Inflammatory cytokine kinetics to single bouts of acute moderate and intense aerobic exercise in women with active and inactive systemic lupus erythematosus

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ABSTRACT

Objectives: The aim of this study was to evaluate changes in the cytokines INF-γ, IL-10, IL-6, TNF-α and soluble TNF receptors (sTNFR1 and sTNFR2) in response to single bouts of acute moderate and intense exercise in systemic lupus erythematosus women with active (SLE_{ACTIVE}) and inactive ($SLE_{INACTIVE}$) disease. **Methods:** Twelve $SLE_{INACTIVE}$ women (age: 35.3 ± 5.7 yrs; BMI: 25.6±3.4 kg/m²), eleven SLE_{ACTIVE} women (age: 30.4 ± 4.5 yrs; BMI: 26.1±4.8 kg/m²), and 10 age- and BMI-matched healthy control women (HC) performed 30 minutes of acute moderate (~50% of VO_2peak) and intense (~70% of VO_2peak) exercise bout. Cytokines and soluble TNF receptors were assessed at baseline, immediately after, every 30 minutes up to three hours, and 24 hours after both acute exercise bouts. **Results:** In response to acute moderate exercise, cytokines and soluble TNF receptors levels remained unchanged in all groups (P>0.05), except for a reduction in IL-6 levels in the SLE_{ACTIVE} group at the 60th and 180th minutes of recovery (P<0.05), and a reduction in sTNFR1 levels in the HC group at the 90th, 120th, 150th, 180th minutes of recovery (P<0.05). The $SLE_{INACTIVE}$ group showed higher levels of TNF-α, sTNFR1, and sTNFR2 at all time points when compared with the HC group (P<0.05). Also, the SLE_{ACTIVE} group showed higher levels of IL-6 at the 60th minute of recovery (P<0.05) when compared with the HC group. After intense exercise, sTNFR1 levels were reduced at the 150th (P=0.041) and 180th (P=0.034) minutes of recovery in the $SLE_{INACTIVE}$ group, whereas the other cytokines and sTNFR2 levels remained unchanged (P>0.05). In the HC group, IL-10, TNF-α, sTNFR1, and sTNFR2 levels did not change, whilst INF-γ levels decreased (P=0.05) and IL-6 levels increased immediately after the exercise (P=0.028), returning to baseline levels 24 hours later (P > 0.05). When compared with the HC group, the $SLE_{INACTIVE}$ group showed higher levels of TNF-α and sTNFR2 in all time points, and higher levels of sTNFR1 at the end of exercise and at the 30th minute of recovery (P<0.05). The SLE_{ACTIVE} group also showed higher levels of TNF-α at all time points when compared with the HC group (P<0.05), (except after 90 min, 120 min and 24 hours of recovery) (P>0.05). Importantly, the levels of all cytokine and soluble TNF receptors returned to baseline 24 hours after the end of acute exercise, irrespective of its intensity, in all three groups (P>0.05). **Conclusion:** This study demonstrated that both the single bouts of acute moderate and intense exercise induced mild and transient changes in cytokine levels in both $SLE_{INACTIVE}$ and SLE_{ACTIVE} women, providing novel evidence that acute aerobic exercise does not trigger inflammation in patients with this disease.

Key-words: exercise training, immune system, inflammation, rheumatic diseases, physical activity, non-active disease, active disease.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a rheumatic autoimmune disease characterized by chronic inflammation as evidenced by higher levels of interferon gamma (IFN-γ), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), interleukin 10 (IL-10), and soluble TNF receptors (sTNFR1 and sTNFR2) (1, 13, 24, 31, 52, 56). This chronic inflammation has been associated with disease-related co-morbidities, such as accelerated atherosclerosis (28), fatigue (66), and impaired cardiac autonomic control (17). As a result, SLE patients show a low aerobic capacity level (28, 33) and poor health-related quality of life (4). In this scenario, physical exercise has been considered as a promising therapeutic tool to partially offset these adverse outcomes.

There is, however, a concern that acute physical exercise in SLE patients could further increase the cytokine levels and, consequently, the inflammatory process, thereby aggravating the disease symptoms. Based on this premise, SLE patients (particularly those with disease flare-ups) have often been recommended to avoid physical activity, but the evidence to support this practice is scarce (16, 43, 60). In fact, physical low-to moderate-intensity exercise programs have been shown not

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to aggravate inflammation in rheumatoid arthritis (6, 19), or idiopathic inflammatory myopathies (30, 35). To date, however, the body of evidence on the safety of exercise in SLE is still lacking and, to our knowledge, restricted to non-active patients undergoing lower-intensity activities (11, 14, 33, 59).

The cytokine kinetics response to a single bout of acute exercise has emerged as an experimental model that provides relevant clues on the impact of exercise upon inflammatory status in patients and healthy populations (46, 57). In SLE patients, da Silva et al. (15) showed preliminary evidence that IL-6, IL-10, and TNF-α levels remained unchanged at the end of a graded exercise session. However, this study did not allow a definitive conclusion, as cytokine levels were measured only at baseline and immediately after the test, in spite of the well-known time-dependent pattern of cytokine response to an acute exercise session (46, 57). Moreover, exercise intensity, which is known to influence cytokine responses to exercise (21, 38, 53), was not explored in this study. Therefore, the time-course responses of cytokines and soluble TNF receptors (sTNFR1 and sTNFR2) to different intensities of aerobic exercise require further investigation in SLE in order to provide further evidence regarding the effects of acute exercise on cytokine kinetics in this disease.

The purpose of this study was to assess the time-course response of cytokines (*i.e.*, INF-y, IL-6, IL-10, TNF-α) and soluble TNF receptors (*i.e.*, sTNFR1 and sTNFR2) to different intensities (*i.e.*, moderate and intense) of acute aerobic exercise bouts in SLE women with active and inactive disease (SLE_{ACTIVE} and $SLE_{INACTIVE}$, respectively). Our hypothesis was that the acute exercise bouts would equally affect cytokine kinetics in the SLE women and healthy controls in an intensity-dependent manner. Furthermore, we speculated that in both SLE_{ACTIVE} and $SLE_{INACTIVE}$ women, cytokine levels would normalize after a 24-hour recovery period following both an acute moderate and intense exercise bout, suggesting no acute exacerbation of disease.

MATERIALS AND METHODS

Patients and healthy controls

From 287 SLE patients followed at our outpatient clinic (Clinical Hospital, School of Medicine, University of Sao Paulo, Brazil), twelve $SLE_{INACTIVE}$ women and eleven SLE_{ACTIVE} women were selected to participate in this study. Ten age- and body mass index (BMI)-matched women also took part in this study as a healthy control (HC) group.

The inclusion criteria for both SLE groups were the following: aged between 20 and 40 years and physically inactive for at least six months before selection. The exclusion criteria for the SLE women included: secondary rheumatic disease (*e.g.*, Sjögren syndrome, Antiphospholipid syndrome), BMI ≥ 30 kg/m², acute renal failure, cardiac and pulmonary involvement, fibromyalgia, and musculoskeletal and joint disorders which could preclude exercise testing. The particular inclusion criteria for $SLE_{INACTIVE}$ group were the following: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score < 4 and not receiving glucocorticoid therapy for at least six months prior to the beginning of the study. The SLE_{ACTIVE} group had SLEDAI scores between 4 and 8 and received daily glucocorticoid treatment of ≤ 20 mg.

This study and was approved by the Local Ethical Committee and registered at clinicaltrials.gov as NCT01515163. All of the subjects signed an informed consent before entering in this trial.

Procedures

SLE diagnosis

All the women in both SLE groups fulfilled the American College of Rheumatology criteria for SLE diagnosis (25) and were regularly followed at the outpatient Lupus clinic of the Rheumatology Division of the School of Medicine at the University of Sao Paulo, Brazil. Disease activity was determined by SLEDAI scores (8). SLE manifestations were defined as follows: cutaneous disease, articular involvement, neuropsychiatry disease, renal disease, cardiopulmonary disease, and hematologic complications.

Study design

The three groups (*i.e.*, $SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC) completed a maximal graded treadmill cardiopulmonary exercise test to determine the anaerobic ventilatory threshold (VAT), the respiratory compensation point (RCP), and the peak of oxygen uptake (VO_2peak). Thereafter, $SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC performed two single bouts of acute aerobic exercise (*i.e.*, moderate and intense) for time-response assessments of cytokines and soluble TNF receptors.

Preliminary Testing

Cardiopulmonary exercise test

A maximal graded exercise test was performed on a treadmill (Centurion 200, Micromed, Brazil), with increments in velocity and grade at every minute until volitional exhaustion, as previously described elsewhere (49). Oxygen consumption (VO_2) and carbon dioxide output were obtained through breath-by-breath sampling and expressed as a 30-s average using an indirect calorimetric system (Cortex - model Metalyzer IIIB, Leipzig, Germany). Heart Rate (HR) was continuously recorded at rest, during exercise and at recovery, using a 12-lead electrocardiogram (Ergo PC Elite, InC. Micromed, Brazil). The cardiopulmonary exercise test was considered to be maximal when one of the following criteria was met: VO_2 plateau (*i.e.*, < 150 ml/min increase between two consecutive stages), HR no less than 10 beats below age-predicted maximal HR (58) and respiratory exchange ratio value above 1.10 (48). VO_2peak was considered as the average of the final 30 s of the test. Ventilatory threshold (VAT) was identified following previously described procedures (64). In brief, VAT was determined when ventilatory equivalent for VO_2 (VE/VO_2) increased without a concomitant increase in ventilatory equivalent for carbon dioxide (VE/VCO_2). Respiratory compensation point was determined when VE/VO_2 and VE/VCO_2 increased simultaneously.

Interventions

At least 72 hours after the cardiopulmonary exercise test, two single bouts of acute aerobic exercise were performed in a treadmill to assess the cytokines and soluble TNF receptors kinetics.

The exercise order was randomized for each group and the sessions were interspaced by at least 72 hours. The first acute exercise bout was performed after at least 72 hour of the cardiopulmonary exercise test. The room temperature was kept at 22°C during all of the experimental conditions. Each acute exercise bout (*i.e.*, moderate and intense) was comprised of 5 minutes of warm-up and 30 minutes of exercise at the predetermined exercise intensity.

Acute moderate exercise bout

The acute moderate exercise bout was performed at an intensity correspondent to 10% below the VAT ($SLE_{INACTIVE}$: 48.5 ± 7.7% of VO_2peak; SLE_{ACTIVE}: 51.5 ± 8.4% of VO_2peak HC: 47.5 ± 8.6% of VO_2peak).

Acute intense exercise bout

The acute intense exercise bout was set at an intensity correspondent to 50% of the delta difference (Δ) between the VAT and the RCP ($SLE_{INACTIVE}$: 67.2 ± 7.0% of VO_2peak; SLE_{ACTIVE}: 68.7 ± 6.4% of VO_2peak; HC: 66.8 ± 6.7% of VO_2peak).

Blood sampling

Before performing each of the acute aerobic exercise bouts, an antecubital vein was cannulated for blood sampling. Blood (5 mL) was sampled and drawn into a dry tube at baseline, at the end of exercise (End-ex), every 30 minutes during a 3-hour recovery period (Rec30, Rec60, Rec90, Rec120, Rec150 and Rec180), and 24 hours after the end of exercise (Rec24h) (36). Blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C, and the serum aliquot was stored at −80°C for subsequent analyses. Baseline values were considered as the average between the baseline assessments obtained before both the acute moderate and intense exercise bouts.

Cytokines assessments

Cytokines (*i.e.*, IFN-γ, IL-10, IL-6 and TNF-α) and soluble TNF receptors (*i.e.*, sTNFR1 and sTNFR2) were measured using a multiplex human panel. The immunoassays were performed according to the manufacturer's procedures (Milliplex®). The reliability of cytokines and soluble TNF receptors measurements were tested using the baseline serum samples from the moderate and intense exercise sessions. The intraclass correlation coefficients [ICC (95% of confidence interval)] for each cytokine [IFN-γ: 0.93 (0.86-0.97); IL-10: 0.97 (0.95-0.98); IL-6: 0.98 (0.98-0.99); TNF-α: 0.84 (0.78-0.94)] and soluble TNF receptors [sTNFR1: 0.89 (0.78-0.94); sTNFR2: 0.93 (0.85-0.96)] suggest a high reliability of the assays.

Statistical analysis

Data are presented as mean ± standard error. The Gaussian distribution of the data was tested by Kolmogorov-Smirnov's test (with Lilliefor's correction). Demographic data of the three groups ($SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC) were compared using one way ANOVA followed by Bonferroni post hoc test. Drugs proportions of both SLE groups were compared with χ^2 test. Within-group serum cytokine levels were analyzed by using Friedman's ANOVA (repeated-measures) followed by Wilcoxon test, while between-group cytokine levels were compared with Kruskall-Wallis test followed by Mann-Whitney U-test. All data analysis was performed using the Statistical Package for Social Sciences (SPSS), version 17.0 for Windows. The level of significance was set at $P \leq 0.05$.

RESULTS

Patients and healthy controls

The main characteristics of the patients and healthy controls are presented in Table 1. Age, weight, height, and BMI were comparable between the $SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC groups ($P > 0.05$). The SLEDAI score was higher in the SLE_{ACTIVE} group when compared with the $SLE_{INACTIVE}$ group (5.8 ± 2.0 *vs.* 1.4 ± 1.0, $P = 0.037$), whereas the disease duration was higher in the $SLE_{INACTIVE}$ group when compared with the SLE_{ACTIVE} group (11.1 ± 6.0 *vs.* 6.1 ± 3.5 years, $P = 0.037$). Cardiopulmonary exercise test data are presented in Table 2. All the aerobic indexes were lower in the $SLE_{INATIVE}$ and SLE_{ACTIVE} groups when compared with their healthy counterparts ($P < 0.05$), while there were no significant differences between the $SLE_{INACTIVE}$ and SLE_{ACTIVE} groups ($P > 0.05$).

Baseline cytokine levels

$SLE_{INACTIVE}$ *vs.* HC

Baseline levels of TNF-α (16.4 ± 1.8 vs. 7.4 ± 1.0 pg/mL, $P < 0.001$), IL-10 (1.5 ± 0.4 vs. 0.4 ± 0.1 pg/mL, $P = 0.021$) and sTNFR2 (6864.3 ± 619.3 vs. 3311.6 ± 352.6 pg/mL, $P < 0.001$) were higher in the $SLE_{INACTIVE}$ than in the HC group, whereas IFN-γ, IL-6 and sTNFR1 baseline levels were not significantly different between these groups (IFN-γ: 17.6 ± 5.9 *vs.* 6.9 ± 1.1 pg/mL, $P = 0.307$; IL-6: 0.88 ± 0.21 *vs.* 0.5 ± 0.24 pg/mL, $P = 0.065$; sTNFR1: 1053.8 ± 72.9 *vs.* 749.5 ± 108.8 pg/mL, $P = 0.070$).

SLE_{ACTIVE} *vs.* HC

The SLE_{ACTIVE} group showed higher baseline levels of IL-6 and TNF-α than the HC group (7.4 ± 5.5 *vs.* 0.5 ± 0.2 pg/mL, $P = 0.043$ and 13.5 ± 2.0 *vs.* 7.4 ± 0.9 pg/mL; $P = 0.020$, respectively), whereas IFN-γ (18.8 ± 9.6 *vs.* 6.9 ± 1.1 pg/mL, $P = 0.944$), IL-10 (3.3 ± 2.0 *vs.* 0.4 ± 0.1 pg/mL, $P = 0.139$), sTNFR1 (864.2 ± 104.8 *vs.* 749.5 ± 108.8 pg/mL, $P = 0.379$), and sTNFR2 (4814.6 ± 770.5 *vs.* 3311.6 ± 352.6 pg/mL, $P = 0.139$) were similar between these groups.

$SLE_{INACTIVE}$ *vs.* SLE_{ACTIVE}

sTNFR2 levels were significantly higher in the $SLE_{INACTIVE}$ when compared with the SLE_{ACTIVE} group (6864.2 ± 604.9 *vs.* 4814.6 ± 703.4 pg/mL, $P = 0.016$). The remaining cytokines and sTNFR1 levels did not differ between these groups ($P > 0.05$).

Effects of acute moderate aerobic exercise on cytokines and soluble TNF receptors kinetics

Cytokines and soluble TNF receptors responses to a single bout of moderate exercise bout in the $SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC groups are showed in Figure 1.

IFN-γ

Serum IFN-γ levels did not change in response to acute moderate aerobic exercise bout in any of the three groups ($P > 0.05$). Additionally, no between-group differences were noticed ($P > 0.05$).

IL-6

Serum IL-6 levels remained unchanged in response to a single bout of moderate exercise in the HC and SLE$_{INACTIVE}$ groups ($P > 0.05$), whereas it was reduced at the 60th ($P = 0.035$) and the 180th ($P = 0.022$) minutes of recovery in the SLE$_{ACTIVE}$ group as compared to baseline levels. Between-group analyses revealed no significant differences between the SLE$_{INACTIVE}$ and HC groups. The SLE$_{ACTIVE}$ group had higher levels of IL-6 at the 60th minute of recovery when compared with the HC group ($P = 0.036$).

TNF-α

TNF-α levels in response to the acute moderate exercise bout did not change in the SLE$_{INACTIVE}$, SLE$_{ACTIVE}$, and HC groups ($P > 0.05$). However, the between-group analysis showed higher levels of TNF-α in the SLE$_{INACTIVE}$ when compared with the HC and SLE$_{ACTIVE}$ group throughout all the recovery period (except at the end of the exercise and at the 90th minute for recovery in comparison to the SLE$_{ACTIVE}$ group). Despite the differences at baseline, the SLE$_{ACTIVE}$ and HC group had similar TNF-α levels at the end of exercise and throughout the recovery period ($P > 0.05$).

IL-10

Serum IL-10 levels remained unchanged in response to a single bout of moderate aerobic exercise in the SLE$_{INACTIVE}$, SLE$_{ACTIVE}$, and HC groups ($P > 0.05$). Although the SLE$_{INACTIVE}$ group had higher levels of IL-10 than the HC group at baseline, there were no between-group differences between the SLE$_{INACTIVE}$ and HC groups in response to the acute moderate exercise bout ($P > 0.05$). Between-group analyses also revealed no significant changes between the SLE$_{ACTIVE}$ and HC groups, nor were there any differences between the SLE$_{INACTIVE}$ and SLE$_{ACTIVE}$ groups ($P > 0.05$).

sTNFR1

sTNFR1 levels did not change in response to the acute moderate exercise bout in the SLE$_{INACTIVE}$ and SLE$_{ACTIVE}$ groups ($P >$

Table 1. Demographic, clinical and therapy data of SLE and health subjects.

	SLE$_{ACTIVE}$ (n = 11)	SLE$_{INACTIVE}$ (n = 12)	HC (n = 10)	*P* SLE$_{ACTIVE}$ *vs.* HC	*P* SLE$_{INACTIVE}$ *vs.* HC	*P* SLE$_{ACTIVE}$ *vs.* SLE$_{INACTIVE}$
Age (years)	30.4 ± 4.5	35.3 ± 5.7	30.6 ± 5.2	1.000	0.117	0.080
Weight (kg)	66.8 ± 10.2	65.9 ± 8.8	63.9 ± 8.9	1.000	1.000	1.000
Height (cm)	160.4 ± 7.2	160.7 ± 5.2	162.6 ± 5.7	1.000	1.000	1.000
BMI (kg/m2)	26.1 ± 4.8	25.6 ± 3.4	24.1 ± 2.3	0.66	1.000	1.000
SLEDAI	5.8 ± 2.0	1.4 ± 1.0	-	-	-	0.037
Disease duration (years)	6.1 ± 3.5	11.1 ± 6.0	-	-	-	0.037
Drugs [nº(%)]						
Glucocorticoid	11 (100%)	0 (0%)	-	-	-	0.001
Antimalarial	10 (91%)	10 (83%)	-	-	-	0.596
Azathioprine	5 (45%)	1 (8%)	-	-	-	0.048
Methotrexate	2 (18%)	2 (16%)	-	-	-	1.000
Mycophenolate mofetil	4 (36%)	2 (16%)	-	-	-	0.357

Data are presented as mean ± standard deviation or n (%). BMI = body mass index; SLEDAI = systemic lupus erythematosus disease activity index; SLE: systemic lupus erythematosus; SLE$_{INACTIVE}$: women with inactive SLE; SLE$_{ACTIVE}$: women with active SLE.

Table 2. Cardiopulmonary data from active and inactive SLE women and HC subjects.

	SLE_{ACTIVE} (n = 11)	$SLE_{INACTIVE}$ (n = 12)	HC (n = 10)	P SLE_{ACTIVE} vs. HC	P $SLE_{INACTIVE}$ vs. HC	P SLE_{ACTIVE} vs. $SLE_{INACTIVE}$
VO$_2$peak (L/min)	1.70 ± 0.27	1.56 ± 0.16	1.95 ± 0.22	0.049	0.001	0.355
VO$_2$peak (mL/kg/min)	25.7 ± 3.7	23.9 ± 3.6	31.0 ± 5.1	0.021	0.001	0.874
HRpeak (bpm)	173 ± 23	178 ± 8	191 ± 9	0.024	0.131	1.000
RERpeak	1.08 ± 0.07	1.07 ± 0.07	1.10 ± 0.09	1.000	0.800	1.000
Time at VAT (min)	5.8 ± 0.9	4.8 ± 1.3	7.1 ± 1.1	0.043	0.001	0.111
Time at RCP (min)	9.5 ± 1.5	9.2 ± 1.8	11.3 ± 1.5	0.010	0.036	1.000
Time to exhaustion (min)	11.8 ± 1.4	11.5 ± 1.5	13.8 ± 1.6	0.013	0.003	1.000

Data are presented as mean ± standard deviation. VAT = ventilatory anaerobic threshold; RCP = respiratory compensation point; VO$_2$ = oxygen uptake, HR = heart rate; RER = respiratory exchange ratio; SLE: systemic lupus erythematosus; $SLE_{INACTIVE}$: women with inactive SLE; SLE_{ACTIVE}: women with active SLE.

0.05), whereas sTNFR1 decreased in the HC group from the 90th to the 180th minute of recovery when compared with baseline ($P = 0.038$, $P = 0.028$, $P = 0.005$, $P = 0.037$, respectively). The between-group analyses revealed that sTNFR1 levels were not different between the $SLE_{INACTIVE}$ and HC group at baseline, at the end of exercise, and at the 60th and 150th minutes of recovery ($P > 0.05$). In contrast, the $SLE_{INACTIVE}$ group had higher levels of sTNFR1 than the HC group at the 30th, 90th, 120th, 180th minute of recovery, and 24 hours after the end of exercise ($P < 0.05$). The sTNFR1 levels were comparable between the SLE_{ACTIVE} and HC groups at all time points ($P > 0.05$). However, the sTNFR1 levels were higher in the $SLE_{INACTIVE}$ group when compared with the SLE_{ACTIVE} group only at the 30th and 60th minutes of recovery ($P = 0.027$, $P = 0.036$, respectively).

sTNFR2

Serum sTNFR2 levels did not change in response to acute moderate aerobic exercise bout in any of the three groups ($P > 0.05$). The $SLE_{INACTIVE}$ group showed higher levels of sTNFR2 when compared with both the SLE_{ACTIVE} and HC

groups at all of the time points ($P < 0.05$), whereas sTNFR2 levels remained comparable between the SLE_{ACTIVE} and HC groups ($P > 0.05$) in response to acute exercise throughout the analysis period.

Effects of acute intense aerobic exercise on cytokine and soluble TNF receptor kinetics

Cytokine and soluble TNF receptor responses to a single bout of intense aerobic exercise in $SLE_{INACTIVE}$, SLE_{ACTIVE}, and HC groups are presented in Figure 2.

IFN-γ

Serum IFN-γ in the $SLE_{INACTIVE}$ and SLE_{ACTIVE} groups did not change in response to the acute intense aerobic exercise bout ($P > 0.05$), whilst the HC group showed decreased IFN-γ levels at the end of exercise ($P = 0.05$) returning to baseline levels at the 30th minute of recovery and remaining at comparable levels to those observed at baseline throughout the recovery period ($P > 0.05$). The between-group analyses did not show any significant differences in any of the comparisons ($P > 0.05$).
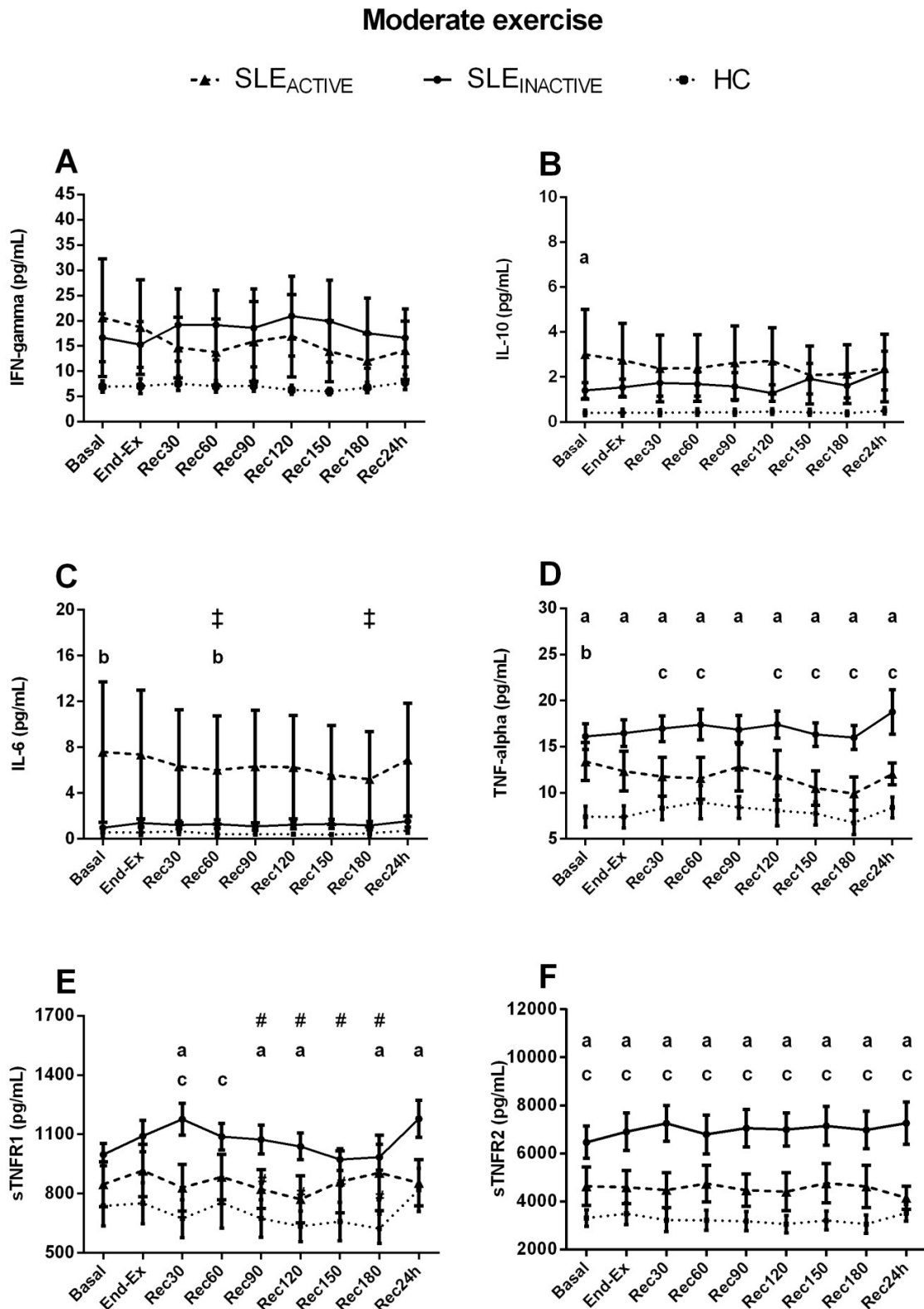
Moderate exercise

-▲- SLE$_{ACTIVE}$ -●- SLE$_{INACTIVE}$ ·●· HC

Figure 1. Cytokines and soluble TNF receptors responses to acute moderate aerobic exercise (30 minutes) in the SLE$_{INACTIVE}$, SLE$_{ACTIVE}$, and HC groups. * within-group differences in SLE$_{INACTIVE}$ when compared with baseline. ‡ within-group differences in SLE$_{ACTIVE}$ when compared with baseline. ‡ within-group differences in HC when compared with baseline. a - between-group differences when comparing SLE$_{INACTIVE}$ vs. HC at the same time-point. b - between-group differences when comparing SLE$_{ACTIVE}$ vs. HC at the same time-point. c - between-group differences when comparing SLE$_{INACTIVE}$ vs. SLE$_{ACTIVE}$ at the same time-point. Panel A – Interferon-gamma; Panel B – Interleukin-10; Panel C – Interleukin-6; Panel D – Tumor necrosis factor-alpha; Panel E – soluble TNF receptor 1; Panel F – soluble TNF receptor 2.

IL-6

Serum IL-6 remained unchanged in response to the acute intense exercise bout ($P > 0.05$) in the SLE$_{INACTIVE}$ group. When compared with baseline, the SLE$_{ACTIVE}$ group showed increased IL-6 levels at the end of exercise ($P = 0.028$), and decreased levels at the 60th, 120th, 180th minutes of recovery ($P = 0.047$, $P = 0.022$, $P = 0.028$, respectively). In the HC group, IL-6 levels increased at the end of exercise ($P = 0.008$)
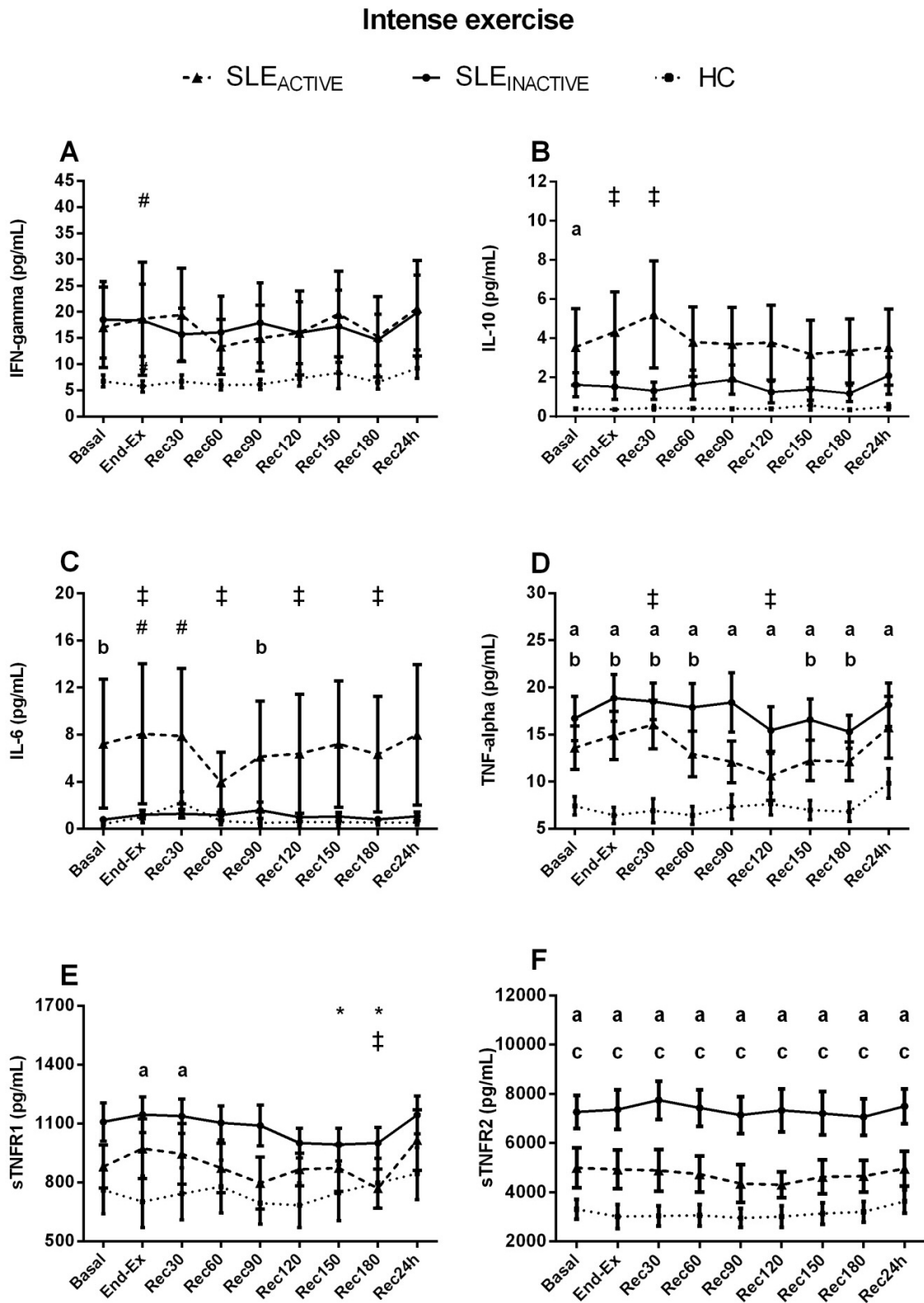
Intense exercise

Figure 2. Cytokines and soluble TNF receptors responses to acute intense aerobic exercise (30 minutes) in the SLE_INACTIVE, SLE_ACTIVE, and HC groups. * within-group differences in SLE_INACTIVE when compared with baseline. ‡ within-group differences in SLE_ACTIVE when compared with baseline. ‡ within-group differences in HC when compared with baseline. a – between-group differences when comparing SLE_INACTIVE vs. HC at the same time-point. b - between-group differences when comparing SLE_ACTIVE vs. HC at the same time-point. c - between-group differences when comparing SLE_INACTIVE vs. SLE_ACTIVE at the same time-point. Panel A – Interferon-gamma; Panel B – Interleukin-10; Panel C – Interleukin-6; Panel D – Tumor necrosis factor-alpha; Panel E – soluble TNF receptor 1; Panel F – soluble TNF receptor 2.

and at the 30th minute of recovery ($P = 0.005$), returning to baseline levels from the 60th minute to the 24th hour of recovery ($P > 0.05$). Between-group comparisons revealed no significant differences in IL-6 levels either between the SLE_INAC-TIVE and HC groups, or between the SLE_INACTIVE and SLE_ACTIVE groups at any of the time points ($P > 0.05$). IL-6 levels in the SLE_ACTIVE group were higher at baseline ($P = 0.043$), but similar during recovery when compared with the HC group ($P >$

0.05), except for higher IL-6 levels seen in the SLE_{ACTIVE} group at the 90th minute of recovery ($P = 0.024$).

TNF-α

Serum TNF-α levels did not change in response to the acute intense aerobic exercise bout in the $SLE_{INACTIVE}$ and HC groups ($P > 0.05$), whereas in the SLE_{ACTIVE} group, TNF-α levels increased at the 30th minute of recovery ($P = 0.038$), decreased at 120th minute of recovery ($P = 0.037$), and returned to baseline levels from the 150th minute to the 24th hour of recovery ($P > 0.05$). Between-group analyses showed that TNF-α levels were higher in the $SLE_{INACTIVE}$ and SLE_{ACTIVE} groups when compared with the HC group at all time points ($P < 0.05$), except for comparable TNF-α levels seen between the SLE_{ACTIVE} and HC groups at the 90th, 120th minute and 24th hour of recovery ($P > 0.05$). There were no significant differences between the $SLE_{INACTIVE}$ and SLE_{ACTIVE} groups at any time point ($P > 0.05$).

IL-10

IL-10 levels did not change in the $SLE_{INACTIVE}$ and HC groups in response to the acute intense aerobic exercise bout ($P > 0.05$), whereas the SLE_{ACTIVE} group showed increased levels at the end of exercise ($P = 0.034$) and at the 30th minute of recovery ($P = 0.039$), returning to baseline levels from the 60th minute of recovery to the end of the recovery period ($P > 0.05$). The between-group analyses revealed that despite differences in the IL-10 levels at baseline, there were no significant differences between the $SLE_{INACTIVE}$ and the HC groups from the end of exercise to the 24th hour of recovery ($P > 0.05$). Also, no significant differences were observed between the SLE_{ACTIVE} and HC groups and between the SLE_{ACTIVE} and $SLE_{INACTIVE}$ groups at any of the time points ($P > 0.05$).

sTNFR1

Serum sTNFR1 levels were reduced at the 150th and 180th minutes of recovery ($P = 0.041$, $P = 0.034$, respectively) in the $SLE_{INACTIVE}$ group, and at the 180th minute of recovery ($P = 0.05$) in the SLE_{ACTIVE} group when compared with baseline levels. The HC group did not show significant changes in the sTNFR1 levels after the acute intense exercise bout ($P > 0.05$). In the between-group analyses, the sTNFR1 levels were higher in the $SLE_{INACTIVE}$ when compared with the HC group only at the end of exercise ($P = 0.009$) and at the 30th minute of recovery ($P = 0.011$), while no significant differences were observed either between the SLE_{ACTIVE} and HC groups or the SLE_{ACTIVE} and the $SLE_{INACTIVE}$ groups throughout the protocol ($P > 0.05$).

sTNFR2

Serum sTNFR2 levels did not change significantly in response to the acute intense aerobic exercise bout in any of the three groups ($P > 0.05$). Between-group analyses showed higher levels of sTNFR2 in the $SLE_{INACTIVE}$ group when compared with both the SLE_{ACTIVE} and the HC groups ($P < 0.05$) at all of the time points. No significant differences were observed between the SLE_{ACTIVE} and HC groups ($P > 0.05$) throughout the protocol.

Effect of exercise intensity on cytokines and soluble TNF receptors kinetics

There were no effects of exercise intensity (moderate vs. intense) on cytokines and soluble TNF receptors kinetics in the $SLE_{INACTIVE}$, SLE_{ACTIVE} and HC groups at any time point ($P > 0.05$).

DISCUSSION

To our knowledge, this is the first study to assess cytokine and soluble TNF receptor kinetics in response to both acute moderate and intense aerobic exercise bouts in $SLE_{INACTIVE}$ and SLE_{ACTIVE} women. Our main results indicated that 30 minutes of an acute aerobic exercise bout, irrespective of its intensity (*i.e.*, roughly 50% or 70% of VO_2peak), caused only minor disturbances in cytokines and soluble TNF receptors, which were normalized after a 24 hour of recovery, suggesting that the acute exercise modes tested in the current study did not exacerbate the disease. In addition, there was no exercise-intensity effect on the responses of cytokines and soluble TNF receptors in both groups.

The effects of a single bout of acute moderate aerobic exercise on cytokines and soluble TNF receptors have been previously assessed in other chronic diseases, with contradictory results. For example, Gomes et al. (23) showed higher levels of sTNFR1 and lower levels of sTNFR2, but did not observe any changes in IL-6 and TNF-α levels in response to a single bout of acute moderate exercise (*i.e.*, 20 minutes of walking at 2 mph) in patients with knee osteoarthritis. Conversely, Rabinovich (50) showed increased levels of TNF-α and unchanged levels of soluble TNF receptors and IL-6 levels after a single bout of acute moderate exercise (*i.e.*, 40% of peak power on a cycle ergometer) in patients with chronic obstructive pulmonary disease. These findings reveal a disease-specific response in relation to exercise-induced changes in cytokines and soluble TNF receptors levels. The current results add to the literature by showing no alteration in these inflammatory parameters in response to the single bouts of acute moderate and intense aerobic exercise in $SLE_{INACTIVE}$ and SLE_{ACTIVE} women. Considering that SLE patients with active and inactive diseases often show very discrepant features as regard to clinical symptoms and drug therapy (61), the results of this study will be discussed separately according to the disease activity.

Effects of acute moderate and intense aerobic exercise on cytokines and soluble TNF receptors kinetics in $SLE_{INACTIVE}$

A single bout of acute moderate aerobic exercise elicited similar cytokine responses in inactive SLE patients and HC subjects, except for the reduction in sTNFR1, which was only observed in the HC subjects. In contrast to the present findings, Drenth et al. (18) and Ostrowski et al. (36) found increased levels of sTNFR1 and sTNFR2 in physically active subjects after more exhaustive/prolonged exercise protocols (i.e., a 5-km time trial or a marathon). A longer exercise duration in these previous studies (18, 36) has been related to increased TNF-α levels, and consequently, increase sTNFRs levels (7). In fact, the short duration of the exercise protocol in the current study may also explain the lack of changes in IL-6 levels in HC. Supporting this hypothesis, Scott et al. (53)

found an increase in IL-6 only after longer periods of moderate-intensity exercise (*i.e.*, > 40 minutes). The INF-γ, TNF-α and IL-10 responses to a single bout of acute moderate aerobic exercise in the HC subjects observed herein were in line with previous reports (9, 21, 32, 37, 38, 53).

In response to a single bout of acute intense exercise, IL-6 increased in HC and, subsequently, returned to baseline levels at 60th minute of recovery, in agreement with other findings (20, 41, 42). Although the chronic increase of IL-6 has been classically associated with exacerbated inflammation in chronic diseases, it has been postulated that transitory rises in IL-6 levels after acute exercise bouts may, in fact, exert anti-inflammatory effects (22, 41, 42, 62, 63). Supporting this notion, *in vitro* and *in vivo* observations (1, 5, 65) suggest that the transitory IL-6 elevation is followed by an increase in anti-inflammatory cytokines, such as IL-10 and soluble TNF receptors, ultimately blocking TNF-α actions. In the SLE$_{INACTIVE}$ women, however, a single bout of acute intense exercise did not promote any significant alterations in IL-6 levels. In addition to the already discussed effect of the exercise duration, which was shorter in the current study as compared to others involving healthy subjects (21, 38, 54), the absolute intensity of the single bout of acute intense aerobic exercise in SLE$_{INACTIVE}$ women was considerably lower than that of the healthy subjects. As IL-6 has been thought to act as an energy sensor, the magnitude of its change in response to exercise is known to respond to substrate availability, particularly to muscle glycogen levels (34). Thus, it may be that the lower absolute intensity achieved by the SLE$_{INACTIVE}$ women led to a lower glycogen depletion during acute exercise when compared with HC, which may have attenuated the IL-6 response. Alternatively, one may speculate that this "blunted" response may be somehow related to the inflammatory profile in SLE$_{INACTIVE}$ women and/or its pharmacological treatment, although the clinical relevance of these findings remains to be elucidated. From a clinical standpoint, the fact that no changes were observed (except for a slight reduction in sTNFR1) in any of the inflammatory markers suggest that even more intense exercise may pose no risk to SLE$_{INACTIVE}$ women, at least acutely.

Effects of acute moderate and intense aerobic exercise on cytokines and soluble TNF receptors kinetics in SLE$_{ACTIVE}$

A single bout of acute moderate aerobic exercise did not lead to cytokines and soluble TNF receptors changes, except for minor reductions in IL-6. Similarly as observed in SLE$_{INACTIVE}$, all cytokines and soluble TNF receptors remained stable in response to a single bout of acute moderate exercise in SLE$_{ACTIVE}$. Thus, one may suggest that acute moderate exercise did not exacerbate the disease in either active or inactive SLE patients. The lack of a transitory increase in IL-6 levels usually seen after a single bout of acute aerobic exercise in healthy subjects (32, 53) may be partially attributed to the characteristics of the acute moderate exercise protocol (*i.e.*, low intensity and/or duration), which may have been insufficient to induce such an effect.

Importantly, the single bout of acute intense exercise did not induce changes in IFN-γ levels in SLE$_{ACTIVE}$ women. This finding is of particular relevance as this cytokine seems to play an essential role in human systemic autoimmunity, particularly in SLE with active disease (47). In support to this notion, there is evidence showing that IFN-γ is uniformly required in both spontaneous and induced animal models of SLE (2). Even though the single bout of acute exercise did not decrease IFN-γ levels as previously showed in multiple sclerosis patients (12), the absence of changes in this cytokine suggests that an acute exercise bout does not exacerbate inflammation in SLE$_{ACTIVE}$ women.

In addition, the IL-10 increase in SLE$_{ACTIVE}$ women after the single bout of acute intense exercise is in accordance with previous observations in Parkinson's patients (10). Considering that IL-10 has an inhibitory action upon nuclear factor kappa B (NF-κB) (29), the transient increase in this cytokine observed after the single bout of acute intense aerobic exercise has been interpreted as an anti-inflammatory response to exercise (22, 39, 41, 42, 62, 63). In contrast to healthy subjects, who seem to require a more prolonged and intense exercise to elevate IL-10 production (38), a relatively shorter-duration and lower-intensity exercise protocol (*i.e.*, 30 min at 70% of VO$_2$max) was shown to be sufficient in eliciting an IL-10 increase in SLE$_{ACTIVE}$ women. Whether this response translates into a chronic anti-inflammatory effect remains to be elucidated.

Another interesting result of the present study refers to the IL-6 response. SLE$_{ACTIVE}$ women showed a transient increase - although smaller than that of the healthy individuals (23% *vs.* 368%, respectively). This followed by a substantial reduction in IL-6 levels 60 minutes after the single bout of acute intense exercise, with a progressive return to baseline. This partially "blunted" response regarding the exercise-induced increase in IL-6 is intriguing, and may be explained by some hypotheses. First, in accordance with previous reports (33, 49), SLE$_{ACTIVE}$ women showed lower physical capacity than HC, implying that their absolute workload was lower than that of the healthy subjects. In theory, this may have led to an insufficient stimulus to stimulate IL-6 production, as previously showed in healthy subjects (32, 53). Alternatively, one may speculate that the pharmacological treatment may have inhibited this response. Corroborating this assumption, it has been demonstrated that 20 mg of prednisolone abrogated the exercise-induced IL-6 increase in healthy subjects (3). Further studies should investigate the mechanisms by which the IL-6 response to exercise is dissonant in SLE$_{ACTIVE}$ and healthy subjects, as well as the clinical repercussions of this phenomenon.

Notably, an increase in TNF-α levels—which was not paralleled by a concomitant increase in soluble TNF receptors—was seen in SLE$_{ACTIVE}$ women at the 30th minute of recovery. A similar increase in TNF-α after the single bout of intense exercise was also observed in patients with chronic obstructive pulmonary disease (50). In healthy subjects, an exercise-induced increase in TNF-α is not usually expected (39, 41, 42, 62, 63), unless large amounts of exercise are performed (*e.g.*, marathon running) (36). TNF-α acts as a growth factor for B cells by stimulating the production of IL-1. Moreover, TNF-α promotes increased IFN-γ production via NF-κB activation. Its role in SLE pathogenesis has been debatable. For example, increased serum levels of TNF-α have been observed in SLE patients and associated with disease activity and some clinical manifestations (51). Conversely, the deletion of a fragment of the TNF-α gene, which reduces TNF-α serum levels, led to a delayed disease onset in a murine "lupus" model (*i.e.*,

NZB/W) (27); in addition, a replacement therapy with recombinant TNF-α delayed the development of nephritis (26, 27). Notwithstanding the controversial involving the role of TNF-α in SLE, it is important to note that in the current study, TNF-α levels peaked at the 30th minute of recovery. TNF-α consistently decreased thereafter (below baseline levels), returning to baseline 24 hours after the single bout of acute intense exercise. This response suggests that a single bout of acute intense exercise does not disrupt TNF-α response permanently, reinforcing the notion that acute exercise bout does not exacerbate the disease.

Study limitations and concluding remarks

It is important to highlight that this study is not without limitations. First, our sample was relatively small and heterogeneous, particularly with respect to the disease-related morbidities and the drug therapy. Whether these are factors affected the inflammatory response to exercise must be further examined. Second, despite the fact that SLE is much more prevalent in females (*i.e.*, female to male ratio ranging from 4.3 to 13.6) (45), our sample was composed only of women, which limited our ability to extrapolate our findings males. Third, our conclusions must be confined to the exercise type (i.e., aerobic exercise) and its respective intensities (*i.e.*, ≤ approximately 70% of VO$_2$peak) tested in the current study. The effects of other acute exercise types (*e.g.,* resistance training, high-intensity interval training, circuit training) on inflammation needs to be carefully evaluated in future studies. Finally, we have assessed neither the full spectrum of cytokines implicated in the pathogenesis of SLE, nor the impact of a long-term exercise program on the inflammatory profile in SLE patients, which should also be assessed in future studies.

Importantly, both single bouts of acute moderate and intense aerobic exercise led to comparable (minor) changes in cytokines and soluble TNF receptors in SLE$_{INACTIVE}$ and SLE$_{ACTIVE}$ women. This observation is in line with the findings of Scott et al. (53), who found similar IL-6, TNF-α, and IL-1ra kinetics in response to 60 minutes of running either at 55 or 65% VO$_2$max. Nonetheless, the same authors found that running at 75% VO$_2$max led to greater IL-6 and IL-1ra levels following acute exercise in comparison with the lower-intensity exercise protocols. Likewise, Peake et al. (38) observed higher levels of cytokines (*i.e.*, IL-6, IL-10, IL-12, and IL-1ra) in response to a single bout of acute intense exercise (*i.e.*, 60 minutes at 85% VO$_2$max) when compared with a lower-intensity one (*i.e.*, 60 minutes at 60% VO$_2$max) in healthy subjects. Altogether, these results suggest that only a single bout of higher-intensity (≥ 75% VO$_2$max) longer-lasting (>40 minutes) acute exercise, which induces a greater amount of glycogen depletion (34, 40), may lead to further increases in IL-6 and, consequently, anti-inflammatory cytokine levels (*e.g.*, IL-10). Further chronic studies should be performed to investigate the safety and efficacy of exercise program with different intensities in SLE patients.

Noticeably, cytokine kinetics in response to a single bout of acute exercise, regardless of its intensity, were very similar in both SLE$_{ACTIVE}$ and SLE$_{INACTIVE}$ women. Perhaps an exception was the lower level of soluble TNF receptors observed at some time points (especially in response to moderate exercise) in the SLE$_{ACTIVE}$ women, possibly reflected by the lower levels of TNF-α in this group. The mechanisms by which acute exercise bout may induce differential responses in TNF-α and its soluble receptors in SLE patients with active and inactive disease remain elusive. However, one may speculate that glucocorticoid treatment might have attenuated TNF-α levels in response to the single bout of acute exercise in SLE$_{ACTIVE}$ women, which is corroborated by *in vitro* experiments showing that dexamethasone can inhibit lipopolysaccharide-induced TNF-α production in a dose-dependent manner (55). Further investigations regarding the possible interaction between drugs and exercise upon inflammation are required.

As evidence against the concern that a single bout of acute exercise could exacerbate the disease, there was some evidence suggesting that exercise could, in fact, alleviate inflammation (39, 44). In this regard, it is noteworthy that the single bout of acute exercise was able to restore, at least temporarily, IL-6 and TNF-α levels in SLE$_{ACTIVE}$ women, which reached comparable levels to those of the HC group. This observation warrants further investigation for the potential anti-inflammatory effects of chronic exercise in SLE.

In conclusion, single bouts of acute moderate and intense exercise led to minor and transient changes in the cytokines and soluble TNF receptors levels, which were fully restored after 24 hours of recovery in SLE$_{INACTIVE}$ and SLE$_{ACTIVE}$ women and their healthy counterparts. Collectively, the current findings demonstrated that single bouts of acute moderate and intense exercise did not exacerbate the inflammatory state of both SLE$_{INACTIVE}$ and SLE$_{ACTIVE}$ women.

ACKNOWLEDGEMENTS

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