International Journal of EXERCISE SCIENCE

Original Research

Combined Physical Training Increases Plasma Brain-Derived Neurotropic Factor Levels, But Not Irisin in People Living with HIV/AIDS

Joice Cristina dos Santos Trombeta*[1], Roberto Carlos Vieira Junior*[2], Cláudia Regina Cavaglieri‡[1], Ivan Luiz Padilha Bonfante‡[1,3], Jonato Prestes‡[4], Ramires Alsamir Tibana‡[4], Morteza Ghayomzadeh‡[5] Vinícius Carolino Souza‡[4], Seyedahmad Seyedalinaghi‡[5], James W. Navalta‡[6], Fabrício Azevedo Voltarelli‡[7]

[1]Laboratory of Exercise Physiology, School of Physical Education, University of Campinas, Campinas, SP, Brazil; [2]Faculty of Health Sciences, State University of Mato Grosso (UNEMAT), Cáceres, MT, Brazil; [3]Federal Institute of Education, Science and Technology of São Paulo, Hortolândia campus, Hortolândia, SP, Brazil; [4]Graduate Program in Physical Education, Faculty of Physical Education, Catholic University of Brasilia (UCB), Brasilia, Brazil; [5]Iranian Research center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences, Tehran, Iran; [6]Department of Kinesiology and Nutrition Sciences, University of Nevada, Las Vegas, USA; [7]Graduate Program in Health Sciences, Faculty of Medicine, Federal University of Mato Grosso (UFMT), Cuiabá, MS, Brazil.

*Denotes undergraduate student author, ‡Denotes professional author

ABSTRACT

International Journal of Exercise Science 14(3): 1004-1017, 2021. This study evaluated plasma levels of brain-derived neurotropic factor (BDNF), irisin, and lactate in people living with HIV/AIDS who completed a combined physical training program. Nineteen HIV+ participants (age: 39.60 ± 10.96 years; carrier time: 7.75 ± 7.88 years; time of ART: 6.41 ± 5.93 years) performed strength/aerobic training (combined physical training) in the same session for 8 weeks and levels of BDNF, irisin, and lactate were assessed. BDNF (pg/mL) was higher post-CPT (Pre: 1258.73 ± 372.30; Post: 1504.17 ± 322.30; $p < 0.001$). Irisin (ng/mL) showed no change (Pre: 115.61 ± 72.41; Post: 125.87 ± 81.14; $p = 0.973$). There was positive correlation between irisin and lactate (mmol/L) pre ($r = 0.55$, $p = 0.04$), and lactate values were higher in the group with the highest value of irisin (3.65 ± 0.69 x 2.82 ± 0.59, $p = 0.02$). Combined physical training results in increased basal BDNF in people living with HIV/AIDS, this finding suggests that increased concentration of BDNF may be associated with decreased chances of developing cognitive disorders or HIV-associated dementia. Further studies involving molecular mechanisms on this subject are necessary.

KEY WORDS: Combined physical training, HIV, BDNF, irisin, blood lactate

INTRODUCTION

AIDS is an infection caused by the human immunodeficiency virus (HIV) and is characterized by the decreased number of circulating TCD4 + lymphocytes, depressing the immune system of

individuals and predisposing them to the development of opportunistic diseases that, if not treated, lead to death (1).

Neurocognitive diseases are found in 30% to 50% of people living with HIV/AIDS (PLWHA), as the virus can cross the blood-brain barrier and infect the cells of glia, inducing damage and neural death (16). A useful biomarker, and one that perhaps will serve as a control for neurological changes, is brain-derived neurotrophic factor (BDNF), an important neurotrophin involved in the development of the parahippocampal region. Neurotrophic factors in general, have functions of neural regulation and differentiation as well as modulation of plasticity and survival of neurons and glial cells (29, 40). Several studies have shown that cognitive changes as well as psychiatric disorders such as depression may decrease the concentration of BDNF in individuals both infected and not affected by HIV (17, 23, 27). In addition, increases in BDNF have been shown to be negatively related to depressive symptoms and Alzheimer's disease (26), leading some researchers to suggest peripheral BDNF as a biomarker of these diseases (18, 31). Thus, it can serve as an instrument to monitor the HIV-Associated Dementia and neurocognitive diseases associated with HIV (HAND), for example.

In addition to neurological changes, metabolic disorders are also common in PLWHA and undergoing Antiretroviral Therapy (ART). The use of nucleotide analogue reverse-transcriptase inhibitors (NRTIs) is commonly related to the onset of mitochondrial toxicity/dysfunction that affects several tissues, including the liver and muscles, leading to injury of the oxidative energy system, a fact that contributes substantially to resting hyperlactatemia and high oxidative stress (38). This condition indicates a possible mitochondrial dysfunction, which in this case is related to the inhibition of the enzyme DNA polymerase gamma by NRTIs, a phenomenon that impairs mitochondrial DNA replication (4).

Currently, it is known that the mitochondrial dysfunction and injury of oxidative phosphorylation, including reduction of mitochondrial DNA and peroxisome proliferator-activated receptor-gamma (PPARγ) expression, exert influence on the metabolic homeostasis of PLWHA, and irisin is one of the molecules affected. Irisin is a protein derived from proteolytic cleavage of the fibronectin type III domain-containing protein 5 (FNDC5) gene and is secreted mainly by skeletal muscle and adipose tissue in humans and animals. It is known that the expression of FNDC5 is increased by the PPARγ activation and by its coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), and may have an effect from physical exercise (7). However, there is little evidence in the literature about this substance and its relationship with PLWHA as well as its influence on resting blood lactate levels in this population (34).

The main function of irisin is to promote energy expenditure through increased activity of brown adipose tissue (BAT) or the conversion of white adipose tissue (WAT) in beige, which have molecular characteristics close to BAT (8). This is due to the presence of a higher number of mitochondria stimulated by uncoupled protein 1 (UCP-1) which, when activated, divert the protons of the electron transport chain, decreasing the production of energy (ATP) at the expense of increased body temperature (thermogenesis) (7). Some studies have shown also

increase in irisin levels in oxidative stress conditions, inflammation and energy production problems (2, 5, 41), and this condition is present in this population due to the ART use (35). However, little is known about irisin and PLWHA, since these participants present major changes in the two main secretory tissues (muscle and fat) of this protein, as decreased muscle mass and the accumulation of adipose tissue in the abdominal area (30, 34). In addition, no study analyzes the irisin relation with blood lactate levels (a useful variable to analyze the metabolism conditions and energy production) in this population.

Interestingly, the secretion of both irisin and BDNF is stimulated by muscle contraction, and peripheral neural stimulation via PGC1-α/FNDC5 by physical exercise enhances the expression and secretion of both (39). Some studies have investigated effects from exercise (39) or in specific populations, such as the elderly (32), Crossfit® athletes (24), endurance athletes (6), and people with multiple sclerosis (10), and the results are controversial depending on the type of intervention and/or studied population.

Because the association between HIV infection and ART provokes the increased risk of metabolic and neurocognitive disorders, as well as the absence of studies that have evaluated the HIV/AIDS x irisin x BDNF x resting blood lactate interaction response to physical exercises, the present investigation aimed to evaluate these markers. In addition, a secondary goal was to examine whether correlations exist among these markers in PLWHA who completed a CPT program.

METHODS

Participants

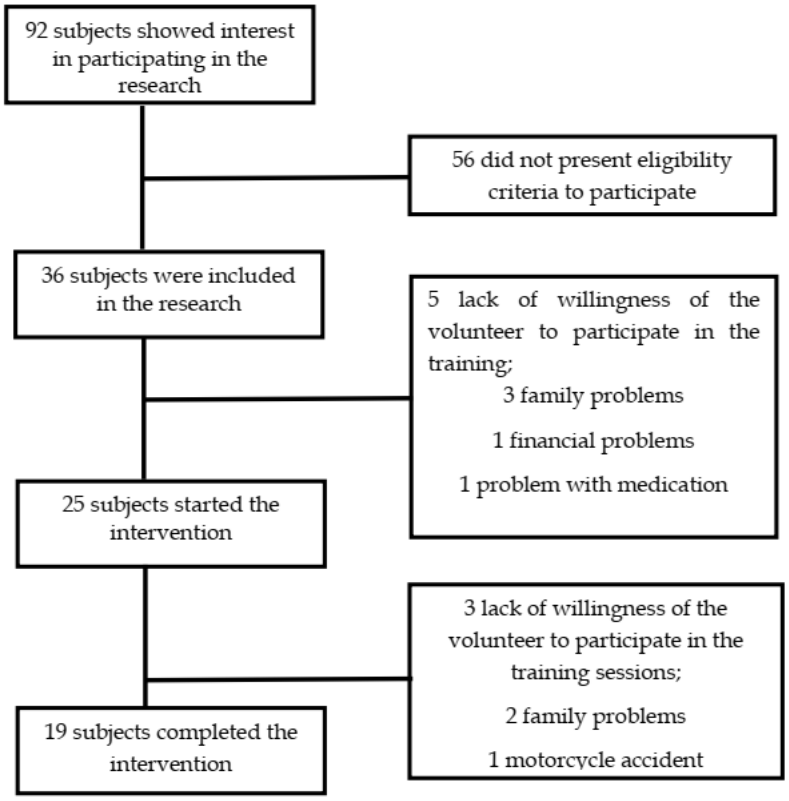
A power analysis conducted a priori with G*POWER 3.1 software (Universitat Kiel, Germany). We based on Cho et al. (12) that aimed to analyze the combined exercise serum BDNF level in mid-aged women. Using the medium, standard deviation and percentage changes values of BDNF levels, we observed in this study an effect size of 1.27 and power of 0.97. Based on these data, effect size and beta power were needed in the present study at least 11 participants as a minimum sample. In addition, to verify the power of the present sample after the experimental period/study, we calculated the Post Hoc power also in the G Power 3.1. This calculation was based on the statistical test used in the study, the "*n*" obtained from 19 participants, an alpha significance level of 0.05, an effect size of 0.79 from the pre/post values of the means and standard deviation of BDNF levels (the main result of the study). As a result, we observed a beta power of 0.90, up from the normally stipulated 0.80, which is usually used as a minimum required to characterize a sample as capable of detecting a difference in a given population.

As mentioned, nineteen participants infected with HIV participated in this study (11 women and 8 men) (age: 39.60 ± 10.96 years; Carrier time: 7.75 ± 7.88 years; Time of ART: 6.41 ± 5.93 years); and were undergoing treatment in specialized service centers, located in the city of Cuiabá, Mato Grosso, Brazil. The inclusion criteria used were: minimum age of 18 years, sedentary or inadequately active, have no impediments that would prevent exercising, should be using ART, and have 85% minimum frequency of the training performed. The patients who

presented with cardiovascular, cancer and inflammatory diseases, TCD4 + cell counts less than 200 cells/mm3, pregnancy, failed to obtain medical release, or did not complete all stages of research were excluded. No dietary intervention was performed, the participants were instructed to maintain food habits prior to the survey.

The research was approved by the Research Ethics Committee of the Júlio Muller Universitary Hospital, which is linked to the Federal University of Mato Grosso (Protocol No: 673/09) and was based on the principles of the Declaration of Helsinki. In addition, this research was carried out fully in accordance to the ethical standards of the International Journal of Exercise Science (25). All participants provided written informed consent prior to participation. Flow of participants through the study is shown in the Figure 1.

Figure 1. Flow of participants through the study.



Protocol

The experimental design is described in the figure 2 below.

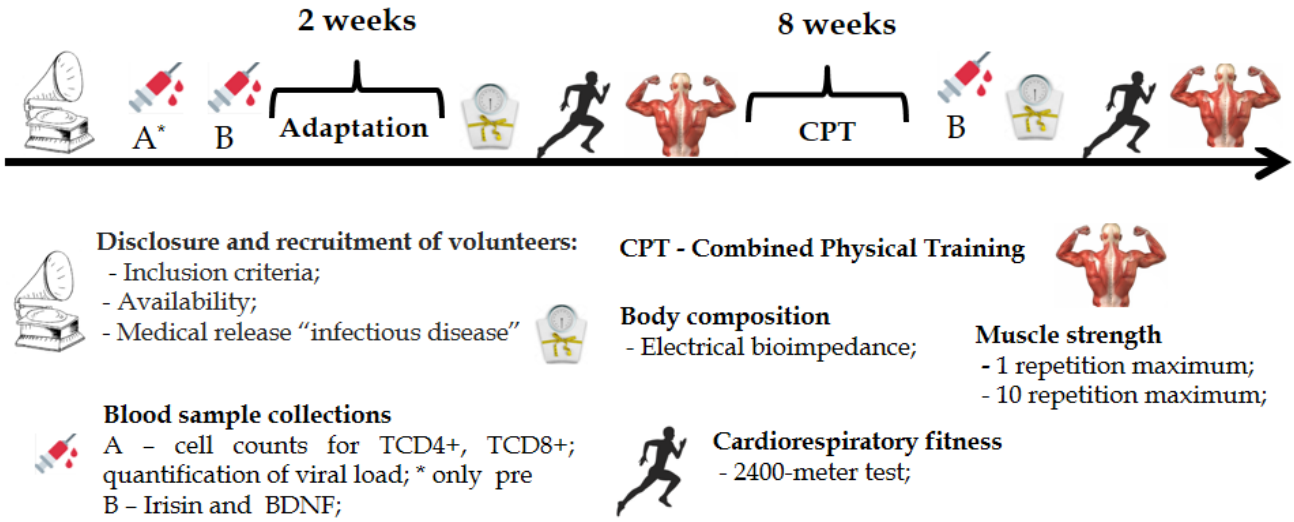


Figure 2. Experimental design

Biochemical analysis: All blood sample collections were performed in the morning (08:00-10:00) after a fast of 12 hours and were completed in two phases. First, for immune profile analysis, blood was collected at a specialized customer service (SAE), Cuiabá, Mato Grosso, Brazil. The variables analyzed were: quantification of viral load (method: b-DNA Kit: HIV RNA 3.0); cell counts for TCD4+, TCD8+, and TCD4+/TCD8 (method: flow cytometry-Facscalibur-multitest). On another day, the participants went to the Laboratory of Biochemistry, Molecular Biology and Exercise of Faculty of Physical education, Federal University of Mato Grosso, Cuiabá, Brazil for another blood sample collection, which was centrifuged and serum stored in a freezer at -80°C for further analysis of BDNF and irisin. BDNF and irisin were analyzed by ELISA (Enzyme-Linked immunosorbent assay test) from commercial kits (R&D System Inc., Minneapolis, MN, USA and MyBioSource Inc., San Diego, CA, USA, respectively). The minimum detectable dose was 184.38 pg/mL for BDNF and 27.85 ng/mL for irisin. The coefficient of variation (irisin) intra- and inter-analysis was 2.9-9.5% and 5.9-7.0%, respectively, and the sensitivity was 0.0093 pg/mL. All samples were determined in duplicate to ensure the accuracy of the results.

The determination of resting blood lactate occurred after adaptation and before the beginning of the CPT and consisted of two blood collections, which was obtained perforation of the index finger (Accutrend Plus Lactimeter/BM-Lactate Tests Tapes Roche®-Germany), performed on two separate days. The value of the final concentration was obtained by the average of the two collections.

Body composition: An electrical bioimpedance device (Maltron Body Composition Analyzer ®, Warwick) was used for the measurement of the following variables: relative body fat (%), relative lean mass (%), body mass index (BMI) and basal metabolic rate (BMR). The participants were told to not ingest alcohol, not consume food or beverages that contain stimulants, ingest a minimum quantity of 2 liters of water, as well as urinating up to a maximum of 30 minutes before the test. On the day of assessment, earrings, chains and/or rings and shoes of the

participants were removed. Hands and feet were cleansed, and the patients were placed supine on a pad where electrodes were fixed in the left hand and foot.

Cardiorespiratory fitness: The 2400-meter displacement test was used to determine aerobic physical training prescription. This test consists of participants walking or running 2400 meters at the maximum speed possible. Maximal oxygen consumption (Vo2max) was estimated by the following formula: VO2max = distance/time x 0.2 +3.5 (13).

Muscle strength: The 1 repetition maximum (RM) test was used to evaluate muscle strength of the participants before and after the CPT, following appropriate recommendations (9). The participants performed two sessions of adaptation in the bench press, leg press 45°, and biceps curls, in order to establish the correct execution of the movement. After the adaptation period, participants performed 1 RM test and re-test on two non-consecutive days (minimum of 72 h between testing sessions). After 5 minutes of walking on a treadmill at a light intensity (based on the scale of perceived exertion), the participants performed a specific warm-up of 8 repetitions with 50% of 1 RM (according to previous loads used in the adaptation sessions), followed by three repetitions at 70% of 1 RM.

Subsequently, repetitions were performed with progressively heavier loads, and the 1 RM was determined within a maximum of three attempts, using rest intervals of 3 to 5 minutes between retries. The intraclass correlation (ICC) coefficient was $r > 0.96$ for the exercises tested, confirming the reliability test re-test.

For the prescription of resistance training, we used the 10 maximal repetitions (10 RM) test, which was performed on the following devices: half squat (guided bar), bench press, leg curl, barbell upright row, leg press 45°, triceps pulley, bending plant, dumbbell press, and biceps curls, following the adapted recommendations: 1) warm-up for 5 to 10 repetitions at 40 - 60% of estimated load, followed by a break of 1 minute; 2) execution of 3 to 5 repetitions at 60% of estimated load and a rest of 3 minutes; 3) load increase, trying to reach the 10 RM in up to five attempts, with rest between each attempt of up to five minutes. The load changes occurred as follows: less than 10 repetitions resulted in a reduction of up to 10%; more than two repetitions, in addition, resulted in increased load in the same proportion. The value registered was that obtained in the last successful repetition (9). The load of abdominal and plantar flexion exercises was analyzed through the located muscular resistance test (maximum number of executions per minute).

Combined Physical Training (CPT): In order to complete familiarization, the participants were subjected to two weeks of adaptation to the gym´s equipment. The participants included in the survey obtained 85% minimum frequency in the training performed. Stretching exercises for the entire body were carried out before and after the training session.

The CPT itself had a total duration of eight weeks and was carried out three times per week (days interspersed). The resistance training was conducted in a circuit, and the participants performed a single set on the following equipment: 1/2 squat (guided bar), bench press, leg curl,

barbell upright row, leg press 45°, triceps pulley, dumbbell press, bending plant and biceps curls. At the end of the circuit, there was a recovery of 90 seconds. The same sequence was then repeated, totaling two laps on the circuit. After resistance training was completed, the participants began aerobic training, which consisted of a walk lasting 30 to 40 minutes (60-70% of maximal heart rate monitored by a frequency meter). The periodization of CPT is described in Table 1.

Table 1. Periodization of combined physical training

Resistance Training				
Weeks	1ª e 2ª	3ª e 4ª	5ª e 6ª	7ª e 8ª
Circuit (number of rounds)	2	2	2	2
Repetitions	12 a 15	10 a 12	8 a 6	4 a 6
Intensity (%)	60	75	85	100
Aerobic training				
Intensity (FC_{max} [%])	60 a 70	60 a 70	60 a 70	60 a 70
Duration (minutes)	30	30	40	40

Statistical Analysis

The analysis of data normality was performed using the Shapiro-Wilk test, and Student's *T* and Mann-Whitney tests for parametric and nonparametric data, respectively. To check for correlations among BDNF, irisin and blood lactate in the moment pre-and between Δ% of change by training, Pearson correlation test (BDNF and irisin) and Spearman (blood lactate with BDNF and irisin) were performed. Taking into consideration that our hypothesis relates irisin and blood lactate and due to the fact that we have found a correlation between these variables at the moment pre-CPT, a cluster analysis was applied (K-means cluster), using the irisin level values of each subject. This analysis divided the "19" irisin values into two groups of clusters with the closest mean (higher [n = 6] and lower [n = 13] levels of irisin). The student's *t*-test was used to analyze the differences between blood lactate levels of two groups/clusters. The software used for all analyses was Statistica (version 6.0). The results were expressed as mean ± standard deviation and established the significance level of 5%.

RESULTS

Prior to the beginning of the CPT, the viral load of the participants was undetectable (< 50 copies/mL); TCD4+ lymphocytes (630 ± 173 cells/mm3) and TCD8+ (988 ± 522 cells/mm3) were obtained in desirable values for the safe practice of regular exercise. The table 2 shows the medications used by the research participants.

Table 2. Class of drugs used by research participants

Participant	Medicines	Class of medicines
1	Nevirapina, Estavudina, Lamivudina	NNTRs, NRTIs, NRTIs
2	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
3	Ritonavir, Estavudina, Lamivudina, Atazanavir	PIs, NRTIs, NRTIs, PIs
4	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
5	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
6	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
7	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
8	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
9	Nevirapina, Estavudina, Lamivudina	NNTRs, NRTIs, NRTIs
10	Nevirapina, Estavudina, Lamivudina	NNTRs, NRTIs, NRTIs
11	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
12	Nevirapina, Estavudina, Lamivudina	NNTRs, NRTIs, NRTIs
13	Lopinovir, Ritonavir, Tenofovir, Lamividuna, Zidovudina	PIs, PIs, NRTIs, NRTIs, NRTIs
14	Efavirenz, Tenofovir, Lamivudina	NNTRs, NRTIs, NRTIs
15	Lamivudina, Zidovudina, Efavirenz	NRTIs, NRTIs, NNTRs
16	Estavudina, Lamivudina, Nevipirina	NRTIs, NRTIs, NNTRs
17	Ritonavir, Raltegravir, Darunavir, Lamivudina,Tenofovir.	PIs, INIs, PIs, NRTIs, NRTIs
18	Lopinovir, Ritonavir, Tenofovir, Lamividuna, Zidovudina	PIs, PIs, NRTIs, NRTIs, NRTIs
19	Efavirenz, Tenofovir,Lamivudina	NNTRs, NRTIs, NRTIs

NRTIs: nucleoside/nucleotide analogue reverse-transcriptase inhibitors, NNTRs: non-nucleoside analogue reverse-transcriptase inhibitors, PIs: protease inhibitors, INIs: integrase inhibitors

The results of BMR and variables related to body composition and physical fitness are shown in table 3. No statistically significant differences were observed to BMR and body composition. With regard to evaluations of muscle strength and cardiorespiratory fitness, patients obtained statistically significant gains post-CPT for muscle strength and VO2max (Table 3).

Table 3. Body composition, basal metabolic rate and physical fitness before and after combined physical training among people living with HIV/AIDS.

Parameter	Pre-CPT	Post-CPT	*p*-value
Body mass (kg)	70.9 ± 18.2	70.6 ± 17.9	0.535
BMI [kg. $(m^2)^{-1}$]	26.7 ± 8.0	26.5 ± 8.0	0.455
Fat mass (%)	30.2 ± 11.3	30.5 ± 11.3	0.531
Lean mass (%)	69.8 ± 11.3	69.5 ± 11.4	0.599
BMR (kcal)	1438.9 ± 227.8	1437.6 ± 222.7	0.712
Bench press (kg)	26.9 ± 13.9	31.9 ± 15.5*	< 0.001
Leg press (kg)	176.6 ± 72.6	201.9 ± 79.7*	< 0.001
Biceps curl (kg)	21.3 ± 8.1	24.4 ± 9.0*	< 0.001
VO_{2max} ($ml.kg^{-1}.min^{-1}$)	23.7 ± 3.2	29.2 ± 5.6*	< 0.001

VO_{2max}: maximal oxygen uptake; Results are expressed as mean ± standard deviation.
* Statistically significant difference ($p < 0.05$).

The pre-post values of irisin (A), BDNF (B) and resting blood lactate (C) levels are presented in figure 3. Only BDNF presented significantly higher values post-CPT ($p < 0.001$). In addition, there was a positive correlation between irisin and blood lactate ($r = 0.55$, $p < 0.05$) pre-CPT; on the other hand, there was no correlation with other variables, regardless of the moment analyzed.

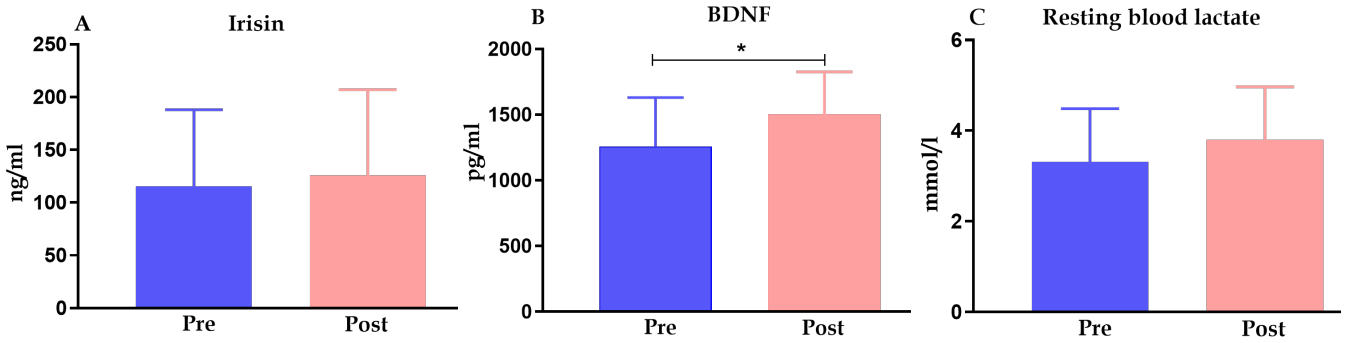


Figure 3. Serum concentrations of irisin, BDNF, and resting blood lactate Serum concentrations of irisin (A), BDNF (B), and resting blood lactate (C), in people living with HIV/AIDS before (pre) and after (post) combined physical training (CPT). Results are expressed as mean ± standard deviation. * Statistically significant difference (p <0.05).

Lastly, the Cluster analysis provided evidence that the group that presented higher values of irisin also displays higher resting blood lactate values (Table 4).

Table 4. Values of irisin and resting blood lactate after Cluster analysis.

Variable	Higher Irisin Group	Smaller Irisin Group	p-value
Irisin (ng.mL^{-1})	203.73 ± 34.74	68.47 ± 35.34*	< 0.001
Blood lactate (mmol.L^{-1})	3.65 ± 0.69	2.82 ± 0.59*	0.02

Results are expressed as mean ± standard deviation. * Statistically significant difference ($p < 0.05$).

DISCUSSION

The present investigation observed changes in plasma concentrations of BDNF, irisin and resting blood lactate as well as analyzed the correlation between these biomarkers in PLWHA who completed an 8-week combined physical training program. The main results showed an increase in BDNF levels as well as an improvement in functional parameters (oxygen consumption and muscle strength) post-CPT. In addition, there was a positive correlation between irisin and blood lactate, where individuals with higher levels of irisin showed higher concentrations of resting blood lactate.

Increase of BDNF: It is known that physical exercise promotes numerous health benefits, and in PLWHA, due to the presence or risk of neurological and metabolic changes it becomes essential, because regular exercise can ensure benefits to many systems including the improvement and/or maintenance of muscle mass, immune system, blood glucose, lipid profile, and cognitive function (20). In the present study, the levels of BDNF were higher post-CPT, suggesting that there was a modulation important, may serve as protection against the onset of Alzheimer's disease, and of psychiatric disorders such as depression common alterations in this population.

As well as, some authors suggest that concentration of BDNF it can serve as an instrument to monitor the HIV-Associated Dementia and neurocognitive diseases associated with HIV (HAND) (18, 31), we suggest that the practice of combined exercise can be part of the daily routine of people living with HIV.

In a study performed with an animal model, increased secretion of BDNF accompanied by increasing neurogenesis was observed as well as decreased neuritis post-endurance training (6). These findings are important because PLWHA present lower levels of BDNF if compared to healthy individuals, strengthening our initial hypothesis.

It is worth mentioning that our aim was not to evaluate the cognitive function of the participants, but to verify the concentrations of BDNF as well as its response to CPT. Thus, it is not possible to say whether there was an improvement in cognitive function of our participants, which would be confirmed by means of specialized tests, such as the mini-exam of the mental state (36). However, despite the results related to BDNF being positive, future studies are needed to examine the pro-BDNF and mad-BDNF isoforms since the binding of mad-BDNF to its membrane receptor (tyrosine kinase B (TrkB)) is needed for effective action on hippocampal plasticity and memory formation (21).

Maintenance of hyperlactatemia: It is known that hyperlactatemia, commonly observed in PLWHA, is related to NRTIs, which can cause mitochondrial dysfunction (22). The patients of the present study displayed high resting blood lactate levels pre- and post-CPT, even with a significant improvement in functional parameters (muscle strength and cardiorespiratory fitness). Usually, the rationale for increases in resting blood lactate is based on the failure of oxidative phosphorylation due to mutation and the deterioration of mitochondrial DNA. The inhibition of the enzyme DNA polymerase γ changes the replication of mitochondrial DNA, which is an encoder of subunits of the respiratory chain enzyme complex (3). To elucidate this question, further analysis of specific biomarkers (e.g. oxidative enzymes [expression and/or activity], and UCPs) is necessary in order to clarify mitochondrial behavior, specifically in PLWHA using ART, as well as the response of these biomarkers to CPT.

Irisin and HIV- The Need for Further Studies: In our study, there was no change in the levels of irisin post-CPT, and in the only other study that determined the concentration of irisin in PLWHA subjected to physical training (37); on the other hand, the values of this peptide in this population compared to healthy participants with similar characteristics considering age, BMI and resting energy expenditure were higher. Interestingly, another work, which corroborated our findings, showed no change in the levels of irisin 48 hours after the last session of physical training (33).

It is important to note that changes in irisin levels have been observed, in healthy participants, when blood sampling is performed immediately after and/or a few hours after the last training session (14), which did not occur in the present study. Another factor that may have contributed to this result may have been the time of training applied (8 weeks), which was relatively short.

The correlation between irisin and resting blood lactate pre-CPT was positive, as well as the Cluster analysis results denoting a possible relation between these metabolites. Hypothetically, we suggest that the increased oxidative stress, induced by ART and HIV infection itself, seems to be an influencer of this finding. This hypothesis is strengthened by the several results found in the literature (2, 5, 19, 28, 41), which shown increased oxidative stress via mitochondrial dysfunction and a concomitant increase in the expression of both PGC1-α and FNDC-5, causing the elevation of plasma irisin levels. These relationships between irisin and oxidative stress are suggested not only by mitochondrial dysfunctions (16, 36) but also as a protective and anti-oxidant effect, since this peptide has been shown to be important in neutralizing free radicals and improving redox balance (2, 5, 28).

Some studies have shown the correlation between irisin and BDNF at the molecular level. In an interesting study (39), it was reported that stimulation of the PGC-1α/FNDC5 pathway by exercise increased the expression and secretion of irisin. Taking into consideration that this same pathway triggers a cascade of signaling which will stimulate an unknown transcription factor and, mainly, the expression of BDNF (40), it is possible to suggest that physical exercise is a potent inducer of this neurotrophic factor, via irisin, in the healthy people.

However, our results did not show a correlation between plasma levels of irisin, and BDNF, even with increased BDNF; and this result confirms the findings of other studies (23) conducted in healthy young individuals. On the contrary, a study performed with athletes found a positive correlation (6). Taken together, these results show that the population studied as well as the fitness level of the subject can be the determining factor for the discrepancy between the results for irisin and BDNF here reported.

The present study had, at the beginning of the activities, with a total number of 25 participants, however, reached the final with nineteen participants and did not have a control group. The reasons for the discontinuity in the research were: lack of willingness of the participants to participate in the training sessions; family problems; motorcycle accident (figure 1). This sample loss characterizes the limitations of our work, although studies with this population normally confirm this difficulty (11, 15). In addition, it is known that the exclusion of participants in order to form a control group may compromise the participation of all participants involved (11, 15).

Conclusion: Combined physical training program increased basal plasma concentrations of BDNF as well as improved muscle strength and cardiorespiratory fitness among PLWHA. There was a correlation between irisin and resting blood lactate levels before the CPT was initiated; in addition, resting blood lactate values were higher in the group with the highest value of irisin. There was no correlation between the plasma levels of irisin and BDNF. In relation to concentration BDNF in PLWHA, this finding suggests that increased concentration of BDNF may be associated with decreased chances of developing cognitive disorders and/or HIV-associated dementia. Future studies can be carried out with a focus on the molecular and mechanistic relation between BDNF, irisin and resting blood lactate, in particular in PLWHA.

ACKNOWLEDGEMENTS

We thank the Brazilian Foundation "Fundação de Amparo à Pesquisa do Estado de Mato Grosso (FAPEMAT)" (Process number: 331264/2012) and "National Council for Scientific and Technological Development (CNPQ)" (Financing Code: 303571/2018-7) for financial support. In addition, the authors thank the participants.

REFERENCES

1. Abbas A, Lichtman A, Pillai S. Cellular and molecular immunology. São Paulo: Saunders Publisher; 2008.

2. Askari H, Rajani SF, Poorebrahim M, Haghi-Aminjan H, Raeis-Abdollahi E, Abdollahi M. A glance at the therapeutic potential of irisin against diseases involving inflammation, oxidative stress, and apoptosis: An introductory review. Pharmacol Res 129: 44-55, 2018.

3. Bauer A-M, Sternfeld T, Horster S, Schunk M, Goebel F-D, Bogner J. Kinetics of lactate metabolism after submaximal ergometric exercise in HIV-infected patients. HIV Med 5(5): 371–6, 2004.

4. Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: Causes, consequences and possible means to prevent it. Mitochondrion 6(1): 1–38, 2006.

5. Belviranli M, Okudan N, Çelik F. Association of Circulating Irisin with Insulin Resistance and Oxidative Stress in Obese Women. Horm Metab Res 48 (10): 653-657, 2016.

6. Belviranli M, Okudan N, Kabak B, Erdoğan M, Karanfilci M. The relationship between brain-derived neurotrophic factor, irisin and cognitive skills of endurance athletes. Phys Sports Med 44(3): 290–6, 2016.

7. Boström P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. A PGC1-α dependent myokine that derives browning of white fat and thermogenesis. Nature 481(7382): 463–8, 2012.

8. Boström P, Fernández-Real JM, Mantzoros C. Irisin in humans: Recent advances and questions for future research. Metabolism 63(2): 178–80, 2014.

9. Brown LE, Weir JP. ASEP Procedures Recommendation I: Accurate Assessment Of Muscular Strength And Power. An Int Electron J 4(3): 1–21, 2001.

10. Briken S, Rosenkranz SC, Keminer O, Patra S, Ketels G, Heesen C, et al. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. J Neuroimmunol 299: 53–8, 2016.

11. Cargill VA, Stone VE. HIV/AIDS: A minority Health Issue. Med Clin N Am 89 (4): 895-912, 2005.

12. Cho HC, Kim JK, Lee NJ, Kim SY, Yoon NK. Effects of combined exercise on cardiovascular risk factors and serum BDNF level in mid-aged women. J Exerc Nutrition Biochem 18(1): 61-7, 2014.

13. Cooper KH. Testing and Developing Cardiovascular Fitness Within the United States Air Force. J Occup Med 10(11): 636–9, 1968.

14. Daskalopoulou SS, Cooke AB, Gomez YH, Mutter AF, Filippaios A, Mesfum ET, et al. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, healthy, active subjects. Eur J Endocrinol 171(3): 343–52, 2014.

15. Dolan SE, Frontera W, Librizzi J, Ljungquist K, Juan S, Dorman R, et al. Effects of a Supervised Home-Based Aerobic and Progressive Resistance Training Regimen in Women Infected With Human Immunodeficiency Virus. Arch Intern Med 166(11): 1225, 2006.

16. Falasca K, Reale M, Ucciferri C, Di Nicola M, Di Martino G, D'Angelo C, et al. Cytokines, Hepatic Fibrosis, and Antiretroviral Therapy Role in Neurocognitive Disorders HIV Related. AIDS Res Hum Retroviruses 33(3): 246–53, 2017.

17. Fields J, Dumaop W, Langford TD, Rockenstein E, Masliah E. Role of neurotrophic factor alterations in the neurodegenerative process in HIV associated neurocognitive disorders. J Neuroimmune Pharmacol 9(2): 102–16, 2014.

18. Gass P, Hellweg R. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker for affective disorders? Int. J. Neuropsychopharmacol 13: 1–4, 2010.

19. Gouni-Berthold I, Berthold HK, Huh JY, Berman R, Spenrath N, Krone W, et al. Effects of lipid-lowering drugs on irisin in human subjects in vivo and in human skeletal muscle cells ex vivo. PLoS One 8(9): e72858, 2013.

20. Lamina S, Ezugwu U, Nwankwo M, Amaeze A, Ezema C, Onwunali A. Effect of aerobic exercise training on cardiovascular parameters and CD4 cell count of people living with human immunodeficiency virus/acquired immune deficiency syndrome: A randomized controlled trial. Niger J Clin Pract 17(5): 543, 2014.

21. Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. Nat Rev Neurosci 6(8): 603–14, 2005.

22. Mamiafo C, Moor VJ, Nansseu JRN, Pieme C, Tayou C, Yonkeu J. Hyperlactatemia in a group of HIV patients living in Yaounde-Cameroon. AIDS Res Ther 11(1): 2, 2014.

23. Molendijk ML, Spinhoven P, Polak M, Bus B.A, Penninx BWJH, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N = 9484). Mol. Psychiatry 19: 791–800, 2014.

24. Murawska-Cialowicz E, Wojna J, Zuwala-Jagiello J. Crossfit training changes brain-derived neurotrophic factor and irisin levels at rest, after wingate and progressive tests, and improves aerobic capacity and body composition of young physically active men and women. J Physiol Pharmacol 66(6): 811–21, 2015.

25. Navalta JW, Stone WJ, Lyons TS. Ethical Issues Relating to Scientific Discovery in Exercise Science. Int J Exerc Sci 12(1): 1-8, 2019.

26. Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RC. Decrease Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. Int J Mol Sci 10: 20(2), 2019.

27. Oral E, Canpolat S, Yildirim S, Gulec M, Aliyev E, Aydin N. Cognitive functions and serum levels of brain-derived neurotrophic factor in patients with major depressive disorder. Brain Res Bull 88: 454-59, 2012.

28. Ost M, Coleman V, Kasch J, Klaus S. Regulation of myokine expression: Role of exercise and cellular stress. Free Radic Biol Med 98: 78-89, 2016.

29. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Exp Physiol 94(12): 1153–60, 2009.

30. Pérez-Matute P, Pérez-Martínez L, Blanco JR, A.Oteo J. Role of Mitochondria in HIV Infection and Associated Metabolic Disorders: Focus on Nonalcoholic Fatty Liver Disease and Lipodystrophy Syndrome. Oxid Med Cell Longev. 2013: e493413, 2013.

31. Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. J. Affect. Disord 174: 432–440, 2015.

32. Prestes J, da Cunha Nascimento D, Tibana RA, Teixeira TG, Vieira DCL, Tajra V, et al. Understanding the individual responsiveness to resistance training periodization. Age (Omaha) 37(3): 55, 2015.

33. Qiu S, Cai X, Sun Z, Schumann U, Zügel M, Steinacker JM. Chronic Exercise Training and Circulating Irisin in Adults: A Meta-Analysis. Sport Med 45(11): 1577–88, 2015.

34. Roca-Rivada A, Castelao C, Senin LL, Landrove MO, Baltar J, Crujeiras AB, et al. FNDC5/Irisin Is Not Only a Myokine but Also an Adipokine. PLoS One. 28(4): 1–10, 2013.

35. Sharma B. Oxidative stress in HIV patients receiving antiretroviral therapy. Curr HIV Res 12(1): 13-21, 2014.

36. Soubelet A, Salthouse TA. Correlates of level and change in the Mini-Mental State Examination. Psychol Assess 23(4): 811–8, 2011.

37. Srinivasa S, Wong K, Fitch K V, Wei J, Petrow E, Aaron M, et al. Effects of lifestyle modification and metformin on irisin and FGF21 among HIV-infected subjects with the metabolic syndrome. Clin Endocrinol (Oxf) 82(5): 678–85, 2016.

38. Trombeta JCS, Vieira-Junior RC, Fernandes TAB, Rubim CC, Prestes J, Voltarelli FA. Parâmetros bioquímicos e cinética de lactato sanguíneo de sujeitos HIV+ submetidos ao treinamento físico combinado. Rev Bras Educ Física e Esporte 29(4): 519–34, 2015.

39. Wrann CD, White JP, Salogiannnis J, Laznik-bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab 18(5):649–59, 2014.

40. Xu B. BDNF (I)rising from Exercise. Cell Metab 18(5): 612–4, 2013.

41. Zhu D, Wang H, Zhang J, Zhang X, Xin C, Zhang F, Lee Y, Zhang L, Lian K, Yan W, Ma X, Liu Y, Tao L. Irisin improves endothelial function in type 2 diabetes through reducing oxidative/nitrative stresses. J Mol Cell Cardiol 87: 138-47, 2015.