The Compensatory Increased BDNF and NGF in Patients with Multiple Sclerosis Following Home-based Aerobic Training and Vitamin D Supplementation During COVID-19 Outbreak

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Abstract

Background: Lifestyle modifications (physical activity and diet) are among the most promising strategies in MS rehabilitation. This study aimed to investigate the effect of home-based aerobic training and vitamin D supplementation in patients with multiple sclerosis during the COVID-19 outbreak.

Methods: In this randomized, single-blinded, placebo-controlled trial, 38 females with Multiple sclerosis with EDSS: 3-5 (aged 20–40 years with body mass index [BMI] of 25–30 kg/m^2) were randomly assigned into four groups: aerobic training + Vitamin D supplementation (AT+Vit D; n=10); aerobic training (AT; n=9); Vitamin D supplementation (Vit D; n=9), and Control (Placebo) (n=10). The AT program consisted of 50-70% of HR_{Max}, 25-40 min/day, three days/wk for eight weeks. Participants in the Vit D group consumed 50000 IU of Vitamin D supplement capsules per week for eight weeks. The data were analyzed through paired t-test and one-way analysis of variance, as well as Tukey's post hoc test at the signification level of $P<0.05$.

Results: BDNF and NGF levels improved significantly from pre-test to post-test within all experimental groups. BDNF and NGF decreased significantly in AT+Vit D, AT, and Vit D compared to C. Also, the results show that the AT+Vit D had significantly lower BDNF and NGF compared to AT (P=0.023 and P=0.011) and Vit D (P=0.001 and P=0.002).

Conclusion: These findings suggest that the combination of AT+Vit D improves BDNF and NGF status more effectively than AT or Vit D alone in female Multiple sclerosis patients.

Background

Multiple sclerosis (MS) is an autoimmune, inflammatory, chronic, and progressive disease in which the immune system attacks the nerve cells in the brain and spinal cord, causing damage to myelin and impairs the body system communication. Creates therapeutic and socio-economic for individuals [1]. MS is the most common neurological disease especially in women [2] occurring between the ages of 20 and 40 years [3]. In recent years, the MS cases are increasing daily and reaching to over 35 per 100,000 individuals [3, 4]. According to the results of studies, the estimated prevalence of MS in Tehran is about 52 per 100,000 individuals, of which 72.2% are women and 27.3% are men [5]. The main cause of MS unknown, however a variety of factors, including the presence of genetic background, autoimmune mechanisms, and environmental factors (especially infections, latitude, vitamin D deficiency, and smoking) are effective in the development of MS [6]. In general, MS-related symptoms include fatigue, muscle weakness, spasm, ataxia, imbalance, and gait disturbance [7]. Aerobic training has been shown to be among the approaches to improve the MS symptoms [8]. Researchers have recently been focused on the effect of aerobic training on neuronal function, especially on effect on neurotrophins, neurogenic, and degenerative factors [9]. Neurotrophins are polypeptide growth factors that cooperate in the growth, survival and function of the central and peripheral nervous system and play a significant role in the nervous system disorders [10, 11]. The results of studies showed the beneficial effects of aerobic training on brain function, partly due to enhanced function and increased levels of neurotrophins such as BDNF and NGF [12]. Cotman et al. (2002) observed increased neurotrophic factors expression including BDNF and NGF in the hippocampus of two animal models, Mice and Rats following aerobic training [12]. Although the role of BDNF in muscle has not yet been elucidated, it might increase the survival of damaged motor neurons. Serum BDNF levels have also been reported to increase immediately after a session of low intensity aerobic training in MS patients [13]. The NGF secretion, which is involved in biological functions such as neuroprotection, neuronal regeneration, and memory improvement, is affected by regular aerobic training; decreased neuronal apoptosis and demyelination has been also reported in spinal cord samples after NGF injection into white matter [14]. Also, several studies have investigated the effects of dietary supplements in MS patients including vitamin D [15, 16]. As a non-genetic factor, the distribution of vitamin D receptor has been reported to play an important role in the susceptibility as well as the severity of the MS [17]. The association between vitamin D receptor gene polymorphisms and MS was first demonstrated in the Japanese population [18]. Another study showed a direct link between mutation in the gene that controls the vitamin D level (causing vitamin D deficiency) and the development of MS in individuals with a family history; Individuals with low vitamin D were more likely to develop MS in the future [17, 19]. Several studies showed significantly lower serum vitamin D level in MS patients compared with healthy individuals [20–22]; however, others have not reported [21]. Vitamin D plays a major role in the occurrence or severity of MS by regulating the immune system function, bone metabolism, cell regulation, proliferation, and differentiation, encephalomyelitis and T cell function [23], and the expression of many important genes in various pathways related to cancers and many autoimmune diseases [24]. Also, increased NGF and BDNF secretion induced by aerobic training might possibly reduce the MS symptoms. However, to date limited studies have been evaluated the simultaneous effect of aerobic training and vitamin D supplementation on nerve cell growth factors in patients with MS. On the one hand, due to the MS complications and limited studies on this individual, and on the other hand, the risk of exercising outside in sports facilities in the outbreak of COVID-19, this study aimed to investigate the effect of eight-week home-based aerobic training with vitamin D supplementation on serum BDNF and NGF in MS patients during COVID-19 outbreak.

Material And Methods

Participants and Study Design

This clinical trial study aimed to investigate the effects of 8-week home-based aerobic training and Vit D supplementation on BDNF and NGF in patients with multiple sclerosis. As detailed in Fig. 1, the study population consisted of 60 participants (aged 20-40 years) from the Kermanshah MS center with a disability scale of 3-5.

In this study, 40 women with multiple sclerosis (20-40 years) in Kermanshah were selected using purposive and available sampling method based on G. POWER 3.1 software with a statistical power of 99 %, the effect size of 95%, and significance level at 0.05.

Inclusion criteria included: at least 2 years MS history, disability scale of 3-5, lack of regular exercise, no history of other diseases, no smoking, and no immunosuppressive drug consumption. Exclusion criteria included a history of heart disease, hypertension, orthopedic disorders, and diabetes, consuming other drugs in addition to MS medications that might affect the individual's response to the intervention, lack of regular attendance in the exercise training and testing sessions muscle injuries, inability to perform the exercise, COVID-19 infection, and severe relapses during the study period.

The trial (IR.RAZI.REC.1400.002) was approved by the Ethics Committee of the Kermanshah Razi University and registered in the Iranian Clinical Trial Registration Center under the code IRCT IRCT20201129049525N; Written informed consent was obtained from all participants, including agreement of the patients to participate as volunteers and feasibility to leave the study. Forty subjects were randomly assigned into four equal (n=10) groups; aerobic training plus vitamin D supplementation (AT+Vit D), aerobic training (AT), vitamin D supplementation (Vit D), and control (C) using the lottery method.

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Intervention

AT experimental groups exercised at home under supervision online three times per week for 2 months. All training sessions were carried out under the supervision of exercise physiologists. Vitamin D supplemented based on the standard amounts.

Aerobic Training

Walking aerobics exercise was performed at home under supervision online. The subjects were instructed to do waking aerobics three times a week, starting with 20 min at 50% of HRmax per session, and to increase their total weekly walking time up to 40 min at 70 % of HRmax per session [25] which was recommended by the Multiple Sclerosis Association of America (MSAA) [26] (Table 1). Every session included 10 min of warm-up and 10 min of cooling down period. The walking program was designed to be of moderate intensity.

Table 1
Aerobic training protocol

Variables	**Week**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Intensity (HR_{max})	50–55%	50–55%	55–60%	55–60%	60–65%	60–65%	**65**–**70**%	65–70%
Time (min)	20	25	25	30	30	35	35	40
Borg scale	10	10	10	11	11	11	12	12

At the outset, the HRmax formula was used to determine the target heart rate [HRmax = 220 − age] [27] The participants learned to count pulse rate and to monitor heart rate in an instructional session using the pulse palpation method. To assure that the desired heart rate (exercise intensity) was achieved and maintained during the walking aerobics phase, the 6–20 rating of perceived exertion (RPE) scale was considered [28] (Table 1). This walking program was continued for 8 weeks.

Diet and vitamin D supplementation

To attend the training program, the participants filled two questionnaires. First, a questionnaire was determined to assess the readiness of participants including demographic data, health status, and PA. A second questionnaire was a detailed semi-quantitative food frequency questionnaire adapted to the Iranian population and composed common food items, serving sizes, and meals, as designed to record and analyze 3-day food, recalls, before and at the end of the intervention. To determine the food intake and the amount of macronutrient consumption (protein, fat, and carbohydrates), the Food Processor nutritionist 4 software (FPN4) was used. Subjects were asked to consume the same food and macronutrient composition, one day before collecting blood samples in the pre and post-test. In general, the subjects' diet consisted of 55% carbohydrates, 30% fat, and 15% protein.

In this study, both the AT + Vit D group and Vit D group received 50000 units of vitamin D supplement (made by the Zahravi Pharmaceutical Company in Iran) once per week for eight weeks [29, 30]. The C and AT groups also received a placebo weekly (made by the Zahravi Pharmaceutical Company, Iran) with the same shape, color, smell, and tastes as vitamin D supplement, for 8 weeks.

Anthropometric Measurements and Body Composition

Three days before the start of the intervention and end of the study, subjects familiarized with the study procedure and primary measurements including anthropometric parameters and body composition were determined. Height was measured to the nearest 0.5 cm using a stadiometer (DETECTO, Model 3PHTROD-WM, USA), and Waist circumference was measured to the nearest 0.5 cm with a non-elastic tape measure. Also, the fat mass of the whole body, BMI, and weight of any patient were determined using INBODY test using bioelectric impedance analysis (Zeus 9.9 PLUS; Jawon Medical Co., Ltd., Kungsang Bukdo, South Korea). To minimize the effect of water consumption on the results, body composition measurements were performed at the beginning and the end of the study early in the morning between 8–9 am after at least 12 hours of fasting overnight and after emptying the bladder. Subjects were asked not to participate in intensive physical activity 48 hours before the test and to refrain from taking diuretic drugs and diuretics.

Biochemical Measurements or Testing and Outcome Variables

Forty-eight hours before testing, subjects did not perform any exercise and were on 12 hours of fasting before testing. Then, in the least possible time, 10 ml of blood samples were taken from the cubital vein at the beginning and the end of the study. Blood samples were collected in heparinized tubes for BDNF and NGF analyses, or frozen and stored at -80˚C. BDNF and NGF were measured by the ELISA method using a human BDNF and NGF kit made in China under the license of Boster Biological Technology, Company of America with a sensitivity of 2 and 2.48 pg/ml, respectively. Serum 25-hydroxyvitamin D level was measured by quantitative luminescence method using DiaSorin kit made in USA.

Statistical analysis

All statistical analyses were performed using the SPSS statistical software (version 21; SPSS Inc., Chicago, IL, USA) was used at a significant level of $P < 0.05$. The Shapiro–Wilk’s test was used for evaluating the normality of distribution. To compare the mean hepatic risk factors between and within groups, ANOVA and t-test were used, respectively. Tukey's post hoc test was used if significant differences were found.

Results

The findings on the participants anthropometric indices and their between-group comparison are presented in Table 2. Based on the results of the t-test, there were significant differences in the mean of BW, BMI, BFP, WHR, and Vit D in the post-test compared to the pre-test. After eight weeks, BW, BMI, BFP, and WHR significantly decreased in all intervention groups, while in the C, these variables increased significantly (Table 2). Also, after eight weeks Vit D increased significantly in all intervention groups, except C.

Table 2
Mean ± SD of anthropometric indices before the intervention among the groups

Variables	**AT + Vit D (n = 10)**	**AT (n = 9)**	**Vit D (n = 9)**	**C (n = 10)**	**P-Value** [a]
Age (years)	27.70 ± 2.68	26.77 ± 2.27	25.44 ± 2.29	28.11 ± 3.62	0.563
Height	163.40 ± 2.63	166.03 ± 2.65	162.33 ± 1.50	164.20 ± 1.54	0.467
Body Weight (Kg)					
Before	71.90 ± 1.91	73.12 ± 1.93	71.11 ± 2.02	73.01 ± 1.33	0.086
After	68.11 ± 1.15 [β]	70.16 ± 1.22 [β]	69.33 ± 1.50 [β]	75.06 ± 1.15	0.001 [¥]
P Value [b]	0.001*	0.001*	0.012*	0.004*	
BMI (kg/m^2)					
Before	26.94 ± 0.93	26.33 ± 1.07	26.98 ± 0.88	27.08 ± 0.66	0.279
After	25.48 ± 0.79 [β]	25.14 ± 0.99 [β]	26.32 ± 0.93[β]	27.82 ± 0.71	0.001 [¥]
P Value [b]	0.001*	0.001*	0.011*	0.004*	
Body Fat Percent (%)					
Before	28.37 ± 1.63	28.11 ± 1.26	27.66 ± 1.58	28.60 ± 1.50	0.213
After	24.90 ± 1.37 [β]	25.77 ± 0.83 [β]	26.55 ± 1.81[β]	30.04 ± 1.33	0.001 [¥]
P Value [b]	0.002*	0.002*	0.048*	0.003*	

AT + TS, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **TS**, Turmeric supplement group; **C**, the control group
p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test
*: Significantly different comparing pre and post-test within the groups
¥: Significantly different comparing pre and post-test between groups
µ: Significantly different between AT + TS compare to the AT group
€: Significantly different between AT + TS compare to the TS group
β: Significantly different between AT + TS, AT, and TS groups compare to the C group

Variables	AT + Vit D (n = 10)	AT (n = 9)	Vit D (n = 9)	C (n = 10)	P-Value a
WHR					
Before	0.84 ± 0.03	0.84 ± 0.01	0.83 ± 0.03	0.84 ± 0.02	0.150
After	0.81 ± 0.02 β	0.82 ± 0.03 β	0.82 ± 0.02 β	0.86 ± 0.01	0.001 ¥
P Value b	0.001*	0.001*	0.001*	0.002*	
Vitamin D (ng/mL)					
Before	25.80 ± 1.81	26.55 ± 1.50	26.44 ± 1.42	27.20 ± 3.45	0.588
After	35.60 ± 1.89 μβ	29.66 ± 1.65 β	32.88 ± 1.90 β	25.10 ± 1.44	0.001 ¥
P Value b	0.001*	0.002*	0.001*	0.111	
AT + TS, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **TS**, Turmeric supplement group; **C**, the control group					
p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test					
*: Significantly different comparing pre and post-test within the groups					
¥: Significantly different comparing pre and post-test between groups					
μ: Significantly different between AT + TS compare to the AT group					
€: Significantly different between AT + TS compare to the TS group					
β: Significantly different between AT + TS, AT, and TS groups compare to the C group					

The results of one-way ANOVA showed no significant difference in BW, BMI, BFP, and WHR and Vit D between the groups in the pre-test, however, in the post-test, there was a significant difference in the above variables between the groups.

The results of Tukey's post hoc test show that BW, BMI, BFP, and WHR and Vit D were significant in AT + Vit D, AT, and Vit D compared to C. No significant difference in the BW, BFP, and WHR were observed between other groups. The results indicate no significant difference in Vitamin D levels in AT + Vit D compare to AT alone; Also, no significant difference was found in Vitamin D levels in AT compared to Vit D (Table 2).

BDNF and NGF levels improved significantly from pre-test to post-test within all experimental groups, as detailed in Figs. 1 and 2. The results of one-way ANOVA showed no significant difference in BDNF and NGF between the groups in the pre-test, however in the post-test, there were significant differences in the above variables between the groups. BDNF and NGF decreased significantly in AT + Vit D, AT, and Vit D compared to C. Also, the results show that the AT + Vit D had significantly lower BDNF and NGF compared to AT and Vit D. Also, the results of this study showed significant differences between AT and Vit D groups in the BDNF and NGF levels.

Discussion

According to the results of the present study, eight weeks of aerobic training with vitamin D supplementation reduced anthropometric indices (body weight, body mass index, and fat percentage) and increased vitamin D levels significantly in women with MS. Although these changes were greater in the AT + Vit D compared with the AT or Vit D alone, only the vitamin D levels were significantly different between the AT + Vit D and AT. Interestingly, the anthropometric indices increased while vitamin D levels decreased significantly in the control group. Few studies have been done on the effects of aerobic training and vitamin D supplementation in MS patients, and the evidence for the preventive and therapeutic effects is largely dependent on epidemiological studies. However, our knowledge of the interactive effects of aerobic training and vitamin D supplementation on anthropometric indices is still limited.

Consistently, Babaei et al. (2014), [31] Hoseini et al. (2017), [32] and Hoseini et al. (2020) [33] reported that regular AT improves metabolic health parameters through increased daily energy intake, improved and increased fat oxidation in skeletal muscles [34, 35] Also, based on the studies the prevalence of demyelinating diseases (e.g. MS) [36], metabolic syndrome, and chronic disease have been reported to be associated with Vit D deficiency [37, 38]. Ascherio et al. (2014) introduced Vitamin D as an early predictor of multiple sclerosis activity and progression [39]. Hosseini et al. (2017) reported improved metabolic indices following 8 weeks of high dose Vit D supplementation [32] The underlying mechanism might be increased parathyroid hormone (PTH) induced by hypovitaminosis D which leads to increased intracellular Ca++. This, in turn, upregulates the insulin receptors and Glut-4 channel activity in the target tissues. Thus, vitamin D plays an important role in insulin function, glucose metabolism, and other metabolic processes [31, 40]. The findings of the present study showed the highest levels of BDNF, and NGF in the AT + Vit D after 8 weeks; Therefore, AT + Vit D had been more effective in improving BDNF, and NGF compared to Vit D or AT alone. The decrease in BDNF and NGF levels in the control group is probably due to the MS-induced Schwann cells demyelination. While BDNF and NGF levels increased significantly in other groups. According to the results of studies, deficiency of neurotrophic factor/receptor is involved in the progression of MS [41]. The increased gene and protein expression of proinflammatory factors, such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), have been observed with the progression of MS [42]. In turn, MAPK activates exon IV (inhibitor of BDNF and NGF protein synthesis) by CAMP receptor phosphorylation, which is a known factor in the regulation of BDNF and NGF expression [43, 44]. Various studies have shown that regular aerobic training increases the regeneration of sensory neurons after axon injury and stimulates gene expression of proteins required for axon growth and regeneration in MS patients [45]. Some of the beneficial effects of increased BDNF and NGF include direct stimulation, migration, and differentiation of oligodendrocytes (which are essential steps in myelinogenesis), upregulation of the activity and expression of cells necessary for myelin production (e.g., the main structural components of myelin, such as astrocytes and neurons), and regulatory proteins [46]. However, studies have reported that gene expression and secretion of neurodevelopmental factors, such as BDNF and NFG, function multiple molecular and non-molecular mechanisms [47, 48]; Aerobic training might affect BDNF and NFG possibly through increased activity of some signaling pathways (PERK, pAkt, and CaMKII), increased expression of growth proteins such as 43-GAP, altered concentrations of hormones such as norepinephrine and serotonin, as well as the secretion of heat shock proteins, HSP27 and HSP70 [49, 50]. In addition, vitamin D might affect the BDNF and NGF secretion and expression through nuclear signaling pathways secondary to the interaction of 1–25 (OH) 2D to vitamin D receptor (VDR) in the nuclear; which begins a genetic response after reacting with RXR and producing Vitamin D response element (VDRE) [51, 52]. VDRE binds to nuclear receptor coactivators (COACs) or corepressors (COREs) that increase BDNF and NGF gene expression [53]. Also, studies in MS patients shows increased free radical production, including nitric oxide that might exacerbate inflammatory reactions and brain lesions consequently due to the disrupted nicotinamide adenine dinucleotide phosphate (NADP+) system in MS patients [54, 55]. Therefore, it is hypothesized that adequate vitamin D levels might help prevent the MS progression by inhibiting nitric oxide production [56].

Conclusions

In conclusion, despite the efficacy of aerobic training and vitamin D supplementation alone on the measured variables in MS patients, the combined aerobic training and vitamin D supplementation seems to induce greater improvements in BDNF and NGF levels; However, the mechanism of interactional effect is still not well understood. On one hand, due to the general recommendations for the application of non-pharmacologic therapies in the MS management, prevention of inactivity associated diseases, and on the other hand the anti-inflammatory and antioxidant effects of vitamin D supplementation during the outbreak COVID-19, combined aerobic training and vitamin D supplementation is recommended as an eligible approach in women with MS under the prescription and supervision of PCP or neurologists. However, further extensive studies are recommended.

Abbreviations

MS: Multiple sclerosis ; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; AT; Aerobic training; Vit D: Vitamin D; RPE: Rating of perceived exertion; FPN4: Food Processor nutritionist 4 software; BW: Body weight, BMI: Body mass index, BFP: Body fat percentage; WHR: Waist–hip ratio; PTH: Parathyroid hormone; IFN-γ; Interferon-gamma; TNF-α: Tumor necrosis factor-alpha; RXR: Retinoid X receptor; VDRE: vitamin D response element; nuclear receptor coactivators; NCOAs; Nuclear receptor coactivators; NCORs: Corepressors; NADP+: Nicotinamide adenine dinucleotide phosphate.

Declarations

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Authors' contributions

RH designed the study. EB experimented. RH analyzed the data and wrote the manuscript. EA involved in the interpretation of data, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the ethics committee of Razi University of Kermanshah (IR.RAZI.REC.1400.002) and registered in the Iranian Clinical Trial Registration Center under the code IRCT20201129049525N1.

Consent for publication

Not applicable.

Competing interests

Authors do not have any competing interests

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Figures

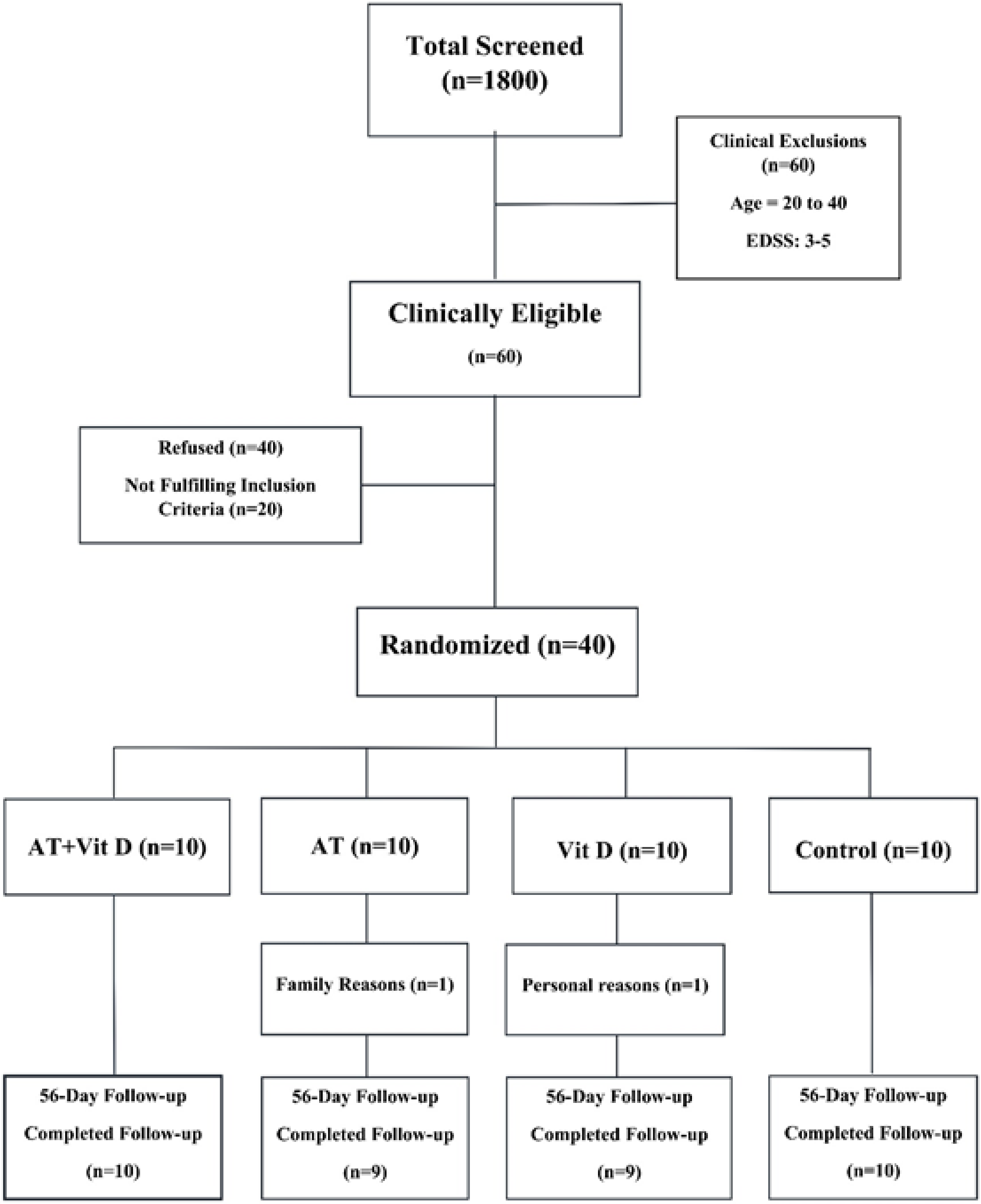

Figure 1

Flow chart of the study population AT+Vit D, Aerobic training + vitamin D supplement, AT, Aerobic training group; Vit D, vitamin D supplement; C, the control group

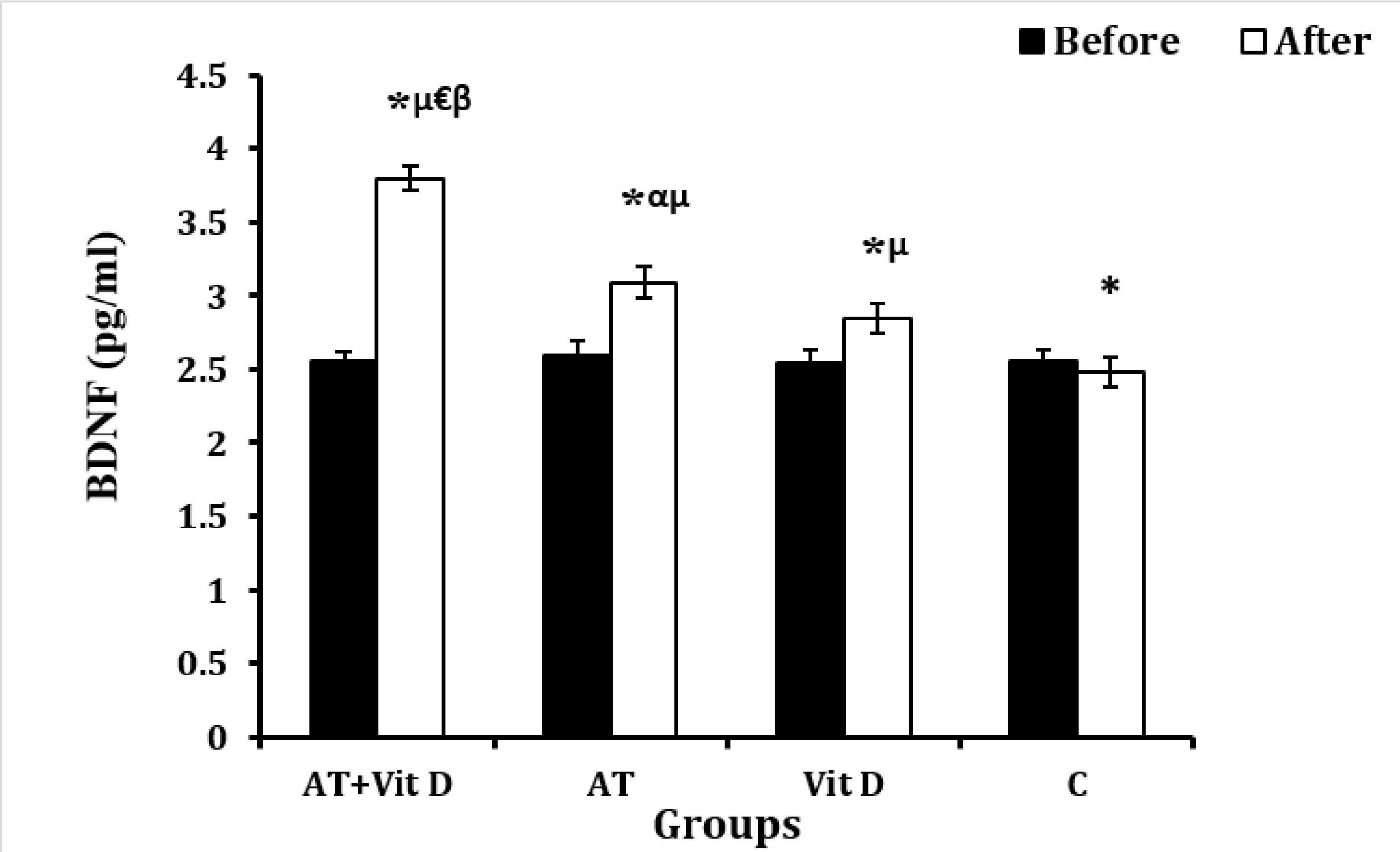

Figure 2

Comparison between mean ± SD of BDNF between groups AT+Vit D, Aerobic training + vitamin D supplement, AT, Aerobic training group; Vit D, vitamin D supplement; C, the control group p values superscript with "a" is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with "b" is calculated using paired t-test *: Significantly different comparing pre and post-test within the groups μ: Significantly different between AT+Vit D compare to the AT group €: Significantly different between AT+Vit D compare to the Vit D group α: Significantly different between AT compare to the Vit D group. β: Significantly different between AT+Vit D, AT, and Vit D groups compare to the C group

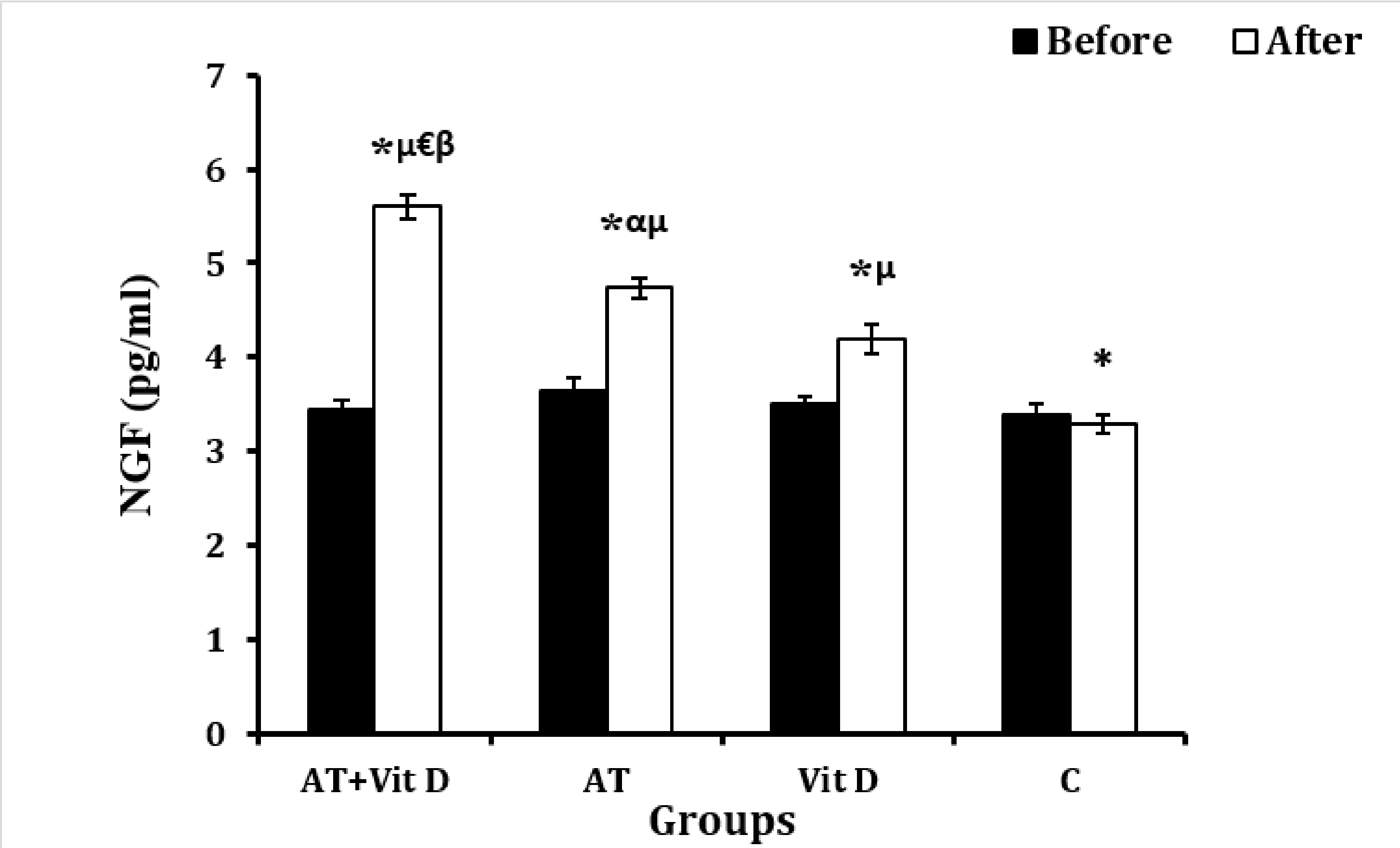

Figure 3

Comparison between mean ± SD of NGF between groups AT+Vit D, Aerobic training + vitamin D supplement, AT, Aerobic training group; Vit D, vitamin D supplement; C, the control group p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test *: Significantly different comparing pre and post-test within the groups μ: Significantly different between AT+Vit D compare to the AT group €: Significantly different between AT+Vit D compare to the Vit D group α: Significantly different between AT compare to the Vit D group. β: Significantly different between AT+Vit D, AT, and Vit D groups compare to the C group