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High- and moderate-intensity training modify LPS-induced *ex-vivo* interleukin-10 production in obese men in response to an acute exercise bout

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ABSTRACT

The aim of this study was to evaluate the inflammatory (peripheral and lipopolysaccharide (LPS)-stimulated released from whole blood) and metabolic (glucose and insulin) profile of inactive obese men in response to two isoenergetic models of aerobic exercise training (~300 kcal each exercise session). Twenty-two participants (28.7 ± 1.6 years; BMI = 34.4 ± 0.1 kg/m^2) were randomized into two groups: I) HIIT: high-intensity interval training (10× 1 bout: 1 min − 100% Maximal Aerobic Velocity) or II) MICT: moderate-intensity continuous training (65% Maximal Aerobic Velocity; kcal equal to HIIT). Both groups trained three times per week for *6-weeks*. Fasting blood samples were collected before and 0, 30, and 60 min after exercise during the first and last training sessions for evaluation of: I) MIP-1α, insulin, glucose, visceral and subcutaneous fat depots, oral glucose tolerance test, and homeostatic model assessment of insulin resistance (HOMA-IR) index; II) Peripheral (TNF-α, IL-6, and IL-10) and LPS-stimulated release of TNF-α and IL-10 were analyzed before, 0, and 60 min after sessions. IL-6 concentration remained elevated up to *60*-min after the acute exercise session ($p < 0.001$), and IL-10 concentration was higher after 30 and *60*-min ($p = 0.001$) compared to rest, independent of training period and protocol. AUC of IL-10 presented effect of type of training ($p = 0.023$) with MICT group showed significantly higher values than the HIIT. The *ex-vivo* assay showed higher IL-10 secretion in response to LPS immediately ($p = 0.003$) after both acute MICT and HIIT exercise sessions, independent of training period. Fifteen subjects presented decreased HOMA-IR after *6-weeks* and seven presented an increase in this index. When we excluded the two least responsive subjects, it was possible to observe a decrease in HOMA-IR ($p = 0.020$) after training. Taken together, our results suggest that both HIIT and MICT (with same energy expenditure) promote similar effects on HOMA-IR and led to elevations in IL-10 production in LPS-stimulated whole blood, suggesting that leukocytes had an enhanced ability to secrete anti-inflammatory cytokines after the exercise bout.

1. Introduction

Obesity is associated with low-grade inflammation, characterized by chronic low-level production of pro-inflammatory cytokines [18]. The initiating events are hypothesized to involve monocyte infiltration to adipose tissue and polarization to a pro-inflammatory classical macrophage "M1" phenotype [18]. Increased production of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) from obese macrophage-resident adipose tissue is thought to spill over into the circulation, exposing other tissues to a chronic inflammatory state [30,32]. In addition to inflammation initiated by adipose tissue, obesity is also linked to gut barrier and microbiome disruption, especially due to high-calorie and high fat food intake, which have been shown to promote a metabolic endotoxemia state, characterized by increased concentrations of circulating lipopolysaccharides (LPS), which through binding to *toll-like* receptors (TLR)

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type 4 (TLR4) on immune cells trigger some inflammatory transcriptional factors such as nuclear factor *kappa* B (NF-κB) [4,14], perpetuating an inflammation condition. In addition, obesity is now recognized as an immunometabolic disease, and increased inflammatory mediators lead to a state of disturbance in several metabolic processes, such as insulin resistance and dyslipidemia, in obese subjects [18].

In this context, aerobic training is recognized as a non-pharmacological anti-inflammatory intervention, which induces morphological (decreased body fat), physiological (increased cardiorespiratory fitness), and metabolic (decreased insulin resistance) adaptations as a response to long-term exercise training [12,16]. Although it is possible to observe these anti-inflammatory improvements after chronic aerobic training, it should be borne in mind that these outcomes are related to acute responses from each exercise session which, at the end of the training period, result in these benefits. Therefore, understanding immunometabolic acute mechanisms of aerobic exercise could help to elucidate chronic anti-inflammatory effects of aerobic training.

It is known that the acute cytokine modulation from an exercise bout is characterized by increased concentrations of IL-6 and IL-10, which induce an anti-inflammatory state [26], while also favoring lipolysis and fat oxidation [34], primarily in visceral depots [36]. In addition, an exercise bout is able to up-regulate anti-inflammatory gene expression [1] and change circulating cytokine release [3], however these studies did not evaluate the impact of chronic aerobic training on acute immunometabolic responses to an exercise bout, as well as which these studies did not use equalized load/volume exercise protocols to better understand the influence of training models.

Only a few short-term studies have examined immune cell and inflammatory parameters following high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT). Robinson et al. [29] showed that ten sessions of HIIT or MICT over *2-weeks* reduced the cell surface protein expression of TLR4 in monocytes and lymphocytes. Furthermore, Barry et al. [6] demonstrated decreases in the percentage of monocytes positive for C-C motif chemokine receptor (CCR2) after MICT, whereas HIIT increased the percentage of $CD14^+$ monocyte expression of the cysteine-cysteine chemokine receptor 5 (CCR5). Both studies demonstrated these short-term alterations in immune cells in the absence of changes in body fat, blood cytokines, and chemokine concentrations. Therefore, there is still no consensus on the effects of HIIT compared to MICT on inflammatory and immunological parameters of inactive individuals. Furthermore, other studies have shown no effects of MICT or HIIT on systemic inflammation in obese individuals [5,7].

However, all of the above mentioned studies measured *in vivo* circulating levels of inflammatory mediators. The current study design analyses the influence of several tissues and cells (i.e., monocytes, adipocytes, endothelial, and muscle cells) in generating circulating inflammatory cytokines. The *ex vivo* stimulation of isolated immune cells, such as monocytes, may permit a more precise estimation of the effects of exercise on leukocyte-related inflammation. Thus, *ex vivo* immune stimulation with LPS, a classical TLR4 agonist, may more accurately reflect immune regulation than the analysis of cytokine levels in peripheral blood. The aim of this study was to evaluate the inflammatory (peripheral and release from LPS-stimulated whole blood) and metabolic (glucose and insulin) profile of inactive obese men in response to two isoenergetic models of aerobic exercise training (~300 kcal each exercise session). We hypothesized that exercising with the same energy expenditure would promote similar changes in the parameters evaluated in both groups.

2. Methods

2.1. Subjects

This study is part of the main study "The impact of two Models of Aerobic Training on Cognitive Function, and Morphological and Systemic Immunometabolic Changes in Young People with Obesity" (RBR-7pdc8y), which is in accordance with the Helsinki Declaration and was approved by the Research Ethics Committee of the Faculty of Science and Technology from Universidade Estadual Paulista (FCT-UNESP) of Presidente Prudente city (CAAE: 46948215.8.0000.5402). Participants between 18 and 35 years old and BMI $\geq$ 30 kg/m^2 were invited to visit the FCT-UNESP laboratory, to be informed of the details of this research and the subsequent interview/screening process. Only healthy inactive individuals (not systematically engaged in physical activities), non-smokers, and non-alcohol abusers ($\leq$30 g/day) were recruited. A total of 172 individuals were enrolled and, of these, 57 were able to participate in this study. After signing the free and informed consent form, each participant was referred to a cardiologist, and only individuals approved by the medical report remained in the project. After this procedure, participants were randomized according to visceral fat (VF) and maximal oxygen uptake ($\dot{V}O_2$max) into three different groups: Moderate-intensity continuous training (MICT), High-intensity interval training (HIIT), and (Control) (VF-MICT = 5.82 ± 2.65 cm; HIIT = 6.05 ± 1.63 cm; Control = 6.81 ± 1.85; p = 0.364, VO_2max-MICT = 34.80 ± 4.96 mL·kg^{-1}·min^{-1}; HIIT = 34.00 ± 4.29 mL·kg^{-1}·min^{-1}; Control = 35.02 ± 4.24 mL·kg^{-1}·min^{-1}; p = 0.808). However, since the aim of the present study was to compare two types of aerobic intensity, the Control group was excluded from this detailed immunological substudy. Thus, the sample consisted of 22 participants (HIIT = 11; MICT = 11). All volunteers were instructed to maintain their habitual dietary habits and daily physical activity during the exercise training period.

2.2. Study design

All participants performed a maximal incremental test on a treadmill (Inbramed - ATL, Brazil) for quantification of $\dot{V}O_2$max and maximal aerobic velocity (MAV). The protocol consisted of a warm-up of *7*-min at 5.0 km/h followed by increments of 0.5 km/h per minute until voluntary exhaustion. The treadmill inclination remained constant at 1% throughout the test. Gas exchange was obtained breath-by-breath with a gas analyzer (Quark PFT, Cosmed®, Rome, Italy) and was averaged over the final 20 s of each stage. The highest value was assumed as $\dot{V}O_2$max.

The MAV was considered as an intensity reference for the HIIT (100% MAV) and MICT (65% MAV) sessions. At the end of the third week of training (9th session), this evaluation was repeated for possible intensity readjustment for the final three weeks of the intervention period.

2.3. Abdominal fat measurements

The parameters and methods for determination of visceral and subcutaneous fat (SF) were based on previously described procedures presented by Ribeiro-Filho et al. [28]. The ultrasonography method was used to quantify these variables (TOSHIBA-Eccocee, convex transducer of 3.7 MHz, Tokyo, Japan). An experienced physician in an institution specialized in imaging diagnostics performed the measurements.

2.4. Exercise training protocols

The exercise training was performed three times a week during six weeks (*3x/week–6-weeks*).

HIIT: The volume was the same for all participants in this group. Ten efforts of *1*-min at 100% MAV interspersed with a *1*-min passive interval (10 × 1:1 min).

MICT: In this group the volume was individualized according to the energy expenditure of a previous HIIT session, as described in Gerosa-Neto et al. [17]. Each participant performed the session at 65% MAV in the time necessary to achieve the caloric expenditure demanded in the HIIT session.

2.5. Blood samples and analysis

Blood samples were collected at five time points: 1) Fasting (12 h); 2) Pre-Exercise (rest – 90 min after standardized breakfast); 3) Post-Exercise (immediately); 4) 30 min and 5) 60 min after the session. This procedure occurred in the first (1st) and last (18th) training sessions of the intervention period. These sessions are referred to as A*cute sessions*.

The samples were obtained by venipuncture of an antecubital vein and the fasting collections were performed 12 h after the last meal. The total blood volume was 8.5 mL for serum (Gel BD SST® II Advance®), 10 mL for plasma (EDTA K2), and 4 mL for glucose analysis (Fluoride/EDTA). The tubes (Becton Dickinson) were then centrifuged at 3000 rpm for 15 min at 4 °C and the aliquots stored at − 80 °C until analysis.

2.6. Whole blood stimulation with lipopolysaccharide ex-vivo

For whole blood stimulation, a similar protocol to that proposed by Abbasi et al. [1] was adopted. Six milliliters of blood sample were collected and separated into two tubes containing K2 – EDTA. Both tubes received stimulation with 3uL of LPS (Escherichia coli, type: 0111: B4, Sigma, St. Louis, MO) with a final concentration of 10 ng/mL diluted with RPMI. The tubes were incubated for 1 h at 37 °C, with slow and constant rotation, and immediately after incubation, the tubes were centrifuged at 3000 rpm for 15 min at 4 °C to obtain the plasma. The aliquots were stored in polypropylene microtubes at − 80 °C until analysis.

2.7. Oral Glucose Tolerance Test (OGTT)

Seven participants from the MICT group and nine from the HIIT group performed the oral glucose tolerance test (OGTT), after 12-h overnight fasting. After oral ingestion of 75 g of glucose, the plasma glucose level was measured at 15, 30, 45, 60, 90, 120, and 180 min. The total areas under the glucose curves during the first two hours were calculated according to the trapezoidal rule, and 2 to yield the mean plasma glucose during the OGTT divided these areas. The area under the curve (AUC) was calculated pre and post *6-weeks* of training in both groups (MICT and HIIT).

Studies have demonstrated that a 1-h post-load plasma glucose > 155 mg/dL during the OGTT was associated with increased insulin resistance and kidney disease, as well as decreased beta-cell function, cardiovascular disease, type 2 diabetes *mellitus,* and mortality [9,19]. Therefore, this point of the curve was also analyzed in the current study.

2.8. Blood analysis

From plasma obtained by whole blood stimulation with LPS, the concentrations of TNF-α and IL-10 at rest were analyzed, immediately post-exercise, and 30 min and 60 min after the end of exercise, using commercial kits (Thermo Fisher, Affymetrix, Inc., CA, USA) with sensitivity of 15.6 to 1000 pg/mL and 7.81 to 1000 pg/mL for TNF-α and IL-10, respectively.

From serum obtained by peripheral blood samples, the concentrations of TNF-α, IL-10, IL-6, and MIP-1α were analyzed at rest -, immediately post-exercise, and 30 min and 60 min after the end of exercise, using kits (Quantikine ELISA; R&D Systems, Inc., MN, USA) with high sensitivities of 15.6 to 1000 pg/mL, 3.13 to 300 pg/mL, 7.8 to 500 pg/mL, and 15.6 to 1000 pg/mL for TNF-α, IL-6, IL-10, and MIP-1α, respectively. The IL-10/IL-6 and IL-10/TNF-α index was calculated in order to determine the inflammatory status using IL-6, IL-10, and TNF-α in peripheral blood. The AUC was obtained by calculating the integral using the trapezoid method, using blood concentrations in the four collection moments of the acute session.

The concentration of insulin was analyzed by the ELISA method using commercial kits (Monobind Inc., USA) and glucose was analyzed by a colorimetric kit (Labtest®, Brazil). The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated according to the formula: (glucose [mmol/L] × insulin [μIU/mL]/22.5) [24].

2.9. Statistical analysis

Descriptive data are shown as mean and standard deviation and data normality was verified using the Shapiro-Wilk test. In addition, the independent Student *t* test was used for comparison of the descriptive variables (age, BMI, VF, and SF) and percentage changes (Δ%) in metabolic (glucose, insulin, HOMA-IR, and 1 h OGTT) and inflammatory (MIP-1α, IL-10, IL-6, TNF-α, IL-10/IL-6, and IL-10/TNF-α) variables pre and post-training. Analysis of variance (ANOVA) with repeated measures, with Sidak adjustment for multiple comparisons was used to compare the inflammatory and metabolic responses to acute exercise sessions according to training period (pre- and post-*6-weeks*), and time of measurement of the collection of the blood samples in the acute session (at rest, immediately, and 30- and 60-min post-exercise) with adjustment for type of training. Mauchly's sphericity test was used to test this assumption, and a Greenhouse–Geisser correction applied when necessary. The AUC of OGTT, IL-6, IL-10 and TNF-α between the type of training and time also was by analysis of variance with repeated measures. Statistical significance was set at 5% for all analysis and the calculations were conducted using SPSS, version 25.0 (SPSS Inc. Chicago. IL).

3. Results

Twenty-two participants performed all assessments before and after *6-weeks* of training. Table 1 presents the characteristics of participants and mean values of both groups.

The baseline values of MIP-1α, IL-6, IL-10, TNF-α, IL-10/IL-6, IL-10/TNF-α, glucose, insulin, HOMA-IR, and 1 h OGTT pre and post *6-weeks* of training presented no differences (Table 2). However, after 1-h, glucose concentrations in both groups were already below 155 mg/dL during the OGTT pre and post-training.

In Fig. 1, it is possible to observe the responsiveness of subjects to training, regardless of the group. In total, 15 subjects presented decreased HOMA-IR after 6-*weeks* and seven presented increases in this index. Thus, when we excluded the two least responsive subjects, it was possible to observe a decrease in HOMA-IR index ($p = 0.020$). The two least responsive subjects to HOMA-IR obtained similar responses for IL-6 and IL-10 concentrations after 6-*weeks* of training, with an increase in IL-10 (%), but a decrease in IL-6 (Δ%).

The AUC for blood glucose during OGTT in the MICT (AUC pre = 789.9; AUC post = 760.7) and HIIT groups (AUC pre = 782.32; AUC post = 801.8) were analyzed. There was no difference in OGTT between MICT and HIIT ($F = 0.026$; $p = 0.874$; partial $\eta^2 = 0.002$) and the pre- and post-training periods ($F = 0.571$; $p = 0.461$; partial $\eta^2 = 0.037$) (Supplementary Fig. 1). The non-stimulated concentrations of MIP-1α, IL-6, IL-10, TNF-α, IL-10/IL-6, and IL-10/TNF-α at rest, immediately, and 30 min and 60 min after the exercise are presented in Table 3. The MIP-1α, IL-10/TNF-α, and glucose did not present any

Table 1
Characteristics of participants and mean values of both groups.

	HIIT (n = 11)	MICT (n = 11)	*p-value*
Age (years)	27.5 (6.9)	29.8 (4.0)	0.357
BMI (kg/m^2)	34.3 (2.9)	34.5 (3.4)	0.932
VF (cm)	5.9 (1.7)	6.7 (1.9)	0.312
SF (cm)	2.9 (0.8)	2.7 (0.5)	0.450

Values are mean (standard deviation); HIIT = High-intensity interval training; MICT = Moderate intensity continuous training, BMI = Body mass index; VF = Visceral Fat; SF = Subcutaneous Fat.

Table 2
Fasting metabolic and inflammatory responses, *pre* and *post* training in high-intensity interval training and moderate intensity continuous training.

		Pre-training	Post-training	Δ%	*p-value*
MIP-1α (pg/mL)	**HIIT**	225.6 (232.8)	183.4 (219.6)	−17.3 (37.0)	0.208
	MICT	279.1 (241.6)	280.8 (229.7)	56.7 (185.0)	
IL-6 (pg/mL)	**HIIT**	1.5 (0.4)	1.7 (0.8)	24.2 (53.5)	0.124
	MICT	2.7 (3.3)	1.7 (0.6)	−6.3 (33.3)	
IL-10 (pg/mL)	**HIIT**	3.2 (0.3)	3.7 (1.3)	14.3 (35.8)	0.567
	MICT	4.6 (2.0)	4.9 (2.7)	6.2 (26.7)	
TNF-α (pg/mL)	**HIIT**	5.9 (1.2)	5.4 (0.9)	−1.4 (23.0)	0.820
	MICT	5.5 (1.4)	5.4 (1.4)	−3.6 (18.4)	
IL-10/IL-6	**HIIT**	0.2 (0.1)	0.3 (0.1)	22.1 (46.4)	0.099
	MICT	0.6 (0.8)	0.3 (0.2)	−8.9 (31.7)	
IL-10/TNF-α	**HIIT**	0.6 (0.1)	0.7 (0.2)	23.4 (41.8)	0.266
	MICT	0.8 (0.6)	0.7 (0.4)	4.0 (30.1)	
Glucose (mg/dL)	**HIIT**	91.9 (9.0)	95.2 (11.1)	4.0 (11.9)	0.130
	MICT	92.7 (24.0)	87.5 (12.8)	−3.7 (11.1)	
Insulin (μIU/mL)	**HIIT**	18.5 (8.3)	14.4 (8.7)	−11.2 (50.5)	0.374
	MICT	18.8 (10.7)	18.2 (10.8)	6.9 (42.7)	
HOMA-IR	**HIIT**	4.2 (2.1)	3.4 (2.1)	−7.8 (55.7)	0.617
	MICT	4.5 (3.5)	4.0 (2.7)	3.0 (43.8)	
1 h OGTT	**HIIT**	133.9 (30.8)	129.1(25.1)	−1.9 (15.8)	0.627
	MICT	123.0 (31.1)	120.7 (29.9)	−5.5 (10.2)	

Values are mean (standard deviation). Variables (participants): MIP-1α = Macrophage inflammatory protein (HIIT = 11; MICT = 11); IL-6 = Interleukin 6 (HIIT = 11; MICT = 11); IL-10 = Interleukin 10 (HIIT = 11; MICT = 10); TNF-α = Tumor necrosis factor (HIIT = 10; MICT = 10); IL-10/IL-6 (HIIT = 10; MICT = 10); IL-10/TNFα(HIIT = 10; MICT = 9); Glucose (HIIT = 11; MICT = 11); Insulin (HIIT = 11; MICT = 11); HOMA (HIIT = 11; MICT = 11); OGTT (HIIT = 9; MICT = 6). HIIT = High-intensity interval training; MICT = Moderate intensity continuous training; *p-value* < 0.05.

condition effect (time, period, and interaction). However, IL-6 ($F = 9.300$; $p = 0.000$; partial $\eta^2 = 0.185$) and IL-10 ($F = 6.231$; $p = 0.001$; partial $\eta^2 = 0.138$) levels presented a main effect of time. TNF-α presented no time effect ($F = 2.593$; $p = 0.056$; partial $\eta^2 = 0.065$), however, when not adjusted by covariance, type of training, the result was different ($F = 4.481$; $p = 0.005$; partial $\eta^2 = 0.105$). Furthermore, IL-10/IL-6 ratio also presented a main effect of time ($F = 3.252$; $p = 0.043$; partial $\eta^2 = 0.073$) (Table 3). The AUC of IL-6 and TNF-α did not present effect of time ($F = 2.608$; $p = 0.122$; partial $\eta^2 = 0.115$; $F = 0.200$; $p = 0.660$; partial $\eta^2 = 0.011$, respectively), type of training ($F = 1.627$; $p = 0.217$; partial $\eta^2 = 0.075$; $F = 0.617$; $p = 0.442$; partial $\eta^2 = 0.033$, respectively) and interaction ($F = 0.703$; $p = 0.412$; partial $\eta^2 = 0.034$; $F = 0.065$; $p = 0.802$; partial $\eta^2 = 0.004$, respectively). The AUC of IL-10 presented effect of type of training ($F = 6.112$; $p = 0.023$; partial $\eta^2 = 0.243$) and MICT group showed significantly higher values than the HIIT group (15.0 ± 6.9 and 9.9 ± 1.8 u.a., respectively) (Fig. 3), but did not effect of time ($F = 0.023$; $p = 0.881$; partial $\eta^2 = 0.001$) and interaction ($F = 0.584$; $p = 0.462$; partial $\eta^2 = 0.029$). The concentrations of IL-10, TNF-α, and IL-10/TNF-α in the stimulated blood with LPS at rest, immediately, and 30 min and 60 min after the *Acute sessions*, are presented in Table 4. TNF-α and IL-10/TNF-α ratio did not present any condition effect (time, period, and interaction). However, IL-10 presented a time effect ($F = 6.229$; $p = 0.003$; partial $\eta^2 = 0.138$) immediately after rest, independent of group (Fig. 2).

4. Discussion

The main results of the study were related to the cytokine modulation induced by MICT and HIIT, with significant increases in serum IL-6, IL-10, and TNF-α concentrations 60 min after acute exercise in the untrained and trained states, and an increase in IL-10 production in response to LPS (*ex-vivo* assay) immediately after A*cute exercise*. In addition, the individual improvement/impairment in HOMA-IR was independent of inflammatory or body fat changes for both groups.

Regular practice of exercise training, Vella et al. [35] showed that an acute bout of high-intensity exercise was able to activate transient signaling of NF-κB in skeletal muscle during the first two hours post-exercise and this activity might implicate in the control of myokines

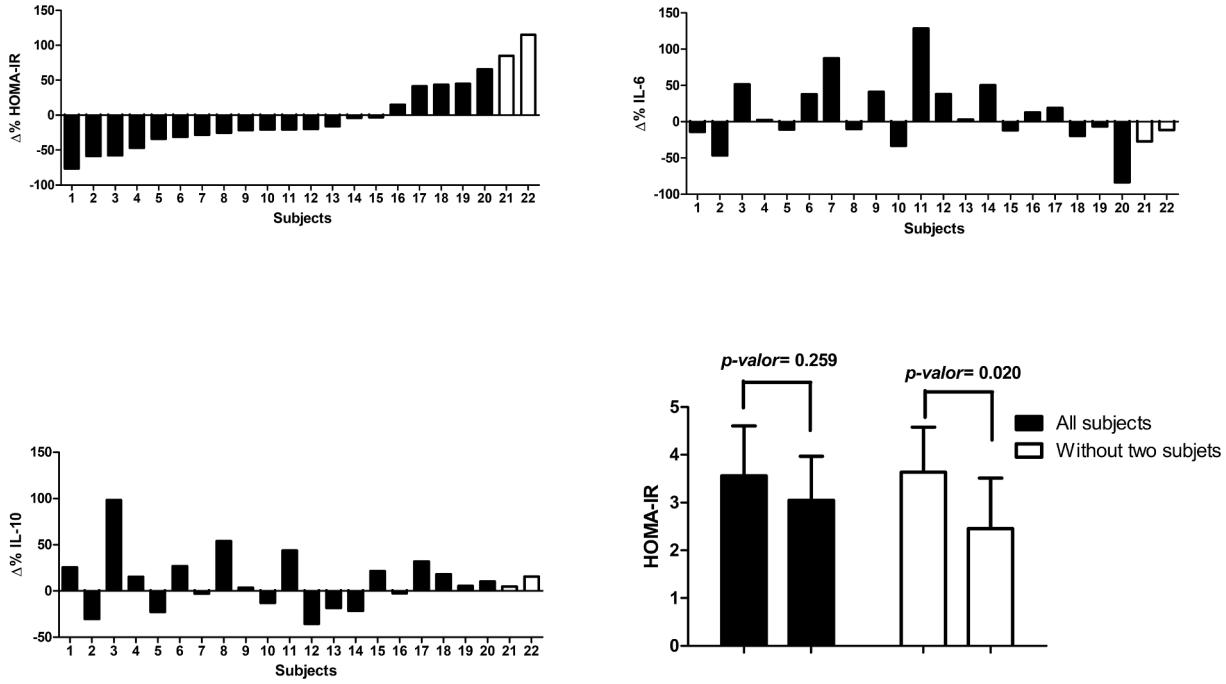

Fig. 1. Responsiveness and effect of training models in the HOMA-IR and inflammatory markers in obese adults. Inter individual variability of HOMA-IR (A), IL-6 (B) and IL-10 (C) levels were found in response to *6-weeks* of training independently of the exercise method adopted. Two subjects presented a significantly increase in HOMA-IR index after exercise training period, and when excluded from the analysis the overall statistical method revealed a significant reduction in insulin resistance (D).

Table 3
Metabolic and inflammatory responses at rest, immediately, and 30-min and 60-min post *Acute session pre* and p*ost 6-weeks* of training.

		Pre-training		Post-training	
		HIIT	MICT	HIIT	MICT
MIP-1α (pg/mL)	**Rest**	194.6 (215.7)	290.8 (254.0)	176.5 (220.4)	281.6 (236.2)
	Immediately	197.7 (216.6)	333.1 (244.0)	183.9 (219.0)	301.1 (243.3)
	30 min	194.6 (217.3)	284.7 (233.8)	147.6 (187.3)	275.0 (232.3)
	60 min	193.0 (218.9)	304.5 (241.5)	177.9 (213.0)	237.2 (228.0)
IL-6 (pg/mL)	**Rest**	1.4 (0.4)	2.3 (1.9)	1.7 (0.6)	1.6 (0.6)
	Immediately*	2.1 (1.0)	2.9 (2.3)	1.9 (1.1)	2.0 (0.6)
	30 min*	2.5 (0.7)	3.2 (1.9)	1.8 (0.6)	2.5 (0.5)
	60 min*	2.4 (0.9)	3.6 (3.0)	2.7 (1.2)	2.9 (0.7)
IL-10 (pg/mL)	**Rest**	2.9 (0.3)	4.4 (1.8)	3.1 (0.5)	4.7 (2.3)
	Immediately	3.1 (0.6)	5.0 (2.4)	3.0 (0.7)	5.2 (2.7)
	30 min*	3.7 (1.0)	5.1 (2.6)	3.4 (0.9)	5.0 (2.5)
	60 min*	3.7 (1.2)	4.9 (2.2)	3.3 (0.7)	5.2 (2.0)
TNF-α (pg/mL)	**Rest**	5.7 (1.0)	5.3 (1.4)	5.8 (1.2)	5.0 (1.8)
	Immediately	5.8 (1.5)	5.0 (1.8)	5.6 (0.8)	5.4 (1.9)
	30 min	6.4 (1.3)	5.1 (1.9)	6.1 (1.4)	6.2 (1.1)
	60 min**	6.4 (1.1)	5.5 (2.1)	6.1 (1.3)	6.3 (2.0)
IL-10/IL-6	**Rest**	2.2 (0.7)	2.5 (1.3)	2.0 (0.6)	2.9 (1.9)
	Immediately*	1.6 (0.7)	2.1 (1.3)	1.8 (0.8)	2.4 (1.4)
	30 min*	1.6 (0.4)	1.9 (1.2)	2.0 (0.7)	1.9 (1.1)
	60 min*&	1.7 (0.9)	1.8 (1.2)	1.5 (0.8)	1.7 (1.0)
IL-10/TNFα	**Rest**	0.5 (0.1)	0.7 (0.4)	0.5 (0.1)	0.7 (0.4)
	Immediately	0.5 (0.1)	0.7 (0.4)	0.5 (0.1)	0.7 (0.4)
	30 min	0.6 (0.2)	0.8 (0.5)	0.6 (0.2)	0.6 (0.4)
	60 min	0.6 (0.2)	0.7 (0.3)	0.5 (0.2)	0.7 (0.4)

Values are mean (standard deviation). Variables (participants): MIP-1α = Macrophage inflammatory protein (HIIT = 11; MICT = 11); IL-6 = Interleukin 6 (HIIT = 11; MICT = 11); IL-10 = Interleukin 10 (HIIT = 11; MICT = 10); TNF-α = Tumor necrosis factor alpha (HIIT = 9; MICT = 10); IL-10/TNF-α = (HIIT = 9; MICT = 10) and Glucose (HIIT = 11; MICT = 11). * = difference from rest; ** = difference from rest when not adjusted by type of group; & = different from immediately; # = different from 30 min. *p-value* < 0.05.

(i.e. IL-6, IL-8, MCP-1). On the other hand, NF-κB-induced cytokine release during exercise may act in other tissues, such as adipose tissue, in order to increase circulating free fatty acid levels to provide energy substrates for contracting skeletal muscle during a prolonged acute exercise bout [33]. These data may explain, at least in part, the elevation in TNF-α concentration after MICT and HIIT, reflecting a transient inflammatory response.

Barry et al. [7] demonstrated that short-term (2-*weeks*) HIIT or

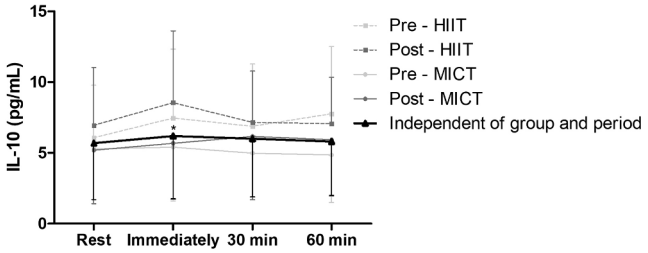

Fig. 2. Effect of two training models on the LPS-stimulated whole blood at rest, immediately, and 30 min and 60 min after the acute sessions.

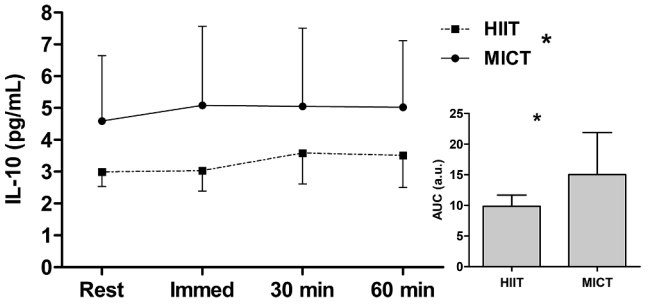

Fig. 3. Blood concentrations of interleukin 10 at rest, immediately (Immed), 30 min and 60 min after acute session and the area under the curve (AUC) in the HIIT and MICT groups. Values expressed as mean and standard deviation represent Pre and Post training together. * difference in AUC between the HIIT × MICT groups; $p < 0.05$.

MICT programs do not change body composition (visceral adipose tissue, percent body fat, total fat mass, and total lean mass), blood cytokines, or chemokines (IL-8, MIP-1α, MCP-1, leptin) in obese adults; however, these protocols appear to differentially modulate chemokine receptors of specific immune cells, with a reduction in CCR2 (MCP-1 receptor) on $CD14^+/CD16^+$ monocytes observed after the MICT, whereas HIIT resulted in an overall increase in CCR5 (MIP-1α receptor) on $CD14^+/CD16^-$ monocytes, $CD14^+/CD16^+$ monocytes, neutrophils, and T cells.

Regarding IL-10 levels after acute exercise session (pre and post-training period), when evaluated AUC, MICT group exhibited augment values than HIIT group. Cabral-Santos et al. [10] have related in a systematic review that the main factor involved with alterations of the IL-10 after acute exercise session in healthy subjects is duration of session. The present study was designed for obtain isoenergetic session, as showed in the study previous [17], but duration of exercise session was superior in MICT group (19.0 ± 0 and 34.0 ± 4.8 min for HIIT

Table 4
Inflammatory responses at rest, immediately, and 30-min and 60-min post *Acute session,* pre and post *6-weeks* of training in stimulated blood with LPS (n = 10).

		Pre-training		Post-training	
		HIIT	MICT	HIIT	MICT
IL-10 (pg/mL)	**Rest**	6.3 (4.0)	4.6 (3.3)	7.1 (4.5)	4.9 (3.8)
	Immediately*	7.8 (5.3)	5.2 (3.9)	8.7 (5.6)	5.4 (4.0)
	30 min	7.2 (4.7)	4.8 (3.2)	7.2 (4.0)	5.7 (4.3)
	60 min	8.1 (5.1)	4.6 (3.4)	7.4 (4.0)	5.4 (3.6)
TNF-α (pg/mL)	**Rest**	172.2 (141.4)	136.8 (83.4)	210.7 (106.2)	178.9 (110.0)
	Immediately	154.2 (151.2)	217.2 (123.5)	236.1 (115.4)	168.2 (103.1)
	30 min	197.9 (129.9)	198.7 (196.0)	225.1 (88.1)	141.1 (138.6)
	60 min	197.2 (89.4)	125.8 (107.5)	185.1 (106.4)	99.2 (86.7)
IL-10/TNF-α	**Rest**	0.1 (0.1)	0.1 (0.1)	0.05 (0.05)	0.05 (0.1)
	Immediately	0.7 (1.7)	0.04 (0.04)	0.05 (0.1)	0.1 (0.1)
	30 min	0.4 (1.0)	0.2 (0.6)	0.04 (0.04)	0.1 (0.1)
	60 min	0.1 (0.1)	0.1 (0.1)	0.05 (0.04)	0.4 (0.9)

Values are mean (standard deviation). IL-6 = Interleukin 6; IL-10 = Interleukin 10; TNF-α = Tumor necrosis factor alpha; HIIT = High-intensity interval training; MICT = Moderate intensity continuous training; * = different from rest; *p-value* < 0.05.

and MICT respectively, $p < 0.001$). This factor can be involved with data found here for IL-10 AUC after acute exercise.

The positive effects mediated by exercise training in the resolution of inflammation induced by overweight/obesity are well documented [13]. As expected, the present study showed greater IL-6 concentration after the exercise sessions, independently of intensity group and training period, parallel with IL-10 increase during recovery when compared to rest. Interestingly, similar effects were observed in physically active subjects submitted to acute high-intensity interval training (1:1 min at 100% MAV) and moderate-intensity continuous training (70% MAV), with increases observed in IL-10 concentration in response to both protocols in a similar manner when session volume was matched [11]. However, when observing the chronic impact on cytokines in obese subjects, a similar peak of cytokines was found after the *Acute session* compared to baseline, especially IL-10, while lean subjects that performed HIIT or MICT exhibited an attenuated peak of IL-10 [21].

The higher production of IL-10 after both acute exercise protocols in the LPS-stimulated whole blood *ex-vivo* assay may denote the role of exercise in the resolution of acute inflammation. IL-10 attenuates the production of TNF-α, IL-6, and IL-12 and thereby limits the inflammatory response through the inhibition of different cells such as T and B lymphocytes, macrophages, and dendritic cells [31]. The production of IL-10 induced by an inflammatory insult such as LPS is driven by Akt-STAT3 axis activation [27]. Furthermore, the increased *ex-vivo* IL-10 production after the bout highlight the anti-inflammatory effect of exercise, which is believed to mediate immunoregulation through: modifications in chromatin structure to selectively silence active inflammatory gene promoters; the inhibition of gene products that post-translationally modify the activity of NF-κB; the enhanced expression of transcription repressors [31].

The different chronic responses between lean and obese subjects may be related, at least in part, by inflammatory background found in both conditions (lean or obese). We suggest that, both inflammatory responses lead to improvements in metabolic and health status. In addition, these data suggest that when the caloric expenditure or workload is matched there seems to be no superiority between the protocols and both lead to an anti-inflammatory status. In fact, Ortega [25] hypothesized that the anti-inflammatory response to exercise is dependent on the individual's "basal set point inflammation". According to this theory, the anti-inflammatory effects of an exercise bout may be induced only in individuals that present basal chronic low-grade inflammation, such as sedentary obese men, and lean individuals may not experience the same short-term immune response to exercise [25]. Corroborating with this, different responses of phagocyte activity, inflammatory mediator production, and monocyte subset profile are dependent on adrenergic regulation after exercise in obese and lean mice [15,23].

Visceral and subcutaneous fat depots were evaluated in the present study, but no significant changes were found after 6 weeks of either training protocol. In a recent systematic review and *meta*-analysis, Andreato et al. [2] compared high-intensity interval training and moderate intensity continuous training; the authors suggested that both protocols could modulate body adiposity with effects of similar magnitude. Lira et al. [22] found improvement in anti-inflammatory status when visceral fat depot was reduced (-49% after intervention) in obese adolescents after long-term interdisciplinary lifestyle therapy. These data suggest that longer-term interventions are needed to induce changes in body composition in HIIT programs [8,20].

Overall, the advantage of our study is the exploration of the kinetics of the inflammatory and metabolic profile during and after acute exercise (pre-training), as well as chronic analysis of the acute effect of the exercise (post-training). On the other hand, the limitations were the low number of participants and the time of intervention, which, as suggested by other studies, might not be sufficient to promote significant changes in body composition, and the metabolic and inflammatory profile. Thus, further studies with longer-lasting interventions deserve investigation.

Taken together, the present findings suggest that a similar adaptation may occur through cytokine release, independent of stimulus, observed in HIIT when compared to MICT. The data from the present study demonstrated that submitting sedentary obese men to an exercise program was associated with beneficial effects on metabolic and inflammatory adaptations through exercise-induced cytokine release after *6-weeks*.

Author contribution

Conceptualization: JGN and PAM. Data Curation: JGN, PAM, DSI. Formal Analysis: PAM. Funding acquisition: DSI and FSL. Investigation: JGN, PAM, DSI and FSL. Methodology: JGN, PAM, DSI and FSL. Project administration: JGN, PAM, DSI and FSL. Resources: FSL. Software: Supervision: FSL. Validation: Writing: original draft: FSL, BMA, GPD, AP, PAM and JGN. Writing - review & editing: PAM, JGN, DSI and FSL.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2020.155249.

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