 ± 0.4	0.5 ± 0.1	0.5 ± 0.2	1.3 ± 1.6	0.271
NGF, ng/L	0.6 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.06	0.230
Irisin, pg/mL	15.1 ± 2.6	14.7 ± 2.4	14.6 ± 2.06	16.2 ± 2.8	0.101

TMT, trail making test; BDI, Beck depression inventory; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

metabolic and cognitive processes in these individuals. However, while the results of studies show that the change in cognitive processes is more consistent, similar consistency cannot be said for BDNF change [27–31]. Our study observed a significant improvement in cognitive functions (p=0.001) because of acute and chronic exercise intervention, but no significant differences were found in BDNF values (p=0.271).

In the study of Ferris et al., which investigated the acute effects of different intensity aerobic exercises on BDNF and cognitive functions, it was found that cognitive processes were improved in both exercise intensities. Still, the BDNF values changed significantly only in high-intensity exercise. While significant changes were observed in both exercise intensity in cognitive functions, no correlation was found with BDNF [28]. The results of our study also support this situation. While there was a significant change in cognitive functions following the acute moderate-intensity exercise program, the difference in BDNF did not reach the desired level. In another study, 28 people aged 57–83 with glucose intolerance were included in a 6-month exercise program. Executive function, memory performance, cardiorespiratory fitness measurements obtained with the maximum grade exercise treadmill test, body fat and fasting plasma insulin, cortisol, BDNF, insulin-like growth factor-1, amyloid-β (Aβ40 and Aβ42) evaluations were made. Significant changes were found in executive function, cardiorespiratory fitness level, and insulin sensitivity in the 6-month exercise group compared to the control group [29]. In our study, we included our patients in a 12-week exercise program and

Table 3: Time-dependent changes in results.

	Time 1–2		Time 2–3		Time 3–4	
	p-Value	Partial eta squared	p-Value	Partial eta squared	p-Value	Partial eta squared
TMT-A time, sn	0.001	0.533	0.009	0.372	0.042	0.247
TMT-B time, sn	0.003	0.460	0.105	0.165	0.074	0.198
BDI	–	–	0.016	0.331	0.593	0.020
HbA_{1c}, %	–	–	0.074	0.197	0.113	0.159
Fasting blood glucose, mg/dL	–	–	0.747	0.007	0.654	0.014
HDL, mg/dL	–	–	0.042	0.247	0.633	0.016
TAS, mmol trolox equiv/L	0.001	0.541	0.000	0.590	0.499	0.031
TOS, μmol H_2O_2 equiv/L	0.125	0.149	0.280	0.077	0.557	0.023
OSI, arbitrary unit	0.009	0.337	0.010	0.367	0.437	0.035
BDNF, μg/L	0.200	0.107	0.591	0.020	0.100	0.170
NGF, ng/L	0.178	0.117	0.569	0.023	0.165	0.124
Irisin, pg/mL	0.091	0.178	0.775	0.006	0.100	0.170

Time 1: baseline, Time 2: acute (after one session exercise), Time 3: chronic (after 12 weeks exercise training), Time 4: one year follow-up. TMT, trail making test; BDI, Beck depression inventory; HbA_{1c}, hemoglobin A1c; HDL, high-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

retook follow-up measurements at the end of one year. Consistent with the results of this study, significant improvements were found in our executive function results (p=0.001) in both evaluations, while no significant change was observed in BDNF values (p=0.271). However, in the study of Zoladz et al., moderate-intensity five-week endurance training significantly increased BDNF levels in healthy individuals. According to another study examining the effect of maximal oxygen consumption at the level of 50–60% of 12-week aerobic exercise on BDNF, NGF, and inflammatory factors in juvenile obese and T2DM individuals, BDNF levels increased significantly. In contrast, NGF and inflammatory factors did not change [27]. In another study evaluating the change of BDNF and irisin levels with 12 weeks of exercise training, while BDNF levels increased significantly, significant changes in irisin levels were observed only in women [32]. Therefore, the literature review showed that BDNF levels were significantly increased ($p<0.05$) while no significant changes were found in NGF ($p>0.05$) and irisin ($p>0.05$) values in long-term exercise programs. In our study, on the other hand, no significant differences were found in all three parameters. In the studies that reported increased BDNF levels, the exercise intensities were higher than the exercise intensity in our study.

In their meta-analysis, which also includes studies containing subjects with depression problems, Szuhany et al. documented the positive effects of exercise on BDNF. It is known that the risk of depression in individuals with T2DM is higher than in the normal population. However, studies on depression and related BDNF levels in individuals with T2DM were not encountered in the literature. In a study conducted on 29 patients with depression problems, individuals were included in a behavioral activation and exercise program. While an improvement was observed in the depression scores of the individuals, the resting BDNF levels did not change significantly. It was emphasized that varying depression scores did not always change BDNF [33]. After the exercise program was applied with six-week telerehabilitation to individuals with T2DM; significant changes were found in the depression scores measured by HbA_{1c} and BDI compared to the control group [34]. We found improvements in depression scores measured by BDI in our study (p=0.031). This result supports the other findings in the literature showing the improving effects of exercise programs on depression. HbA_{1c} values were also decreased in our study after 12 weeks of exercise training (p=0.074), but this decrease was limited. They increased again (p=0.113) upon discontinuation of the exercise program and reached the initial value.

It has been shown that oxidative stress is increased in individuals with T2DM, and lower HDL cholesterol levels are associated with worse metabolic status [4, 35]. TAS (p=0.005), OSI (p=0.009), and HDL cholesterol (p=0.044) parameters that we evaluated regarding metabolic processes showed positive changes. In contrast, TOS (p=0.254), HbA_{1c} (p=0.177), and fasting plasma glucose (p=0.907) parameters were decreased following exercise applications, but this decrease was not at the expected level. While the average normal TOS value in humans is 4.00–6.00 μmol/L, the initial average value of T2DM appeared to be 31.82 μmol/L in the subjects with T2DM. The normal TAS value in humans is 1.20–1.50 mmol/L, and the antioxidant values of the cases in our study were within normal limits while it increased significantly with acute exercise (p=0.001) and chronic exercise training (p=0.000) and decreased again after discontinuation of the exercise program (p=0.499). According to these results, the positive change in the antioxidant processes of our patients decreased the oxidative stress indices. HDL cholesterol values of the cases were increased with exercise training (p=0.044). These results show us the positive effects of regular exercise on metabolic variables and the need for regular exercise. Improvements in HDL cholesterol and oxidative parameters with exercise in individuals with T2DM are similar to our study in the literature [36–38].

Acute (after one session) and chronic (after 12 weeks) effects, and long-term results at the end of one year of supervised exercise training were evaluated in patients with T2DM. This study observed that 12-week supervised exercise training had a positive effect on metabolic and cognitive outcomes, and this effect developed independently of neuroprotective and metabotropic effects (BDNF, NGF, and irisin). Although the metabolic changes, which are the primary problems in patients, can be controlled with exercise, it has been observed that exercise also plays a regulatory and protective role against cognitive and depression problems that may occur secondarily. When the levels of the gains obtained with exercise were tested one year later, it was determined that there was a decrease in the gains. It was concluded that the subjects should be monitored and motivated at specified intervals to maintain the gains obtained with the supervised exercise training. Due to the regressions in the gains we achieved with exercise training, there was no change in the drug use of the patients. However, we estimate that pharmacological agents and hospitalization costs can be reduced by applying and monitoring regular exercise training in the patient group with T2DM.

Considering the lack of exercise experience of the patients and the comorbid conditions present in most of the patients, safe exercise intensity was preferred, but it was seen that the exercise intensity should be kept higher to obtain a change in neuroprotective and metabotropic factors. Including and comparing high-intensity aerobic exercise programs in future studies is recommended. It is recommended to study larger samples and encourage continuity in future studies. In our study, we had a limitation on the number and continuity of cases due to the Covid-19 pandemic.

Ethical approval: Permission for the study was obtained from the Clinical Research Ethics Committee of Marmara University Faculty of Medicine (09.2019.484).

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