Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia

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HIGHLIGHTS

- The concurrent exercise protocol reduced body mass and BMI in SZ individuals.
- The intervention induced short and long-term histone H4 hypoacetylation status.
- The levels of cortisol and IL-4 remain unchanged after exercise intervention.
- A remarkable reduction was found in IL-6 levels 60 and 90 days after intervention.
- Diminished IFN-γ levels were observed in the 90 days period.

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ABSTRACT

The present study aimed to investigate the short and long-term effects of a concurrent exercise protocol on global histone H4 acetylation levels and inflammatory markers (interleukin-4 (IL-4), interleukin-6 (IL-6), interferon gamma (IFN-γ) and cortisol) in phytohemagglutinin-stimulated peripheral blood mononuclear cells (PBMC) and in peripheral blood of patients with schizophrenia (SZ), as well the intervention impact on anthropometric characteristics. Seventeen individuals were submitted to the intervention three times a week and blood samples were collected pre, 30, 60 and 90 days after the intervention started. A remarkable reduction on body mass index and body mass were observed following intervention. The protocol also induced a histone H4 hypoacetylation status in PBMC all times evaluated when compared to the pre intervention period. Although the IL-4 and cortisol levels were not altered in response to the intervention, a reduction in IL-6 production during the 60 and 90 days compared to the pre intervention period was observed. Finally, diminished IFN-γ production was found in the 90 days period compared to the pre intervention and 30 days after periods. In addition, systemic IL-6 levels were lower at 60 and 90 days compared to the pre intervention. The concurrent exercise protocol was able to improve anthropometric characteristics in patients with SZ, engaging the modulation of cytokine and histone H4 acetylation levels.

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1. Introduction

Approximately 1% of the world's population is affected by schizophrenia (SZ), a chronic and debilitating neurodevelopmental disorder [1,2]. Despite its unknown physiopathology, several lines of evidence have pointed out the pivotal role of immune-inflammatory pathway activation and dysregulation [3–7]. It has been reported markedly elevated levels of pro-inflammatory cytokines, including interleukin-12 (IL-12), interleukin-6 (IL-6), interferon-γ (IF-γ) and tumor-necrosis factor alpha (TNF-a) [7–9] as well decreased levels of anti-inflammatory interleukin-4 (IL-4) in peripheral blood from SZ patients compared to healthy controls [10]. In addition, an abnormal cytokine production by stimulated peripheral blood mononuclear cells (PBMCs) in vitro from schizophrenic patients was reported in association with altered expression of pro-inflammatory genes, such as IL-6 gene [11–13].

Moreover, emerging experimental and clinical evidences also suggest the imbalance of epigenetic machinery on SZ physiopathology and progression [14–18]. Epigenetic modifications are caused by external environment and act on DNA and histone proteins to rearrange

chromatin conformation to alter gene expression [19]. Histone acetylation, an important epigenetic marker, it is controlled by histone acetyltransferases (HAT) and histone deacetylases (HDAC) enzymes, which are related to enhanced and reduced transcriptional activity, respectively [19]. Analysis of peripheral blood cells and/or buccal mucosa of ZS patients revealed an association of specific HDACs genes with schizophrenia [14]. In addition, it is also suggested that HDAC could modulate chromatin structure in specific brain regions that are affected in patients with SZ [18], demonstrating a central and peripheral imbalance on histone acetylation status in this population. Interestingly, the histone acetylation is implicated in the inflammatory responses [9,20–25].

The patients with SZ usually adopts a sedentary lifestyle, which has been partly associated with the increase in obesity incidence rates, metabolic syndrome, type 2 diabetes and coronary heart disease [26,27]. On the other hand, exercise, a non-invasive and low cost intervention, has been considered an important additional therapeutic option for this population, promoting benefits to physical and mental health [28,29].

It is well established that different regular exercise programs increase muscle strength, [30] improve functional and cardiorespiratory fitness [31,30], significantly reduce body weight [32,33], improve the quality of life [34] and cognitive performance in patients with SZ [35]. Despite these clinical findings, mechanistic studies regarding the impact of exercise in SZ patients are scarce.

Recent studies indicate a link between the epigenetic modulation and improvement of general health in both healthy individuals and in pathological situations [36–39]. Furthermore, our research group has demonstrated that the anti-inflammatory effects of exercise in obese individuals engage changes on HDAC levels [40]. Still, it was recently reported that a single exercise session is able to modulate histone H4 acetylation levels and cytokine profile in cancer patients [41]. However, no studies have been investigating this interaction in patients with SZ until the present moment.

Finally, it is known that the outcomes of exercise may vary depending on the type, intensity, duration and time after training [42,43]. Specifically regarding the modulation of histone acetylation status following exercise, experimental studies have been reporting different responses when the rats were submitted to a single session or a chronic protocol, as well when the measurements are done immediately or days/hours after training [44–46]. For instance, Elsner and colleagues [44] showed that a single session of exercise (20 min) in a treadmill increased HAT and decreased HDAC activities immediately and 1 h after exercise in young adult rat hippocampus, without any effect 18 h after. Furthermore, these enzymes remain unaltered in response to the chronic exercise protocol (20 min/day during 2 weeks). It was also showed that the chronic exercise protocol increased the global histone H4 acetylation levels in hippocampi from aged rats 1 h after training with no changes 18 h, 3 and 7 days after [46]. Taken together, these findings suggest a time window of exercise impact on histone acetylation status. However, clinical data concerning the short- and long-term impacts of exercise on epigenetic biomarkers are poorly investigated.

Therefore, this study aimed to evaluate the effect of a concurrent exercise protocol on global histone H4 acetylation levels and inflammatory markers (IL-4, IL-6, IFN-γ, cortisol) in peripheral blood of SZ patients in different time-points: 30, 60 and 90 days after the intervention began.

2. Methods

2.1. Subjects

Twenty-five individuals with SZ diagnostic of both genders were invite to participate in the study. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction. For a diagnosis, symptoms must have been present for six months and include at least one month of active symptoms. DSM is the manual developed by The American Psychiatric Association (APA) used by clinicians and researchers to diagnose and classify mental disorders [47].

All participants were recruited at the Associação Gaúcha de Familiares de Pacientes Esquizofrênicos (AGAFAPE). Inclusion criteria were as follows: should have schizophrenia according to the diagnostic criteria of DSM-V; 18–50 years; in medical treatment and regular use of medication for their illness; not be in a psychotic crisis, not be making use of alcohol and other drugs; not physically active (does not regularly exercise or engage any physical activity program during the past six months) and agreed to sign the Instrument of Consent. The exclusion criteria adopted for participation in the study were the presence of musculoskeletal and joint disorders that made it impossible to carry out physical exercise; individuals with a history of autoimmune disease; cancer and cardiovascular complications and/or have medical contraindications.

This study was approved by the Research Ethics Committee of the Methodist University Center-IPA (number 1.243.680/2015) and all experimental procedures were performed in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

2.2. Concurrent exercise protocol

A concurrent exercise protocol, i.e., the combination of aerobic and resistance training was used, which has been shown to improve physical health and fitness. This program followed the recommendations of the American College of Sports Medicine [48] and lasted for three months (90 days).

Aerobic training was composed by 20 min walking at 60% of maximal cardiorespiratory capacity. Anaerobic training was composed by resistance exercises (described below), 3 sets of 15 repetitions, loads were adjusted so that individuals could not perform >15 repetitions.

The participants trained thrice weekly and each session lasted approximately 1 h. All sessions were monitored and supervised by an exercise physiologist to ensure the safety of participants. Also, the participants received constant verbal motivation during the training and were asked to adhere to their regular diet throughout the intervention course.

Initially, the participants underwent a week of adaptation, characterized by the same exercises described below in training, but in a light intensity corresponding to 40% effort of the maximum cardiorespiratory capacity controlled by the scale of perceived exertion (Borg). The adaptation week was intended to instruct the correct technique of performing the exercises. The other sessions were divided into initial warming-up period (5 min), localized muscular resistance exercises (30 min), walk (20 min), and ended with stretching (5 min).

The exercises performed sought to understand the major muscle groups in aerobic and anaerobic activities. The exercises developed were squats without weights, biceps curls, shoulder lateral raise, plantar flexion, hip abduction, knee extension, back extension, abdominals curls and 20-minute walk as mentioned above. For each exercise, there were three sets of 15 repetitions each. The intensity was controlled over the range of perceived exertion (Borg), which was used to add weights to the exercises, adjusted to maintain the maximum strain in 15 repetitions as well as the speed of walking in order to keep an effort of 60% of maximal cardiorespiratory capacity.

Adherence/frequency to the intervention was measured by attendance in each session.

2.3. Experimental design

In order to evaluate the short- and long-term effects of the concurrent exercise program on the peripheral levels of global histone H4

acetylation and inflammatory markers, blood samples were taken (15 mL) in the antecubital region of individuals in 4 times: before the exercise program (pre), 30, 60 and 90 days after the intervention started. Subjects were instructed to avoid strenuous physical exertion and alcohol or caffeine in a 24-hour period prior to blood collections.

2.4. Sample procedure

To carry out the analysis mentioned above, the venous blood collected was stored in tubes with EDTAK3. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized blood by gradient concentrations with Ficoll-Histopaque 1077 (Sigma, USA) as described by Bicalho et al. [49]. Cell viability was assessed by Trypan Blue exclusion and viability was always >95%. Then, 1×10^6 cells/mL were suspended in Roswell Park Memorial Institute (RPMI-1640, Sigma, USA) medium supplemented with L-glutamine (2 mM), 0.5% gentamicine, 1% glutamine, 1% hepes, 0.1% fungizone, and 10% fetal calf serum (all from Sigma). Cells were stimulated with 3% phytohemmaglutinin (PHA, GICBO, USA) for 24 h at 37° and 5% CO_2. After culture period, cells were collected, washed in phosphate-saline buffer (PBS) and frozen at −80 °C for later analysis of global histone H4 acetylation levels. In addition, supernatants from cell culture were frozen at −20 °C for cytokine determination.

2.5. Global histone H4 acetylation levels measurement

The global histone H4 acetylation levels in PBMCs were determined using the Global Histone H4 Acetylation Assay Kit (Colorimetric Detection, catalog number P-4009, EpiQuik USA) according to the manufacturer's instructions. The samples were incubated with the capture antibody followed by incubation with detection antibody. Afterwards, they were incubated with a developing solution followed by the addition of Stop Solution. The absorbance was measured on a spectrophotometer at a wavelength of 450 nm. The global histone H4 acetylation levels in PBMCs were expressed as ng/mg protein. The protein concentration of each sample was measured by the Coomassie Blue method using bovine serum albumin as standard [50].

2.6. Cytokine determination

The concentrations of IL-4, IL-6 and IFN-γ in the supernatants of PBMCs as well as in plasma samples were stimulated with 3% phytohemaglutinin and then evaluated by the method of Enzyme-Linked Immunosorbent Assay (ELISA) using specific kits and following the manufacturer's recommendations (Peprotech Inc., NJ, USA). Cytokine concentrations were expressed as pg/mL.

2.7. Cortisol analysis

Enzyme Immunoassay (EIA) measured plasma cortisol levels following the manufacturers' recommendations (AccuBind, California, USA). The cortisol levels were expressed as μg/mL.

2.8. Statistical analysis

After the normality (Shapiro-Wilk) and variance (Levene's) tests, data were considered parametric and presented as mean ± standard deviation. Changes in anthropometric characteristics (body mass, BMI and abdominal circumference) before and after training were evaluated through paired Student t-test. A repeated measure variance analysis was adopted to evaluate the effect of time (baseline, 30, 60, 90 days). The Bonferroni post-test was used for multiple comparisons. Significance level was set at p ≤ 0.05 and SPSS 20.0 (SPSS Inc., Chicago, USA) was used.

3. Results

A total of 25 individuals were recruited for the study. However, 10 were excluded for disagreeing to perform blood collection. During the program, no participants withdrew, and therefore 15 individuals successfully completed the 3-month intervention period (66.6% male and 33.3% female). Mean attendance to the exercise sessions was highly consistent (~97%). The sample characterization is described in Table 1.

3.1. Global histone H4 acetylation analysis

Fig. 1 highlights the effect of exercise concurrent protocol on the global histone H4 acetylation levels in PBMC of patients with SZ in different time-points: pre, 30, 60 and 90 days after the intervention started. We observed a significant reduction in this marker in all times when comparing it to the pre intervention period (p = 0.005; p = 0.007; p = 0.03, respectively), an indicative of transcriptional repression.

3.2. Inflammatory parameter measurement

As shown in Table 2, plasma IL-6 levels were significantly lower 60 days (p = 0.013) and 90 days (p = 0.021) compared to the pre intervention. In addition, there was a reduction in IL-6 production by stimulated-PBMC during the periods of 60 (p = 0.01) and 90 (p = 0.008) days when compared to the pre intervention period. Furthermore, the exercise protocol induced a reduction in IFN-γ production 90 days after intervention compared to the pre intervention (p = 0.05) and 30 days (p = 0.045) periods. However, concurrent training was not able to reduce the systemic levels of IL-4, INF-γ and cortisol or the production of IL-4 by stimulated PBMC.

4. Discussion

To our knowledge, this is the first evidence demonstrating that patients with SZ are vulnerable to epigenetic changes induced by exercise. The present study also provides important insights about exercise-modulated cytokine profiles in this population, suggesting that both epigenome and the immune system may interact to dictate the molecular mechanisms involved in the outcomes of training.

In agreement to several studies pointing out that physical activity acts as a powerful epigenetic modulator in many tissues [37–40,51,52] we showed a significant histone H4 hypoacetylation status in PBMCs following the concurrent exercise protocol, an indicative of reduced transcriptional activity and gene expression [19]. Although it is impossible to establish at this moment the exact clinical relevance of this data, we tentatively suggest that exercise could transcriptionally silence

Table 1
Sample characteristics before and after intervention.

	Before	After
Gender (female/male)	33.3%/66.6%	
Age (years)	45.80 ± 8.06	
Height (meters)	1.69 ± 0.12	
Prevalence of medications		
Antipsychotics	15 (100%)	
Antidepressants	5 (33%)	
Mood stabilizers	3 (20%)	
Benzodiazepines	3 (20%)	
Drugs for cardiovascular disease	3 (20%)	
Antiparkinsonian drugs	3 (20%)	
Other	1 (6,66%)	
Body mass (kg)	73.90 ± 13.01	53.06 ± 34.57[*]
BMI (kg/m^2)	26.02 ± 5.14	18.89 ± 12.47[*]
Abdominal circumference (cm)	83.56 ± 35.52	68.86 ± 43.66

Data presented as mean ± standard deviation (numeric data) or relative frequency (categorical data).

[*] Denote statistical differences from before physical training (p < 0.05).
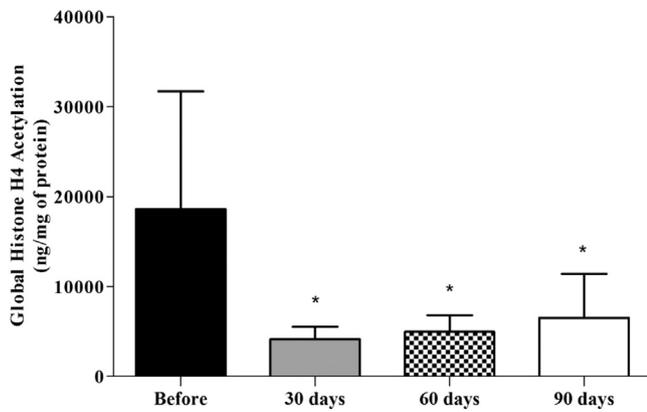
Fig. 1. Effect of the concurrent exercise protocol on global histone H4 acetylation levels in PBMCs of SZ individuals in different time-points after intervention.

genes that exert a pivotal role in the physiopathology and progression of SZ through epigenome modulation. This idea might be supported by a recent study conducted by Denham and colleagues [37], who reported that 3 months of aerobic exercise training was able to alter DNA methylation levels in sperm of young healthy men. Interestingly, they found that the genes associated with several diseases, including SZ, were hypermethylated after the intervention.

Another remarkable point to discuss is that 3 months of concurrent exercise intervention also reduced the BMI and body mass. It is known that the inclusion of aerobic exercise with strength exercises in the same session is effective in improvements in the cardiovascular risk profile in association with reduction of fat mass in obese individuals with or without mental disabilities [53,54]. Then, our study is in agreement with mounting evidence regarding the correlation between epigenetic modulation and the health phenotype benefits promoted by exercise intervention [37–40]. However, it is important to note that these authors focused their studies in evaluating DNA methylation parameters; therefore, our data supports the premise that the modulation of histone acetylation markers may also underpin the favorable health responses induced by therapeutic exercise interventions.

It was previously reported that single bouts of exercise strongly modulated histone H4 acetylation levels in peripheral blood of cancer patients [41]. Nevertheless, no studies investigating the impact of

chronic exercise exposure in this mark have been published yet. Our work presents a first approach regarding this matter. Altogether, these findings led us to infer that physical activity could alter the histone H4 acetylation status in an acute and delayed-manner.

In association with these changes in global histone H4 acetylation in PBMCs, our findings also reveals that the cytokine profile was strongly affected by the concurrent exercise training. In accordance, previous studies showed that histone H4 acetylation is a key factor for pro-inflammatory monocyte polarization induced by IFN-γ [55,9]. Histone H4 also alters the cell phenotype and cytokine pattern from acquired immunity, since activated T cells also showed histone H4 acetylation when stimulated with PHA or IL-2 in vitro [56–58]. Collectively, global histone H4 acetylation status influences both the natural and acquired immune system and the production of cytokines, such as IL-6, INF-γ and TNF-α. In this way, we found that the decrease in this epigenetic signal in PBMCs from SZ patients was accompanied by lower mitogen-stimulated IL-6 and INF-γ production by PBMCs after the intervention.

Our data corroborates previous studies demonstrating the importance of exercise training on immune system modulation of patients with SZ [59,60]. Others studies with psychiatric diseases, such as bipolar disorder and elderly individuals with mild cognitive impairment (MCI) also demonstrated the benefits of chronic physical training to attenuate inflammatory mediators [61].

In this sense, Nascimento and co-workers [62] reported that exercise training reduced TNF-α and IL-6 levels. It also showed elevations on brain-derived neurotrophic factor (BDNF) in elderly MCI. In addition, individuals who did not engage in moderate physical activity presented higher depressive symptoms, which were correlated with serum IL-6 levels [63]. The overproduction of inflammatory cytokines for immune cells inhibits the synthesis and secretion of BDNF in the hippocampus of mice [64] and in the peripheral blood [65].

Importantly, none of these studies cited above conducted with psychiatric patients who were submitted to systematic exercise training evaluated the cytokine production by stimulated PBMCs culture. Our study was the first to show that mitogen-stimulated cytokine production decreases when SZ patients engaged in concurrent training. The decrease of IL-6 and INF-γ production reveals that exercise was able to attenuate the inflammatory state of PBMCs. We used the mitogen PHA to trigger T-lymphocyte division and activation. It has been shown that PHA-induced T cells activation and proliferation is mediated through binding of CD3 cell surface molecules [66,67]. After stimulation, PBMCs cultured with PHA secreted a variety of cytokines in accordance with their inflammatory state [68,69]. Previous studies also documented that chronic exercise is able to reduce the cytokine production in peripheral tissues, such skeletal muscle and adipose tissue [70,71], as well as the pattern of cytokine production by lymphocytes incubated with two others mitogens types, CD3 or phorbol myristate acetate as a stimulating agent, [72] in healthy individuals. Interestingly, a 12-week concurrent exercise intervention was able to attenuate the production of IL-6, TNF-α and INF-γ in T-cell culture with CD3/CD28 mitogens in patients with multiple sclerosis [73]. In addition, exercised-rats with congestive heart failure had higher PHA-stimulated IL-4 production than the control group [74]. Thus, chronic exercise training causes a trend toward reversion of the cytokine production imbalance in inflammatory diseases. Concordantly, habitual physical training alters the ratio between the phenotype of T-helper cells, leading to diminished frequency of T cells expressing INF-γ [75].

In addition, concurrent training has an immunoregulatory potential, once a significant reduction on cytokine levels was reported in obese individuals who engaged in systematic concurrent exercise regime [76, 77]. It is believed that chronic exercise training might control cytokine production across the reduction of body mass, once that weight loss impairs the infiltration of pro inflammatory macrophages and T cells to adipose tissue, an important source of cytokine production [11]. Indeed, circulating leukocytes also showed lower cytokine messenger RNA expression in obese individuals after weight loss [78,79]. In addition, the

Table 2
Effect of the concurrent exercise protocol on inflammatory markers of SZ individuals in different time-points after intervention.

	Before	30 days	60 days	90 days
Plasma inflammatory markers				
IL-4 (pg/mL)	7.60 ± 3.91	9.47 ± 3.20	7.46 ± 3.93	7.84 ± 3.11
IL-6 (pg/mL)	36.65 ± 9.04	36.00 ± 7.55	30.05 ± 5.03*	29.72 ± 5.25*
INF-γ (pg/mL)	8.70 ± 2.84	9.00 ± 3.04	6.71 ± 2.61	6.72 ± 1.89
Cortisol (μg/mL)	100.28 ± 50.38	130.12 ± 90.27	100.37 ± 50.09	80.99 ± 40.60
Phytohaemagglutinin-induced cytokines				
IL-4 (pg/mL)	50.43 ± 20.89	40.08 ± 10.45	50.23 ± 20.60	40.88 ± 20.12
IL-6 (pg/mL)	60.06 ± 10.21	50.03 ± 10.98	40.46 ± 20.06*	40.19 ± 10.35*
INF-γ (pg/mL)	120.08 ± 10.95	120.25 ± 10.82	110.70 ± 10.77	110.29 ± 10.16*,†

Data presented as mean ± standard deviation. IL, interleukin; INF-γ, interferon-gamma.
* Denotes statistical difference when compared with before of exercise training (p < 0.05) (ANOVA repeated measurements).
† Denotes statistical difference when compared with 30 of exercise training (p < 0.05) (ANOVA de repeated measurements).

expression of nuclear factor kappaB (NF-Kb) on PBMCs of obese individuals, a pivotal protein complex that controls transcription of DNA related to inflammatory events, has diminished after a 12-week intervention [79]. As mentioned above, our sample also reduced body mass and BMI significantly after the intervention. Therefore, these findings support the idea that physical exercise is able to control the pro inflammatory state of PBMCs through reduction in body mass. In this way, the reduction of serum IL-6 can be attributed at least in part due to attenuation in the PBMC activation and the reduction of fat mass. At rest, approximately 30% of circulating IL-6 arises from the adipocytes and adipose tissue-resident macrophages [80], and exercised individuals had progressively less IL-6 secreted from adipose tissue [81]. Corroborating with our data, weight loss mediated by exercise training can reduce the inflammatory milieu of adipose tissue, where a correlation between decrease in circulating levels of cytokines and attenuated expression of cytokines in adipose tissue was found [82,83].

In this context, the management of body weight status may be an important focus for controlling the inflammatory state, since obese patients with SZ display higher levels of TNF-α and IL-1β in the supernatant of cultured PBMCs than lean SZ patients [84]. However, no previous study has documented the cytokine production response to physical training in patients with SZ. In this line, our group was the first to demonstrate a decrease of INF-γ production and maintenance of IL-4 production by stimulated PBMCs after the training period in SZ patients. Our data can be related to those obtained by Golzari and colleagues [85] who showed that 8 weeks of combined exercise training reduces INF-γ production without changes on IL-4 production in women with multiple sclerosis.

The lack of changes on IL-4 production after exercise training in our study was similar to those found in previous studies with healthy [86, 87] and ill patients [84]. Indeed, it was postulated that the changes in IL-4 and other type 2 cytokines are linked with the intensity of physical training [88].

Confirming this, Balducci and colleagues [89] showed that high-intensity exercise, but not moderate-intensity exercise, was effective in decreasing the systemic levels of IL-4 and IL-10 after 12 months of physical training in type 2 diabetes patients. However, more studies are needed to clarify the impact of physical training on the balance of cytokine production in psychiatric disorders, including SZ.

It is known that glucocorticoid concentrations decrease after a period of exercise training [90,91]. Surprisingly, no changes on cortisol levels were observed in the present study. A possible factor that could justify this response is that people suffering from SZ or bipolar disorder had higher cortisol [92] and the hyper activity of hypothalamic-pituitary-adrenal (HPA) axis is one of the causes for the progression of these conditions [93]. However, evidences about the HPA axis control across the exercise training are scarce. Plag and colleagues [94] showed that cortisol reactivity was reduced only after 7-months of endurance training in patients suffering from panic disorder. Thus, we may suggest that 90 days of physical training is insufficient to reduce cortisol levels, and possibly a longer period of training is necessary to influence the HPA axis.

It is important to note that the patient's attendance to the intervention in the present study was highly significant. Our data are in accordance with other studies based on structured, supervised and group-based exercise programs [95–97]. Taken together, these findings support the idea that interventions with this profile might result in best treatment adherence compared to those characterized as non-structured and non-group-based [98].

Finally, all SZ patients included in our study used pharmacological treatment, which could have influenced the effect of exercise on the evaluated biomarkers. However, this limitation is inevitable regarding interventions with psychiatric patients. In fact, this limitation are present in the majority studies conducted with this population [33,95, 99] since the medicaments are integral part of psychiatric patient management.

5. Conclusions

Summarizing, our data presents a first attempt to bridge the gap between exercise-induced epigenetic and inflammatory changes in patients with SZ. When combining this data, it appears entirely possible that the improvement in anthropometric characteristics after intervention is related, at least in part, to the histone H4 hypoacetylation status and the reduction on anti-inflammatory cytokines IL-6 and INF-γ levels.

Notably, the present study should be considered within the context of its limitations. First, we measured only one epigenetic mark: global histone H4 acetylation levels. Thus, it is recommended that future studies should consider the modulation of other parameters that could epigenetically respond to exercise, such as histone H3 acetylation levels, modifications in histone methylation status and miRNA regulation as well as the expression of specific genes. These findings might contribute to elucidate the complete and exact epigenetic pathways involved to the exercise effects in SZ patients. Another limitation is the pre-post intervention design used and the absence of a control group. We believe that our findings will encourage future investigations with a larger sample, which could include a control group which could enable verify other issues such as the influence of gender and age on epigenetic modulation in response of exercise in patients with SZ.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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