J Musculoskelet Neuronal Interact 2022; 22(3):352-363

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Effects of low and high intensity interval training exercises on VO_{2max} and components of neuromuscular and vascular system in male volunteers

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Abstract

Objectives: To evaluate the effects of different intensity exercises on maximal oxygen consumption (VO_{2max} and levels of components, namely brain-derived neurotrophic factor (BDNF), tyrosine kinase receptor B (TrKB), vascular endothelial growth factor (VEGF), peroxisome proliferator activated receptor-gamma coactivator (PGC-1α), and irisin. **Methods**: Thirty-six male participants were divided into control (CNT), low-intensity (LIIT), and high-intensity interval training (HIIT) groups. LIIT and HIIT groups consisted of 8 exercises (20 s work and rest in each repetition, respectively) conducted for 4 weeks. VO_{2max} and protein component levels were determined pre- and post-training. VO_{2max} capacity was also determined using the Yo Yo Intermittent Recovery Test-1 (Yo Yo IR-1). Statistical analysis was conducted to determine significance of the differences observed. **Results**: According to the YoYo IR-1, VO_{2max}, serum BDNF, VEGF, PGC1α, irisin, and TrkB data obtained in the study, a statistically significant difference between the groups was observed ($p<0.05$). While the interaction effect was found to be statistically significant in the study using PGC1α, VEGF, and TrkB data ($p<0.05$), it was not found to be statistically significant using YoYo IR-1, VO_{2max}, serum BDNF, or irisin data ($p>0.05$). **Conclusion**: HIIT and LIIT improved all study parameters, while HIIT showed a greater effect than LIIT.

Keywords: Brain Function, Cellular Restoration, Exercise, Mitochondria, Neural Development

Introduction

Intensity is one of the most important elements of any exercise training design because of its direct effect on performance[1]. The effects of high-intensity interval training (HIIT) and low-intensity interval training (LIIT) on performance have been extensively studied[2–5]. HIIT, in which the maximum heart rate (HR_{max}) is maintained at 80-95%, is associated with both positive and negative outcomes. Although HIIT may result in loss of interest, excessive tiredness, leading to increased anxiety, anger, and depression[6–8], it also positively impacts health and performance[9,10]. Furthermore, HIIT is an training modality that is time-efficient, provides motivation, and safe to practice for long-term[11,12]. HIIT also offers similar or stronger physiological effects on cardiovascular, metabolic health, and brain function when compared with traditional long-term, low-to-moderate intensity training[13–15]. LIIT are exercises where the HR_{max} level is maintained in the range of 57-64%[16]. LIIT has been shown to affect brain, coronary vascular dysfunction, preserves Ca^{2+}-sensitive K^+, and provides cardiopulmonary and metabolic benefits[17–19]. To identify and determine the the most effective training intensity at individual level, the effects of HIIT and LIIT on brain, neural, and vascular functions need to determined. This can be achieved by looking at the changes in levels of key neuromuscular and vascular components in response to different intensity interval trainings.

Exercise affects neuromuscular pathways, and the exercise-induced adaptations occur in both pre and postsynaptic components of brain. Exercise enhances

The authors have no conflict of interest.

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Edited by: G. Lyritis
Accepted 20 April 2022

Table 1. Training practice procedures.

Microcycle	2 Units per Week
Mesocycle	Monthly 2x4= 8 Units
F	2 Units per Week (3 Groups in Total)
I	HIIT= 85-90%, LIIT=57-64%
T	T
T	HIIT (work:rest ratio)= 20-20 (1:1), LIIT=20-20 (1:1)
V	HIIT Protocol; Unit Volume: 20 sec + 20 rest X 8 movements = 320 sec x 3 cycles = 960 sec (16 min) + 9 min (rest time between cycles) = 25 min LIIT= 20 sec+20 rest X 8 moves= 320 sec x 3 cycles= 960 sec (16 min) + 9 min (rest time between cycles)= 25 min
P	Same as First 4 Weeks

(F: Frequency; I: Intensity; T: Type; T: Time; V: Volume; P: Progression; HIIT: High intensive interval training; LIIT: Low intensive interval training).

presynaptic nerve terminal branching and the number of vesicles with more postsynaptic receptors[20]. It is known that the nerve tissue growth promotion and survival are mediated by brain-derived neurotrophic factor (BDNF)[21]; it is synthesized in the brain and released in response to cognitive activity, disease, and exercise[22]. Since BDNF can easily cross the blood–brain barrier, the brain releases to 70-80% of peripheral BDNF during exercise[23]. Therefore, peripheral BDNF accumulation is an indicator of changes in the brain[21]; exercise positively affects BDNF levels[24,25]. Tropomyosin-related kinase B, also known as tyrosine receptor kinase B (TrkB), is a BDNF receptor; BDNF-TrkB signaling determines exercise-enhanced neuron adaptation and memory[26]. The peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) plays an important role in brain functions and its deficiency is associated with neurodegeneration and GABAergic dysfunction[27,28]. It has also been reported that PGC-1 α plays a role in the formation and protection of neuronal dendritic sprouts[29]. PGC-1α is a key regulator of exercise-induced mitochondrial biogenesis[30]. There are limited studies on the effect of HIIT on PGC-1α[31–34]. However, the effects of LIIT on PGC-1α have not been studied. PGC-1α also plays an important regulatory role in mediating exercise-induced angiogenesis through its effects on vascular endothelial growth factor (VEGF)[35]. VEGF stimulates vessel formation and angiogenesis and increases the permeability of capillaries[36]. Studies have shown that VEGF is associated with exercise[37,38].

The protein 5-containing fibronectin type III domain (FNDC5) encodes a PGC1α-dependent myokine and is secreted as irisin. It ensures the transdifferentiation of adipose tissue with increased expression of distinctive protein 1 (UCP1)[39]. The literature reports that FNDC5 plays important roles in various processes such as energy metabolism, proliferation, metastasis, and neural differentiation[40]. Studies have also been conducted on the effect of HIIT on irisin[3,5,41,42].

In this study, we determined the effects of HIIT and LIIT on key protein components of neuromuscular and vascular pathways, including BDNF, TrkB, PGC-1α, VEGF, and irisin.

Materials and Methods

Study subjects

A criterion sampling method was used to determine the sample group. Volunteers were selected using the inclusion criteria; volunteers did not have any health problems in performing tests and practicing exercises. The consent of all volunteers was obtained, and their participation was ensured regularly. This study is approved by the Inonu University (IU) and Human Research Ethics Committee of the IU (2019/123). Thirty-six male participants formed the following groups (12 participants in each group): (1) control (CNT) group; average age, height, and body weight= 22.00±1.65 years, 178.83±6.32 cm, and 70.08±8.92 kg, respectively; (2) LIIT group (%HR_{max}=57-64%); average age, height, and body weight= 22.66±2.74 years, 176.41±6.22 cm, 68.14±7.38 kg, respectively; and the (3) HIIT group, (%HR_{max}= 85-90%), average age, height, and body weight= 20.83±2.32 years, 177.08±5.26 cm, and 72.40±11.34 kg, respectively. None of the participants had regular exercise habits and there was no injury to the upper or lower extremities in the last 6 months. Furthermore, all participants had similar body composition parameters (age, weight, body mass index, body fat ratio, and hip and waist measurements) and heart rate (Table 1). The G-Power (3.1.9.3 version) analysis program was used to determine the sample group. The confidence interval (CI) of the test was 0.95, alpha 0.05, beta 0.80, and effect size 0.30. For the power analysis of the study, BDNF mean and standard deviation values (mean 1= 72.0, mean 2= 84.0, standard deviation (SD)=8.0) obtained from a study by Rasmussen et al. were used[21]. The power analysis indicated a minimum of nine participants in each group.

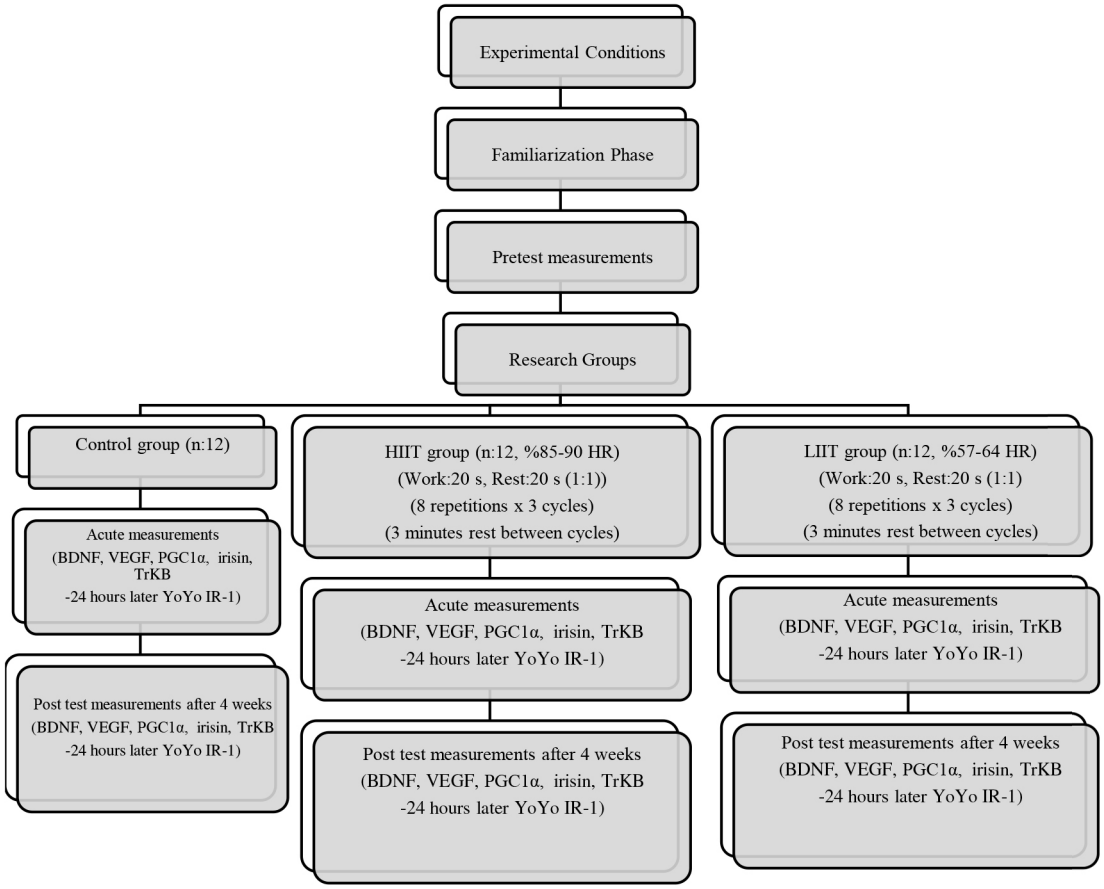

Figure 1. Experimental Design Diagram.

Experimental procedure

This study used a three parallel-group randomized controlled trial design. Subjects were randomly allocated to one of following three intervention groups: (1) control (n=12), (2) HIIT (n=12), and (3) LIIT (n=12). Before, acute, and 4 weeks after the intervention, body composition was measured, and VO_{2max} (maximal oxygen consumption), BDNF, TrKB, VEGF, PGC-1α, and irisin levels were assessed. Each volunteer's body mass and standing height were measured to the nearest 0.1 kg (Tanita SC-330S, Amsterdam, Netherlands) and 0.1 cm (Seca Ltd., Bonn, Germany)[43], respectively. Waist circumference was measured with a measuring tape, while standing at the end of light expiration, between the rib cage and the lowest part of the iliac crest, and at the anterior midpoint between the xiphoid process of the sternum and the navel[44]. The body mass index and body fat ratios of all volunteers were measured and recorded using an electronic scale (Tanita SC-330S, Amsterdam, Netherlands)[43].

Yo Yo Intermittent Recovery Test-1 (Yo Yo IR-1) was conducted on a 20-m indoor running track. Participants repeated running distances of 40 m at a gradually increasing pace controlled by the auditory beeps of the Yo Yo IR-1 installed on the laptop. Participants underwent a 10-s active recovery phase between each 40-m run. Exercise specialists were placed on each end line to ensure that the participants completed the entire distance. All Yo Yo IR-1 tests were controlled by the same exercise experts to minimize inter-rater variability. The test was terminated when the participants failed to reach the finish line a second time at the auditory beep. The number of 40-m runs was recorded, and the total running distance was calculated. Participants' VO_{2max} was calculated using the following formula: VO_{2max} (ml/min/kg)= running distance (m) × 0.0084 + 36.4 [44].

Participants were randomly assigned to a HIIT group (n=12), exercising at 85 to 90% HR intensity; LIIT group (n=12), exercising at 57–64% HR intensity and a non-exercising control group (CNT) (n=12). Training groups (HIIT and LIIT) participated in an interval training program 2 times per week on non-consecutive days for 4 weeks. Each exercise was performed for 20 s of work and 20 s of rest; each cycle consisted of eight repetitions that were completed in a total of 320 s with 3 min of rest between each cycle (a total of 3 cycles were completed in 25 min period). The workouts were performed on different days of the week at 48-h intervals.

Table 2. Descriptive characteristics of the subjects (n=36).

Parameters	Control Group		HIIT Group		LIIT Group	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Age (years)	22.00	1.65	20.83	2.32	22.66	2.74
Height (cm)	178.83	6.32	177.08	5.26	176.41	6.22
BW (kg)	70.08	8.92	72.40	11.34	68.14	7.38
BMI (kg/m^2)	21.95	2.73	23.07	3.38	21.85	1.48
BFR (%)	13.20	3.72	14.40	5.60	11.97	2.67
HR_{rest} (b.min)	62.75	9.64	64.58	8.89	63.91	11.78
WC (cm)	77.00	4.30	84.16	9.59	78.16	5.27
HC (cm)	93.91	3.44	98.50	8.06	96.00	4.82

(BW: Body weight (kg); BMI: Body mass index (kg/cm^2): BFR: Body fat ratio (%); HR_{rest}: resting heart rate (b.min); WC: Waist circumference (cm); HC: Hip circumference (cm)).

In these workouts, main exercise types were squat jump, inchworm, walk down-shoulder tap, plank get ups, goblet squats, jackknife crunch, and burpee mountain climbing movements; they were determined by the researcher and the consultant based on published interval training practices. The participants performed following complementary protocols: (1) 20 s of work with a maximum HR intensity of 85-90% followed by 20 s of rest (HIIT), and (2) 20 s of work with a maximum HR intensity of 57-64% followed by 20 s of rest (LIIT) (Figure 1). Each participant (except the control group) was fitted with a polar heart monitor to determine their HR_{max}; the polar heart monitor was tracked using app on an iPad (Polar TM V800, Kempele, Finland). HR_{max} was also predicted from age using the following formula from Tanaka et al. (2001): HR_{max} (age-predicted)=208-0.7 × age in years. The target heart rate was calculated using the Karvonen formula as follows: (HR_{max} - HR_{rest}) × training intensity + HR_{rest} [45,46]. In situations of target heart rate deviations, the participants were encouraged to move slowly (if the target heart rate was high) or faster (if the target heart rate was low). Table 2 shows data on the following parameters: microcycle, mesocycle, frequency (F), intensity (I), type (T), time (T), volume (V), and progression (P).

Blood sample analysis

After a 12-h fasting, blood samples were collected prior to the exercise, immediately after the first exercise protocol (acute), and immediately after the last exercise modality of the 4-week exercise protocol (chronic). The blood was centrifuged at 4000 rpm at 4°C for 10 min. Obtained serum samples were equally divided into polypropylene tubes and frozen at -800C until further analysis.

Biochemical analyses

BDNF, TrkB, VEGF-A, PGC-1α, and irisin levels were determined by enzyme-linked immunosorbent assay (ELISA) using commercialy available kits (Elabscience Biotechnology Co. Ltd.). Identical protocols was followed for determining levels of these protein components in the serum samples of the participants. Briefly, 100 µL of sample was added to antibody-coated microplate wells and incubated at 37°C for 90 min. After washing, 100 µL of biotinylated detection antibody was added and incubated at 37°C for 60 min. After washing the wells three times using the wash buffer, 100 µL of streptavidin-HRP was added followed by incubation at 37°C for 30 min. After extensive washing step, 90 µL of TMB was added to the wells and incubated at 37°C for 15 min in the dark. The reaction was terminated by adding 50 µL of stop solution to the wells and the absorbance was measured at 450 nm using a Biotek SYNERGY H1 microplate reader. The concentration of components in the samples was calculated from a standard curve, and the results are expressed as pg/mL (ng/mL for PGC-1α).

Statistical analysis

Owing to the unavailability of multivariate analysis assumptions for the groups (multiple Normal Distribution and homogeneity of variance), researchers used the two-way PERMANOVA (Permutational Analysis of Variance) Program in conjunction with the PAST 4.03 program to determine whether there was a difference between the groups, within the groups, and whether there was an interaction effect in the data.

Results

Table 3 shows the changes in Yo Yo IR-1 distance parameters of the participants. According to the study's data, no statistically significant difference between the measurements was found (F=2.819, p_1=0.063) (p>0.05). According to the study's data, a statistically significant difference between the groups was found (F=9.236, p_2=0.001)

Table 3. Comparison of the measured values of YoYo IR-1.

Groups	Mean ± sd	Median	Min-Max	Between Measurements	Between groups	Interaction
				F Value p_1 Value	F Value p_2 Value	
HIITYOYO1	1310 ± 597,78	1180,0	800 - 2800	F= 2,819, p_1=0,063	*F= 9,236, p_2=0,001** Group 1 – Group 2 p_3 = 0,837 ***Group 1 – Group 3 p_3 = 0,002**** ***Group 2 – Group 3 p_3 = 0,002****	F= 0,817, p=0,523
LIITYOYO1	1540 ± 861,29	1230,0	800 - 3560			
CNTYOYO1	1103,33 ± 316,44	1220,0	400 - 1520			
HIITYOYO2	1716,67 ± 691,18	1360,0	960 - 2980			
LIITYOYO2	1700 ± 811,73	1520,0	760 - 3200			
CNTYOYO2	1150 ± 351,67	1240,0	400 - 1600			
HIITYOYO3	2003,33 ± 741,78	1820,0	1120 - 3480			
LIITYOYO3	1906,67 ± 817,86	1700,0	1000 - 3560			
CNTYOYO3	1130 ± 333,85	1260,0	400 - 1520			

Mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

Table 4. Comparison of the measured values of VO_{2max}.

Groups	Mean ± sd	Median	Min-Max	Between Measurements	Between groups	Interaction
				F Value p_1 Value	F Value p_2 Value	
HIITVO_{2max}1	47,43 ± 5	46,3	43,1 - 59,9	F= 2,732, p_1=0,667	***F=9,319, p_2=0,004**** Group 1 – Group 2 p_3 = 0,819 ***Group 1 – Group 3 p_3 = 0,001**** ***Group 2 – Group 3 p_3 = 0,002****	F= 0,817, p=0,523
LIITVO_{2max}1	49,4 ± 7,2	46,9	43,1 - 66,3			
CNTVO_{2max}1	45,72 ± 2,66	46,7	39,8 - 49,2			
HIITVO_{2max}2	50,82 ± 5,79	47,8	44,5 - 61,3			
LIITVO_{2max}2	50,7 ± 6,83	49,2	42,8 - 63,3			
CNTVO_{2max}2	45,99 ± 2,88	46,9	39,8 - 49,2			
HIITVO_{2max}3	53,23 ± 6,23	51,7	45,8 - 65,6			
LIITVO_{2max}3	52,38 ± 6,89	50,7	44,8 - 66,3			
CNTVO_{2max}3	45,91 ± 2,8	47,0	39,8 - 49,2			

Mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

(p<0.05). There was find statistically significant differences between Groups 1 and 3 (p_3=0,002), or between Groups 2 and 3 (p_3=0,002) and there was no statistically significant differences between Group 1 and Group 2 (p_3=0,837). The interaction effect was not found to be statistically significant based on the data obtained in the study (F=0,817, p=0,523) (p>0.05).

Table 4 shows the changes in VO_{2max} values of the participants. According to the study's data, no statistically significant difference between the measurements was discovered (F=2,732, p_1=0,667) (p>0.05). According to the study's data, a statistically significant difference between the groups was discovered (F=9,319, p_2=0,004) (p<0.05). Altough there was no statistically significant difference between Group 1 and Group 2 (p_3=0,819), there was find statistically significant difference between Group 1 and Group 3 (p_3=0,001) or Group 2 and Group 3 (p_3=0,002). The interaction effect was not found to be statistically significant based on the data obtained in the study (F=0,817, p=0,523) (p>0.05).

The observed changes in irisin levels in the participants are presented in Table 5. According to the study's data, there was find statistically significant difference between the measurements (F=4,072, p_1=0,016). There was find statistically significant difference between Measurements (Meas) 1 and Meas 3 (p_3=0,036). There was not find statistically significant difference between Meas 1 and Meas 2 (p_3=0,206), Meas 2 and Meas 3 (p_3=0,364). According to the

Table 5. Comparison of the measured values of Irisin (pg/ml).

Groups	Mean ± sd	Median	Min-Max	Between Measurements	Between groups	Interaction
				F Value p_1 Value	F Value p_2 Value	
HIITirisin1	197,08 ± 89,77	165,3	103,57 - 376,66			
LIITirisin1	133,3 ± 43,88	121,1	83,34 - 235,79	***F= 4,072, p_1=0,016****	***F= 4,177, p_2=0,001****	
CNTirisin1	88,55 ± 8,71	91,0	73,34 - 99,79			
HIITirisin2	246,81 ± 117,99	200,8	123,61 - 480,62	Meas 1 – Meas 2 p_3 = 0,206	***Group 1 – Group 2 p_3 = 0,004****	F= 1,236, p=0,308
LIITirisin2	160,27 ± 42,94	150,2	105,6 - 248,99			
CNTirisin2	89,58 ± 7,76	90,4	72,2 - 101,21	***Meas 1 – Meas 3 p_3 = 0,036****	***Group 1 – Group 3 p_3 = 0,001****	
HIITirisin3	291,23 ± 143,99	220,9	142,55 - 599,52	Meas 2 – Meas 3 p_3 = 0,364	***Group 2 – Group 3 p_3 = 0,002****	
LIITirisin3	186,08 ± 37,5	183,4	131,94 - 263,42			
CNTirisin3	89,08 ± 9,03	90,9	73,46 - 100,74			

Meas; Measurements, mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

Table 6. Comparison of the measured values of BDNF (pg/ml).

Groups	Mean ± sd	Median	Min-Max	Between Measurements	Between groups	Interaction
				F Value p_1 Value	F Value p_2 Value	
HIITbdnf1	985,2 ± 631,88	667,1	197,22 - 1999,27			
LIITbdnf1	725,66 ± 320,34	769,2	317,11 - 1306,23	***F= 0,565, p_1=0,047****	***F= 17,348, p_2=0,001****	
CNTbdnf1	586,72 ± 230,97	540,2	317,11 - 1064,28			
HIITbdnf2	1363,25 ± 804,47	1079,7	356,88 - 2717,2	Meas 1 – Meas 2 p_3 = 0,093	***Group 1 – Group 2 p_3 = 0,021****	F=1,305, p=0,270
LIITbdnf2	996,01 ± 467,23	1005,0	398,69 - 1601,24			
CNTbdnf2	592,33 ± 209	587,9	331,5 - 993,53	***Meas 1 – Meas 3 p_3 = 0,003****	***Group 1 – Group 3 p3 = 0,001****	
HIITbdnf3	1738,02 ± 972,58	1379,9	583,75 - 3451,4			
LIITbdnf3	1222,61 ± 481,12	1370,0	429,2 - 1917,3	Meas 2 – Meas 3 p_3 = 0,198	***Group 2 – Group 3 p_3 = 0,001****	
CNTbdnf3	628,02 ± 231,82	543,4	347,4 - 1093,21			

Meas; Measurements, mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

study's data, a statistically significant difference between the groups was discovered (F=4,177, p_2=0,001) (p<0.05). There was find statistically significant difference between Group 1 and Group 2 (p_3=0,004), Group 1 and Group 3 (p_3=0,001), Group 2 and Group 3 (p_3=0,002). The interaction effect was not found to be statistically significant based on the data obtained in the study (F= 1,236, p=0,308) (p>0.05).

The observed changes in BDNF levels in the participants are presented in Table 6. According to the study's data, there was find statistically significant difference between the measurements (F=0,565, p_1=0,047). There was find statistically significant differences between Meas 1 and Meas 3 (p_3=0,003). There was not find statistically significant difference between Meas 1 and Meas 2 (p_3=0,093), Meas 2 and Meas 3 (p_3=0,198). According to the study's data, a statistically significant difference between the groups was discovered (F=17,348, p_2=0,001) (p<0.05). There was find statistically significant difference between Group 1 and Group 2 (p_3=0,021), Group 1 and Group 3 (p_3=0,001), Group 2 and Group 3 (p3 = 0,001). The interaction effect was not

Table 7. Comparison of the measured values of PGC-1α (ng/ml).

Groups	Mean ± sd	Median	Min-Max	Between Measurements F Value p_1 Value	Between groups F Value p_2 Value	Interaction
HIITpgc1alfa1	2,32 ± 1,59	1,5	0,99 - 5,24	***F= 9,887, p_1=0,001****	***F= 19,681, p_2=0,001****	***F= 2,768, p=0,031****
LIITpgc1alfa1	1,9 ± 1,14	1,5	0,47 - 4,13			
CNTpgc1alfa1	1,43 ± 0,48	1,4	0,86 - 2,37			
HIITpgc1alfa2	3,66 ± 2,21	2,7	1,22 - 7,59	***Meas 1 – Meas 2 p_3 = 0,028****	***Group 1 – Group 2 p_3 = 0,044****	
LIITpgc1alfa2	2,79 ± 1,47	2,2	1,09 - 5,21			
CNTpgc1alfa2	1,54 ± 0,39	1,6	0,84 - 2,08	***Meas 1 – Meas 3 p_3 = 0,008****	***Group 1 – Group 3 p_3 = 0,001****	
HIITpgc1alfa3	5,37 ± 2,71	4,5	2,25 - 9,14			
LIITpgc1alfa3	3,63 ± 1,6	3,3	2,06 - 6,29	***Meas 2 – Meas 3 p_3 = 0,091****	***Group 2 – Group 3 p_3 = 0,001****	
CNTpgc1alfa3	1,52 ± 0,62	1,3	0,64 - 2,92			

Meas; Measurements, mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

Table 8. Comparison of the measured values of TrkB (pg/ml).

Groups	Mean ± sd	Median	Min-Max	Between Measurements F Value p_1 Value	Between groups F Value p_2 Value	Interaction
HIITTrKB1	812,42 ± 194,77	768,1	522,76 - 1192,12	***F= 18,194, p_1=0,001****	***F= 43,883, p_2 = 0,001****	***F= 6,337, p=0,003****
LIITTrKB1	868,14 ± 444	685,0	408,61 - 1793,27			
CNTTrKB1	588,6 ± 132,16	589,2	356,72 - 793			
HIITTrKB2	1277,64 ± 336,2	1246,7	888,09 - 1999,56	***Meas 1 – Meas 2 p_3 = 0,015****	Group 1 – Group 2 p_3 = 0,092	
LIITTrKB2	1050,92 ± 440,08	916,5	535,92 - 1891,88			
CNTTrKB2	590,69 ± 127,95	541,3	450,49 - 762,47	***Meas 1 – Meas 3 p_3 = 0,002****	***Group 1 – Group 3 p_3 = 0,001****	
HIITTrKB3	1709,62 ± 322,82	1630,6	1349,62 - 2369,05			
LIITTrKB3	1316,75 ± 445,36	1178,6	883,15 - 2176,13	Meas 2 – Meas 3 p_3 = 0,063	***Group 2 – Group 3 p_3 = 0,001****	
CNTTrKB3	591,31 ± 147,53	619,1	312,52 - 794,81			

Meas; Measurements, mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

found to be statistically significant based on the data obtained in the study (F=1,305, p=0,270) (p>0.05).

Table 7 shows the changes in PGC-1α levels of the participants. According to the study's data, there was find statistically significant difference between the measurements (F=9,887, p_1=0,001). There was find statistically significant difference between Meas 1 and Meas 2 (p_3=0,028), Meas 1 and Meas 3 (p_3=0,008) (p<0.05). There was not find statistically significant difference between Meas 2 and Meas 3 (p_3=0,091) (p>0.05). According to the study's data, a statistically significant difference between the groups was discovered (F=19,681, p_2=0,001) (p<0.05). There was find statistically significant difference between Group 1 and Group 2 (p_3=0,044), Group 1 and Group 3 (p_3=0,001), Group 2 and Group 3 (p_3=0,001). The interaction effect was found to be statistically significant based on the data obtained in the study (F=2,768, p=0,031) (p<0.05).

Table 8 shows the changes in TrkB levels of the participants. According to the study's data, there was find statistically significant difference between the measurements (F=18,194, p_1=0,001). There was find statistically significant difference between Meas 1 and Meas 2 (p_3=0,015), Meas 1 and Meas 3 (p_3=0,002*) (p<0.05). There was not find statistically significant difference between Meas 2 and Meas 3 (p_3=0,063) (p>0.05). According to the study's data, a statistically significant difference between the groups was discovered

Table 9. Comparison of the measured values of VEGF (pg/mL).

Groups	Mean ± sd	Median	Min-Max	Between Measurements	Between groups	Interaction
				F Value p_1 Value	F Value p_2 Value	
HIITvegf1	21,09 ± 4,17	21,7	13,79 - 26,98	***F= 32,649,***	***F= 44,078,***	
LIITvegf1	21,42 ± 4,38	20,5	16,51 - 30,47	***p_2 = 0,001****	***p_2 = 0,001****	
CNTvegf1	16,2 ± 3,41	16,0	11,51 - 23,98	***Meas 1 – Meas 2***	Group 1 – Group 2	
HIITvegf2	32,92 ± 9,28	31,8	20,17 - 56,48	***p_3 = 0,003****	p_3 = 0,681	
LIITvegf2	32,07 ± 10,61	27,0	20,47 - 56,34	***Meas 1 – Meas 3***	***Group 1 – Group 3***	***F= 6,915,***
CNTvegf2	17,76 ± 6,31	17,1	9,25 - 31,92	***p_3 = 0,001****	***p_3 = 0,001****	***p=0,001****
HIITvegf3	44,74 ± 7,42	44,1	29,7 - 59,67	***Meas 2 – Meas 3***	***Group 2 – Group 3***	
LIITvegf3	41,68 ± 13,89	33,6	29,65 - 66,31	***p_3 = 0,031****	***p_3 = 0,001****	
CNTvegf3	17,54 ± 5,53	17,2	11,36 - 29,72			

Meas; Measurements, mean; mean values, sd; standard deviation, p_1 Value; significance test result between measurements, p_2 Value; Intergroup PERMANOVA significance test result, p_3; the results of the in-group comparison significance test.

(F=43,883, p_2=0,001) (p<0.05). There was find statistically significant difference between Group 1 and Group 3 (p_3=0,001*), Group 2 and Group 3 (p_3=0,001) (p<0.05). There was not find statistically significant difference between Group 1 and Group 2 (p_3=0,092) (p>0.05). The interaction effect was found to be statistically significant based on the data obtained in the study (F=6,337, p=0,003*) (p<0.05).

Table 9 shows the changes in VEGF levels of the participants. According to the study's data, there was find statistically significant difference between the measurements (F=32,649, p_2=0,001). There was find statistically significant difference between Meas 1 and Meas 2 (p_3=0,003), Meas 1 and Meas 3 (p_3=0,001), Meas 2 and Meas 3 (p_3=0,031) (p<0.05). According to the study's data, a statistically significant difference between the groups was discovered (F=44,078, p_2=0,001) (p<0.05). There was find statistically significant difference between Group 1 and Group 3 (p_3=0,001*), Group 2 and Group 3 (p_3=0,001*) (p<0.05). There was not find statistically significant difference between Group 1 and Group 2 (p_3=0,681 (p>0.05). The interaction effect was found to be statistically significant based on the data obtained in the study (F=6,915, p=0,001*) (p<0.05).

Discussion

The effects of different intensity exercises on VO_{2max}, YoYo IR-1 and serum levels of the components of neuromuscular and vascular systems such as BDNF, TrKB, PGC-1α, VEGF, and irisin before, during, and after interventions. This study design of conducting exercise interventions pre-test, acute test, and 4-week after is novel and not reported before. The results of this study can be summarized as follows: (1) there were differences in VO_{2max}, Yo Yo IR-1, and levels of BDNF, TrKB, PGC-1α, VEGF, and irisin in the control, HIIT, and LIIT groups, (2) the high values of VO_{2max}, YoYo IR-1, BDNF, VEGF, PGC-1α, and irisin values were observed in the HIIT group. The results suggest the positive effect of HIIT protocols on irisin levels, Yo Yo IR1, and VO_{2max}; similar findings were made by other studies[1,3,41,47–50]. No study has described the effect of both LIIT and HIIT on irisin levels.

The main reason for the increase in VO_{2max} during internsity exercises is related to the development of mitochondrial biogenesis, largely mediated by PGC-1α upregulation[51]. Irisin is secreted in a PGC-1α-dependent manner[52], and plasma irisin levels increased with high intensity training[53]. It has also been reported that irisin elevation and secretion after exercise were affected by exercise intensity; however, it is independent of energy expenditure[54].

Tofighi et al. reported that HIIT may lead to the transdifferentiation of adipose tissue (from white to brown), and therefore may play a key role in preventing the negative consequences of obesity[3]. In the aforementioned study, it was reported that HIIT causes energy consumption and heat production by increasing the ratio of muscle tissue to adipose tissue, lowering body mass index, changing fat type, and increasing UCP1, suggesting that HIIT exercises pave the way for increased PGC-1α, FNDC5, and irisin. Rezaeimanesh has shown that HIIT and moderate-intensity continuous training (MICT) may be effective in preventing and treating overweight and obesity by increasing irisin levels and insulin resistance[48]. This is associated with exercise-related changes such as choosing the appropriate duration and intensity, observing the gradual load increase, and making the training intensity appropriate. It has also been concluded that MICT and HIIT can increase the amount of myokines such as irisin by changing the body composition and increasing the muscle-adipose tissue ratio, especially in sedentary and overweight people. In addition, with exercise, it may develop due to increased glucose uptake in muscle, increased lipolysis in adipose tissue, increased glycogenesis in the liver, and

increased irisin[55]. Murawska-Ciałowicz et al. (2020) found that HIIT resulted in beneficial effects in the increase in blood irisin concentration, physical performance, and reduced fat content[56]. Consistent with these previous reports, we also found increase in irisin levels.

We also detected increase in PGC-1α after HIIT and LIIT; there are limited studies investigating the effect of HIIT and LIIT exercises on PGC-1α[31,32,55,57,58]. Barlett et al. determined that acute HIIT and moderate-intensity continuous (CONT) running induce activation of molecular signaling pathways associated with the regulation of mitochondrial biogenesis, causing increased PGC-1α mRNA. In addition, the study also first report contractile-induced p53 phosphorylation in human skeletal muscle, identifying an additional pathway by which exercise can initiate mitochondrial biogenesis[31]. Vincent et al. found that HIIT significantly increased mitochondrial function in skeletal muscle in 2 weeks, independent of detectable mitochondria-associated changes and mitogenic protein expression[58]. Kucuk et al. conducted six training sessions over 2 weeks for seven participants to determine the molecular adaptation, metabolic response, and performance of LIIT. After training, PGC-1α levels were 25% higher, but the total PGC-1α protein content remained unchanged. This study demonstrated that LIIT is a potent stimulant that increases mitochondrial capacity of the skeletal muscle and improves exercise performance[34,57].

Wahl et al. investigated the effects of HIIT and high-volume endurance training (HVT) on cytokines involved in angiogenesis and showed significantly increased serum VEGF concentration 10 min after the exercises[59]. Alavi and Mirdar investigated the effect of 8 weeks of HIIT and body fat ratio (BFR) on protein expression (VEGF and endothelial nitric oxide synthase (eNOS)) in the vastus lateralis of male runners. The results showed that VEGF and eNOS levels increased significantly in the experimental groups compared with those in the control group[60]. Studies evaluating VEGF in humans are limited. Mortensen et al. (2019) found no change in its levels after HIIT treatment. They also found no difference in capillarization, capillary structure, and exercise hyperemia between moderate-intensity endurance training and LIIT[61]; however, our study showed ments at three different time-points of the effects of HIIT on VEGF.

Previous studies have shown that the HIIT modalities do not affect BDNF levels. This is inconsistent with our results, e to factors such as individual participant-specific differences, current fitness levels, and participants training backgrounds. that in comparison to non-exercise or light-intensity exercises, an immediate increase in BDNF levels may occur when young adults perform HIIT[62]. Furthermore, Renteria et al. showed that a 12-unit HIIT session can significantly increase circulating BDNF concentrations in healthy young women[25]. Similarly, Antunes et al. found that short-term high-intensity exercise was more effective in increasing BDNF concentration[63]. In a study by Marquez et al. (2015), a shorter duration of HIIT was slightly more effective than continuous HIIT in raising serum BDNF, suggesting that present an effective and preferred intervention for raising BDNF levels and potentially improving brain health[24]. Since HIIT modalities have the potential to increase systemic BDNF levels, there may be an increase in brain BDNF concentrations as well. It has been reported that this may lead to an increase in BDNF synthesis in the peripheral storage and release system of the brain[25]. by Murawska-Ciałowicz et al., the participants applied three 1-h exercise sessions 9 days a week; ter 9 weeks of different forms of high-intensity training (HIIT) showed no change. Resting BDNF levels measured on the 3rd (before GXT [Graded Exercise Test] at stage 9) and 6th day after long-lasting HIITs (before WAnT at stage 9) did not differ (before GXT), but in comparison to the resting value before WAnT, the BDNF levels were lower in the three groups[64].

HIIT modalities have been reported to increase TrKB levels in rats and were attributed to increased TrkB receptor levels in astrocytes. It has also been suggested that astrocytes respond actively and may counteract the positive effects of physical exercise on the central nervous system, potentially triggering degenerative processes, and neurodegenerative disorders during aging[65]. Rahmati-Ahmedabad et al. examined the independent and combined effects of HIIT and flaxseed oil supplementation on cognitive and executive functions in middle-aged rats, and found that both independently decreased sedentary behavior and increased the expression of hippocampal BDNF and TrkB coding genes[66]. Our study makes a significant contribution by detecting that the increase in TrKB in humans after HIIT and LIIT.

The limitations of this study include the small sample size, which may limit the applicability of our results to wider population, and the involvement of healthy male participants only. Future studies that delve into the effects of LIIT and HIIT on female participants and individuals with different body mass indexes are warranted.

In conclusion, HIIT and LIIT exercises performed with 20 s of activity followed by 20 s rest improved VO2 max and the levels of BDNF, TrkB, Irisin, VEGF, and PGC-1α. Furthermore, HIIT exercises were found to have a more significant effect on these parameters than LIIT exercises. We conclude that HIIT exercises are more suitable for improving brain and metabolic parameters in physically inactive volunteers.

Funding

This study was supported by the Coordinatorship of Scientific Research at Inonu University with project no TDK-2020-2001.

Acknowledgments

Contributing to the biochemical measurements, We would like to thank Prof. Dr. Mehmet Çağatay Taşkapan and all the participants for their voluntary support.

The study was produced from the doctoral dissertation.

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