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REVIEW ARTICLE

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Interleukin-10 responses from acute exercise in healthy subjects: A systematic review

Carolina Cabral-Santos[1] | Edson Alves de Lima Junior[2] | Isabela Maia da Cruz Fernandes[1] | Rafael Zambelli Pinto[3] | José César Rosa-Neto[2] | Nicolette Charllote Bishop[4] | Fábio Santos Lira[1]

[1]Exercise and Immunometabolism Research Group, Postgraduation Program in Movement Sciences, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente, São Paulo, Brazil

[2]Immunometabolism Research Group, Department of Cell and Developmental Biology, University of São Paulo, Butantã, São Paulo, Brazil

[3]Department of Physical Therapy, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil

[4]School of Sport, Exercise, and Health Sciences and National Centre for Sport and Exercise Medicine, Loughborough University, Loughborough, United Kingdom

Correspondence
Fábio Santos Lira, Exercise and Immunometabolism Research Group, Department of Physical Education, University of the State of São Paulo (UNESP), Rua Roberto Simonsen, 305, CEP 19060-900, Presidente Prudente, SP, Brazil.
Email: fabio.lira@unesp.br

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Abstract

Purpose: Interleukin 10 (IL-10) is a cytokine that plays a critical role with potent anti-inflammatory properties when produced during exercise, limiting host immune response to pathogens and preventing tissue damage. The purpose of this systematic review was to assess the response of IL-10 after acute exercise session in healthy adults.

Methods: Databases of Ovid Medline (1978–2016), CINAHL (1998–2016), EMBASE (2003–2016), SportDiscus (1990–2016), and Web of Science library (1990–2016) were carefully screened. Clinical trials comparing exercise types in healthy individuals were included for pooled analysis. The trials of exercise were methodologically appraised by PEDro Scale.

Results: Twelve randomized controlled and crossover trials containing 176 individuals were identified for inclusion. The Kruskal-Wallis test showed no significant differences between type of exercise and the corresponding values in IL-10 [$X2(4) = 2.878$; $p = 0.449$]. The duration of exercise was significantly correlated with increase in IL-10 changes (Pearson's $r = 1.00$, 95%CI: 0.015–0.042, $p < 0.0001$) indicating that 48% of the variation in IL-10 levels can be explained by the duration of the exercise performed. In addition, despite a linear increase, we did not find a significant correlation with the intensity of exercise and IL-10 changes (Pearson's $r = 0.218$, 95%CI: −0.554–0.042, $p < 0.035$).

Conclusion: Overall, the duration of the exercise is the single most important factor determining the magnitude of the exercise-induced increase of plasma IL-10.

KEYWORDS

acute exercise, anti-inflammatory response, inflammation, interleukin 10 (IL-10)

1 | INTRODUCTION

In healthy individuals, acute and chronic exercise is known to alter circulating concentrations of inflammatory markers, reduce incidence of infection and promote a lower risk of chronic disease associated with morbidity (Pedersen & Saltin, 2015). Physical exercise induces strong metabolic and immunological responses – seen by release of some cytokines such as serum and skeletal muscle interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor-alpha (TNF-α) – that act on inflammatory responses altering the pro/anti-inflammatory balance with crucial role in tissue repair and energy metabolism (Fischer, 2006; Pedersen & Febbraio, 2009). However, these responses are dependent on duration, intensity and therefore the volume of exercise performed in a session (Lira et al., 2012).

IL-10, a small soluble protein that mediates communication between immune and nonimmune cells, was first described by

Fiorentino, Bond, and Mosmann (1989) and termed cytokine synthesis inhibitory factor. It is expressed and endogenously released by cells of the immune system including macrophages, dendritic cells, natural killer cells, eosinophils and neutrophils, B cells, several T-cell subpopulations including T-helper 1 cells (Th1), Th2, and T-regulatory cells (Kwilasz, Grace, Serbedzija, Maier, & Watkins, 2015). IL-10 acts as an immune mediator and inhibits the production of interferon gamma (IFN-γ) and the synthesis of cytokines by Th1, monocyte, and macrophage (Fiorentino et al., 1989; Steensberg, Fischer, Keller, Møller, & Pedersen, 2003).

The principal role of this interleukin is to prevent the exacerbation of the pro-inflammatory response, blocking a possible persistent inflammatory state (Pedersen & Febbraio, 2009). Classically, IL-10 acts to inhibit cytokine synthesis mainly at the level of cytokine gene transcription (Wang, Wu, Siegel, Egan, & Billah, 1994) and has strong down regulatory effects on secretion of pro-inflammatory cytokines such as IL-1, IL-1β, TNF-α (de Waal Malefyt, Abrams, Bennett, Figdor, & de Vries, 1991) which are all involved in chronic inflammatory processes and acute exercise. Furthermore, IL-10 enhances the release of anti-inflammatory mediators such as IL-1 receptor antagonist (IL-1ra), an antagonistic cytokine that competes with IL-1 for receptor binding without inducing signal transduction, and also soluble TNF receptors from innate immune cells (Kwilasz et al., 2015). Dysregulation of IL-10 is associated with impaired immune responses to infection, chronic inflammation, and increased risk for the development of many autoimmune diseases (Iyer & Cheng, 2012).

Recently, a study by Wadley, Chen, Lip, Fisher, and Aldred (2016) suggests that the magnitude of increase in the concentration of circulating cytokines in response to exercise is dependent on exercise volume. The effects of physical exercise on IL-10 levels have been used to recommend exercise as an anti-inflammatory therapy. Studies have demonstrated that in healthy subjects acute moderate running at 70% of speed associated with maximum rate of oxygen consumption (sVO_2max) and high intensity exercise at 100% sVO_2max resulted in a significantly increase in IL-10 during and after exercise until 60 min (Cabral-Santos et al., 2015) leading to an temporary increase in the circulating anti-inflammatory status. Rosa-Neto et al. (2009) observed that exhaustive exercise exerted an anti-inflammatory effect observed by most prominent changes in IL-10 and the IL-10/TNF-α ratio in skeletal muscle (especially in type 2 fibers), where the opposite response was observed in white adipose tissue with pro-inflammatory effect (increase in the protein expression of IL-6 and TNF-α) possibly contributing to increased lipolysis to provide energy for the exercising muscle.

Given these documented differences in the effects of acute exercise on IL-10 responses according to intensity and duration (and therefore, as a result, volume), it is important to consider these factors when investigating immune responsiveness to exercise performed. Our aim was to assess the effect of acute exercise on the IL-10 response in healthy subjects. Understanding what are the effect of the exercise session and the magnitude required to increase IL-10 following different types of exercise program is necessary to provide an evidence-based approach to exercise prescription for individuals.

2 | METHODS

2.1 | Systematic review registration

The protocol was registered with the International Prospective Register of Systematic Reviews on November 15, 2016 at: http://www.crd.york.ac.uk/PROSPERO. FDA device/drug status: Not applicable.

2.2 | Electronic searches

A computerized systematic search was first performed in Ovid MEDLINE and subsequently adapted to CINAHL, EMBASE, Web of Science, and SPORTDiscus databases. The search was conducted from 1978 to January 2017. The search strategy consisted of a combination of database-specific combinations of key terms (text words contained in the title and abstract, and of the index terms used to describe articles) and Boolean operators ("AND," "OR," "NOT"). The detailed search strategy was performed with the following descriptors: "inflamm$ or biomarkers or immune$ or inflammatory mediators or inflammatory biomarkers or serum mediators or interleukin-10 or IL-10, health$ or healthy individuals, physical exercise, physical training, continuous exercise, high intensity interval exercise, high intensity interval training, sprint interval training, sprint interval exercise, resistance exercise, endurance exercise, aerobic exercise, strength exercise" and all combined (Appendix 1). The search terms were modified according to the specific vocabulary map of each database.

2.3 | Study selection

Citations were assessed based on all fields. Study selection, full publications of potentially relevant studies, critical quality appraisal and data extraction were conducted independently by two reviewers using the pre-defined eligibility criteria. Disagreements were resolved via discussion, with a third party if necessary, until a consensus was reached.

Additionally, the reference lists of all identified reviews were used Endnote (version X7.3.1, Thomson Reuters, Philadelphia, PA) to create a bibliographic database to manage the search results. Titles and abstract were retrieved and screened by three independent reviewers (CCS, IMCF, EAL).

2.4 | Inclusion criteria of studies

Study design: randomized and non-randomized controlled and uncontrolled interventions.

- Acute exercise and interleukin-10;
- Participants: healthy individuals without any age restriction;
- Interventions: acute aerobic and/or resistance exercise and/or endurance and/or high-intensity interval exercise;
- Outcome measures: all parameters of the immune function (e.g., cytokines, mediating proteins, cell counts, and functions);
- IMC ≤ 24.9.

Articles were excluded if they were case reports, if they were written in a language other than English, – did not provide enough information, – articles without exercise protocols, articles that used animal models, sample related to a disease, or duplicate publications, and studies without full text manuscript available (e.g., abstracts, conference proceedings, presentations).

2.5 | Quality assessment

Methodologic quality was evaluated using the Physiotherapy Evidence-based Database criteria – PEDro scale (Moseley, Herbert, Sherrington, & Maher, 2002). This scale is scored the methodological quality of clinical trials in relation to their internal validity according to 11 items; that indicates the quality in scores range from: high quality (9–10), good (6–8), moderate (4–5), or poor (<4). In case of conflicting evaluations, disagreements were resolved through discussion between the authors.

2.6 | Statistical analyses

Descriptive data are shown as means and standard deviation (Table 1). Kruskal–Wallis Analysis of variance was used to compare the delta changes from IL-10 (Δ) were as the ratio between the pre-exercise values in relation to postexercise values [Δ = postexercise − pre-exercise values] in the type of exercise. All pairwise comparisons were performed using the Dunns method.

Correlations between the exercise duration, intensity, and changes in plasma IL-10 were evaluated using Pearson correlation coefficients (*r*). Statistical significance was set at 5% for all analysis and the calculations were conducted using GraphPad Prism 7.

3 | RESULTS

3.1 | Study selection

The initial electronic database search identified 3,147 articles, of which 2,825 were screened (after removal of duplicates −322). In total, 2,738 publications were excluded on the basis of title and abstract. On application of the review inclusion criteria to the 57 studies of potential relevance full-text papers, a further 45 papers were excluded and the most common reasons for exclusion were that the study did not evaluate IL-10 values in the timepoint pre- and immediately postexercise or did not collect and evaluate IL-10 from blood samples. The least common reason was that the exercise protocol utilized was chronic rather than acute (i.e., repeated bouts over a period of time), exercise performed in a climatic chamber, or other placebo supplementation procedures. Therefore, 12 publications met the inclusion criteria and were included in the systematic review. Figure 1 shows a flowchart of the article search.

3.2 | Description of studies

To investigate the effects in IL-10 behavior after acute exercise, the results were grouped according to the type of exercise. Four articles studied the effects of exercise and IL-10 on strength (Agostinete et al., 2016; Gerosa-Neto et al., 2016; Peake, Nosaka, Muthalib, & Suzuki, 2006; Rossi, Gerosa-Neto, Zanchi, Cholewa, & Lira, 2016), three on continuous running versus intermittent running performed on treadmill (Cabral-Santos et al., 2015; Dorneles et al., 2016; Ghafourian, Ashtary-Larky, Chinipardaz, Eskandary, & Mehavaran, 2016), one on cycling ergometer (Cullen, Thomas, Webb, & Hughes, 2016;) and four on strenuous exercise – lasting at least 3 hr of outdoor long distance race (which the runners were allowed to choose their own speed) associated or not to other type of exercise (Comassi et al., 2015; Kaoru, Suzuki, Yoshitani, Shiraishi, & Kometani, 2013; Krzemiński et al., 2016; Nickel et al., 2012).

3.3 | Effects of interventions

the Kruskal–Wallis test showed no significant differences between grouped type of exercise and the corresponding values in ΔIL-10 [$X^2(4) = 2.878$; $p = 0.449$], as shown in Figure 2. 10 of the 12 eligible articles showed an increase in IL-10 levels, two did not report statistically significant differences after acute exercise.

The duration of exercise was significantly correlated with an increase in IL-10 changes (Pearson's $r = 1.00$, 95%CI: 0.0159–0.0425, $p < 0.0001$, Figure 3) indicating that 48% of the variation in IL-10 levels can be explained by the duration of exercise. However, despite a linear increase, there was no correlation of intensity and increase in IL-10 levels (Pearson's $r = 0.212$, 95%CI: −0.554–0.927, $p < 0.035$; Figure 4).

4 | DISCUSSION

This study investigated the influence of type and intensity of acute exercise on to a better understanding of the amount of exercise is required to increase anti-inflammatory response in health individuals. The physical exercise represents an acceptable model to induce an inflammatory response, commonly seen by increase the mobilization and activation of granulocytes, lymphocytes, and monocytes, as well release of inflammatory factors and soluble mediator (Shek & Shephard, 1998). However, regular physical exercise seems to play an important role in health benefits by increasing IL-10 levels which appears to be a pivotal function for reducing the ability of macrophages to respond to IFN-γ and their microbicidal activity, and the negative feedback response to the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, IL-12 (Oswald, Wynn, Sher, & James, 1992; Pedersen & Febbraio, 2009).

The plasma IL-10 increases seen during exercise are mediated by IL-6 from contracting muscles. Steensberg et al. (2003) evaluated young healthy volunteers that received a low dose of recombinant human (rh)IL-6 or saline for 3 hr in the femoral arteries of both legs (approximately 140 pg/ml) and observed that muscle-derived IL-6 plays a key role in exercise-induced enhanced the plasma levels of cortisol, IL-1 receptor agonist (IL-1ra), and IL-10 compared with saline infusion. In addition, rhIL-6 induced increased levels in

TABLE 1 Characteristics of the included studies

Reference	Characteristics of participants	Design	Exercise protocol	Outcome IL-10 (pg/ml)	PEDRO escore
Agostinete et al. (2016) (Brazil)	Eight physically active healthy men, 23.5 ± 3.1 years, 80.7 ± 6.4 kg	Three randomized session: Short: 70%1RM, 30 s of rest; Moderate: 70%1RM, 90 s of rest; Volume-equated Short: 70%1RM, 30 s of rest	Four sets of Squat, Bench Pess and T-Barrow exercises until movement failure	30" ↑ Pre: 2.82 ± 2.24 Pos: 5.11 ± 3.81 90" ↑ Pre: 2.93 ± 2.64 Pos: 4.59 ± 4.61 Volume-equated ↑ Pre: 2.94 ± 5.17 Pos: 3.06 ± 4.90	7
Cabral-Santos et al. (2015) (Brazil)	Eight physically active healthy men, 24.56 ± 6.02 years, 74.69 ± 7.48 kg	High-intensity intermittent aerobic exercise (HIIE) and steady-state exercise (SSE)	HIIE: 5-km run on a treadmill performed in intermittently at 1-min at the sVO_2peak followed by 1-min of passive recovery SSE: continuous 5-km run on a treadmill at 70% of sVO_2peak	HIIE ↑ Pre: 1.389 ± 0.407 Pos: 2.553 ± 0.913 SSE ↑ Pre: 1.144 ± 0.952 Pos: 2.436 ± 1.508	6
Comassi et al. (2015) (Italy)	27 well-trained men NR	Ironman (IR) and Half Ironman triathlon (HIR)	The duration of exercise was 12:48:21 ± 1:14:18 hr for IR and 6:14:43 ± 0:37:25 hr for HIR	IR ↑ Pre: 11.5 ± 6.6 Pos: 63.5 ± 65.9 HIR ↑ Pre: 14.2 ± 19.2 Pos: 35.0 ± 32.8	6
Cullen et al. (2016) (United Kingdom)	10 healthy active individuals (five males and five females), 24 ± 4 years, 1.70 ± 0.9 m, 67 ± 11 kg, VO_2max 49 ± 5 ml/kg/min	Three exercise sessions on a cycle ergometer: Low: 35 min cycling at 50% VO_2max; Moderate: 5 × 5 min bouts at 50% VO_2max interspersed 2 min intervals at 80% VO_2max; High: 5 × 4 min bouts at 80% VO_2max interspersed with 3 min intervals at 50% VO_2max		LOW ↓ Pre: 0.17 ± 0.06 pg/ml Pos: 0.16 ± 0.10 pg/ml MOD ↓ Pre: 0.18 ± 0.09 pg/ml Pos: 0.17 ± 0.07 pg/ml HIGH ↓ Pre: 0.13 ± 0.07pg/ml Pos: 0.12 ± 0.09 pg/ml	5
Dorneles et al. (2016) (Brazil)	Lean individuals (n = 10) with 26.5 ± 6.11 years, 66.07 ± 7.61 kg and 1.73 ± 0.06 m	High-intensity exercise (HIIE): 10 bouts × 60 s (85–90%PMax) interspersed 75 s active (50%PMax); and Moderate exercise (MIIE): 10 bouts × 60 s (70–75% PMax) interspersed 60 s active (50%PMax)	The duration of exercise was approximately 30 min	HIIE ↑ Pre: 2.48 ± 0,58 Pos: 3.97 ± 1.62 MIIE ↔ Pre: 1.67 ± 0.74 Pos: 1.69 ± 0.85	7

(Continues)

TABLE 1 (Continued)

Reference	Characteristics of participants	Design	Exercise protocol	Outcome IL-10 (pg/ml)	PEDRO escore
Gerosa-Neto et al. (2016) (Brazil)	8 healthy subjects age 25.2 ± 4.1 years, 76.4 ± 7.7 kg, 1.78 ± 0.10 m	Two randomized sessions with different rest intervals on the treadmill: Short: 90% of 1RM and 30 s rest allowed between sets; Moderate: 90% of 1RM and 90 s rest allowed between sets	Four sets until movement failure in the squat and bench press exercises	90" ↔ Pre: 18.2 ± 12.7 Pos: 16.4 ± 10.7 30" ↔ Pre: 17.0 ± 10.0 Pos: 16.6 ± 10.9	8
Ghafourian et al. (2016) (Iran)	20 healthy man 21.3 ± 1.6 years, 74.1 ± 8.3 kg, 1.80 ± 0.6 m, VO_2max 53 ± 4.2 ml/kg/min	Two protocols of a single bout of treadmill: Submaximal: 30 min of running at a speed of 65% of VO_2max Maximal: six periodic repetitions with three minutes at a speed of 85% of VO_2 max with 90 s of rest among each repetition	-	65% VO_2max ↔ Pre: 2.19 ± 0.20 Pos: 2.58 ± 0.45 85% VO_2max ↑ Pre: 2.91 ± 0.77 Pos: 3.38 ± 0.37	7
Kaoru et al. (2013) (Japan)	14 male triathletes, 28.7 ± 7.9 years, 63.2 ± 6.0 kg	One session of duathlon race	The race consisted of 5 km of running, 40 km of cycling, and 5 km of running (~17 hr). Measurements at pre, 0, 1.5, and 3 hr after race	Pre: 3.1 ± 8.2 ↑ Pos: 16.1 ± 31.4	5
Krzemiński et al. (2016) (Poland)	9 healthy trained male 30.0 ± 1.0 years, 72.0 ± 2.0 kg, 1.78 ± 0.20 m, VO_2max 54.1 ± 3.0 ml/kg/min	A 100-km ultra-marathon (runners had to reach the finish line within 17 hr)	The runners were allowed to choose their own speed and had free access to fluids and carbohydrate-rich food available in support tents at the refreshment points	Pre: 0.31 ± 0.06 ↑ Pos: 5.04 ± 1.34	6
Nickel et al. (2012) (Germany)	16 lean elite group (regular intensive exercise > 55 km/week): 74.4 ± 11 kg; 40 ± 7 years, BMI 22 ± 1 kgm^2 16 lean nonelite (regular intensive exercise < 40 km/week): 78.5 ± 9 kg, 40 ± 6 years, BMI 24 ± 2 kgm^2;	Marathon	Race results LE: 217 ± 28 min LNE: 235 ± 28 min	LE ↑ Pre: 1.48 Pos: 16.9 LNE ↑ Pre: 1.47 Pos: 16.6	5
Peake et al. (2006) (Japan)	10 healthy young men, 22.9 ± 4.7 years, 76.2 ± 11.8 kg, 1.80 ± 0.08 m	Cross-over design Submaximal: 10 sets of 60 lengthening contractions at 10% maximum isometric strength, or Maximal: 10 sets of three lengthening contractions at 100% maximum isometric strength	Elbow flexor on preacher curl bench placed alongside an isokinetic dynamometer measured before exercise, immediately after, 3 hr, 1, 2, 3, and 4 days after exercise	Submaximal ↔ Pre: 1.7 ± 1.3 Pos: 2.1 ± 1.9 Maximal ↔ Pre: 1.5 ± 1.4 Pos: 1.6 ± 1.8	6
Rossi et al. (2016) (Brazil)	Eight healthy subjects with strength training experience, 24.6 ± 4.1 years, 76.4 ± 7.7 kg	Two randomized sessions with different rest intervals: Short:70% of 1RM with 30 s of rest between sets, or Moderate: 70% of 1RM with 90 s of rest between sets	Four sets of squat and bench press until movement failure	Short ↔ Pre: 16.30 ± 9.88 Pos: 17.52 ± 12.83 Moderate ↔ Pre: 16.64 ± 11.86 Pos: 15.88 ± 11.34	6

Note. Values are the mean ± standard deviation. In studies investigating the effect of any intervention, only the result from the control group exercise is presented. 1RM: One maximum repetition; MaxHR: maximal heart rate; PMa: maximal potency; ↑: increase; ↓: decrease; ↔: no diferences in IL-10 levels.

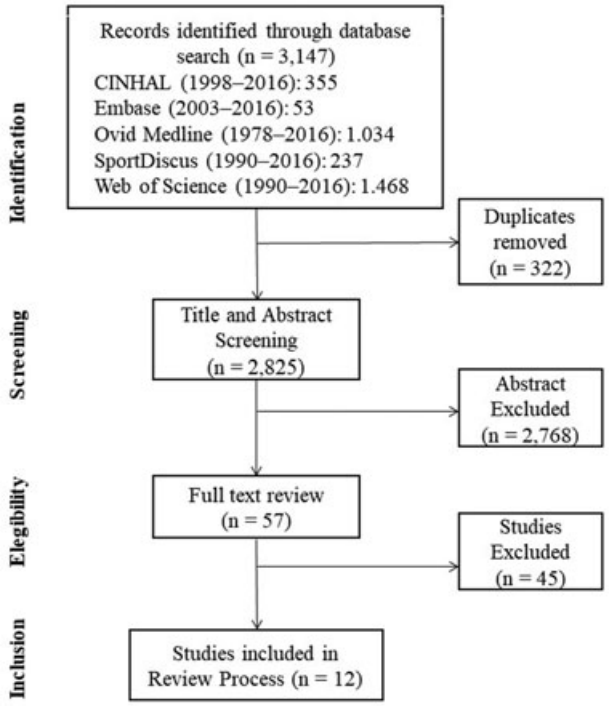

FIGURE 1 Inclusion flowchart of the selected studies

circulating neutrophils and a decreased the lymphocyte number without effects on plasma epinephrine, body temperature, mean arterial pressure, or heart rate. Cytokines have a short half-life in the circulation. Regardless of, levels of IL-10 tend to peak at the cessation of the exercise or shortly thereafter. One previous study shows that after acute exercise (5-km continuous run on a treadmill at 70% of sVO_2max) peak concentrations of IL-10 were reached 60 min after the cessation of acute exercise compared with baseline levels (Cabral-Santos et al., 2016). Thus, the systemic effects induced

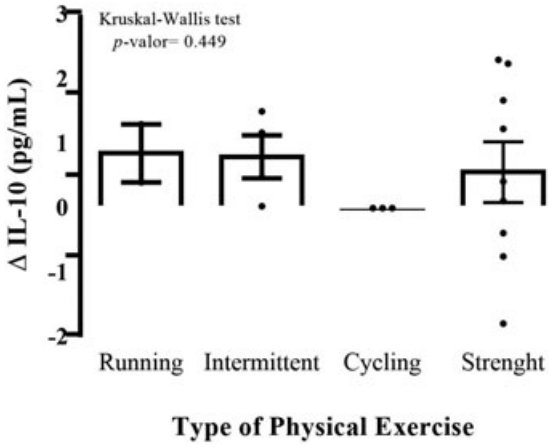

FIGURE 2 Effect of different types of acute exercise and the corresponding increase in plasma IL-10 (delta change from pre-exercise level) in humans. Based on the 12 studies, the graphs represent approximately 164 subjects (listed in Table 1). Each dot represents one exercise protocol, while the corresponding bars show geometric means and standard error of mean. IL-10: interleukin 10

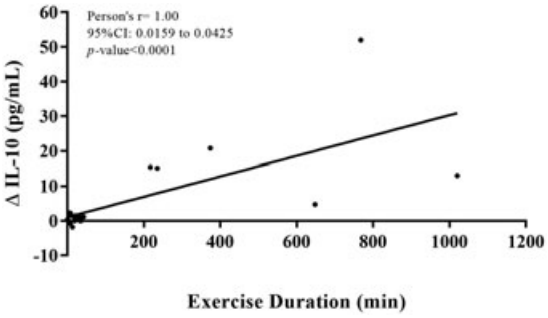

FIGURE 3 Linear relation between exercise duration and changes in plasma IL-10. Each dot represents one exercise protocol. IL-10: interleukin 10

by IL-10 are for the most part perceived to occur during recovery time from exercise. However, in the present study only IL-10 levels at baseline and immediately after exercise were evaluated due these timepoints that all eligible studies had in common.

4.1 | Effects of aerobic exercise

When observed in cycle ergometer type, Cullen et al. (2016) studied the behavior of IL-10 with different intensities and volume in cycle ergometer protocols (Low: 35 min at 50% VO_2max; Moderate: five bouts of 2 min at 80% VO_2max; and High: five bouts of 4 min at 80% VO_2max). However, none of this appears to be sufficient stimulus to induce alterations in plasma or at level of gene expression in peripheral blood of IL-10, independent of being performed continuously or intermittently.

Clearly, physical exercise can be a significant stress to organism and indicators of injury or energy imbalance increase the synthesis and subsequent release of IL-6 from contracting the muscle. This cross-talk between skeletal muscle and immune cells may facilitate broad IL-10 response effects on muscle as well as on different tissue (Pedersen, 2017). Thus, the magnitude of the increase in IL-10 is related to the active muscle mass and therefore exercise intensity.

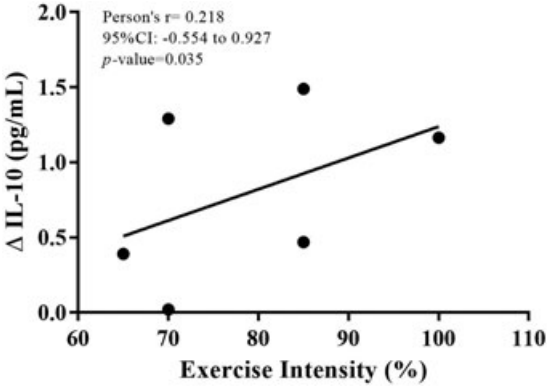

FIGURE 4 Linear correlation between exercise intensity and changes in plasma IL-10. Each dot represents one exercise protocol. IL-10: interleukin 10

It has been demonstrated that IL-6 mRNA expression and protein release increase when intramuscular glycogen is low, indicating that IL-6 is a regulator of energy metabolism during exercise (Chan, McGee, Watt, Hargreaves, & Febbraio, 2004). For the two eligible studies of treadmill running, Ghafourian et al. (2016) found no significant differences in plasma IL-10 and IL-10/TNF-α ratio concentrations after 30 min of running at 65% of sVO_2max, but interleukin-1β (key pro-inflammatory mediator of β-cell damage in Type 2 diabetes mellitus) and soluble intercellular adhesion molecule-1 decrease (sICAM-1) significantly 24 hr after. Once the acute bout of exercise triggers the anti-inflammatory effect at least in part mediated by muscle-derived IL-6 release, the current protocol was not of high enough intensity to increase the IL-6 release into the circulation and therefore is not surprising that there was no counter-effect of IL-10 levels.

However, Cabral-Santos et al. (2015) found a significant increase in the expression of IL-10 immediately after exercise from baseline (two-fold) after protocol at 70% sVO_2max – but peak levels were reached 60 min after exercise (four-fold) as well as the IL-10/TNF-α ratio peak. The increase in systemic production of IL-10 carry on augmenting resistance to infections in the immune system function via leukocyte recruitment, enhance B cell survive and differentiation, as well as inhibiting dendritic cells-mediated antigen presenting function limiting immunopathology (Hedrich & Bream, 2010; Mocellin, Marincola, Rossi, Nitti, & Lise, 2004).

In contrast, intermittent protocols may stimulate greater changes in metabolic demand. We identified a total of three articles that verified the relationship between IL-10 and intermittent exercise with a duration of approximately 30 min. Cabral-Santos et al. (2015) observed an increase circulating IL-6 values with a peak immediately after exercise, and increased IL-10 levels (three-fold) and IL-10/TNF-α ratio with peak at 60 min postexercise in the intermittent running protocol (1:1 min at sVO_2max with passive rest). Similarly, Dorneles et al. (2016) found an increase in IL-10 immediately after intermittent exercise (10 × 60 s at 85–90% of Maximal Power Output-PMax with 75 s active rest at 50%PMax) and peak values at 30 min postexercise compared with baseline level, suggesting an anti-inflammatory role promoted by this exercise type. The authors attributed this result to possible large physiological stress, principally due anaerobic metabolism (seen by increase in adrenergic response, cortisol and lactate levels) and changes in markers of muscle damage (observed by increase in lactate dehydrogenase levels) that were positively correlated with leukocyte mobilization into peripheral blood described (including lymphocytes, monocytes and neutrophils).

These results differ from the moderate intermittent protocol in which Dorneles et al. (2016) did not find any differences in IL-1ra, IL-8, and IL-10 concentrations (10 × 60 s at 70–75% with 60 s active intervals at 50%PMax). Additionally, Ghafourian et al. (2016) observed no significant differences in IL-10 levels after an intermittent protocol comprising 6 × 3 min intervals at 85% of VO_2max with a 90 s passive rest but increased IL-6 (two-fold) and ratio of IL-6/IL-10 levels. Thus, the immune modulation (and therefore anti-inflammatory benefits) come with intermittent exercise performed at higher intensities.

In response to amount of time, prior research has showed that in high-intensity intermittent exercises of different exercise volumes (running 1.25 and 2.5 km with 1:1 min at sVO_2max) the increase in IL-10 concentration was related to the duration of exercise indicating the importance of this variable (Cabral-Santos et al., 2016). Taken together, these results showed that changes in IL-10 production are remarkably related to the duration of exercise.

4.2 | Effects of strength/resistance exercise

The effect of strength/resistance exercise on plasma IL-10 is less evident. The dynamics of this type of exercise is influenced by different variables such as intensity, workload, number of repetitions, interval between sets, and the size of muscle mass involved in muscle contraction. The metabolic cost of this type of exercise is lower compared with aerobic exercise and consequently, the IL-10 levels is less pronounced. Agostinete et al. (2016) utilized strength exercises with 70% one maximum repetition-1RM and observed increased levels of IL-6 and IL-10 immediately after the exercise which remains elevated post-1hr than basal levels. The others studies analyzed did not show this dynamic, although it was observed an increase of IL-10 in the period of exercise recovery

Peake et al. (2006) tested submaximal (10 sets × 60 at 10% maximum isometric strength with 1 min rest) versus maximal (10 sets × 3 at 100% maximum isometric strength with 3 min rest) lengthening contractions performed on an isokinetic dynamometer by elbow flexors. The authors found that the muscle damage (evidenced by creatine kinase activity) was not accompanied by differences in markers of inflammation such as IL-1ra, IL-10, TNF-α, and plasma C-reactive protein (CRP). Since contracting skeletal muscle per se is an important inducer of IL-6, the use of isolated muscle contractions have low metabolic cost compared with aerobic exercises and the increase of circulating cytokine concentrations is less marked (Fisher, 2006), however the absence of systemic changes does not mean that there is no local inflammation response in the exercised muscles.

It is well know that glycogen depletion during contraction leads to the transfer of p38MAPK to the nucleus, which can upregulate IL-6 (Chan et al., 2004), however, only higher metabolic demand during the exercise session could influence the IL-10 response. Rossi et al. (2016) performed two randomized sequences at 70% of 1RM (Short: 30 s of rest between sets; Moderate: 90 s of rest) with four sets until movement failure in the squat and bench press exercises. The authors observed that short rest intervals showed statistically significant decreases in IL-6 and glucose at post-15 of recovery and there were no differences between IL-10 levels for both conditions. This can be attributed, in part, to low exercise volume in short protocol (significantly less weight was lifted and fewer repetitions executed) adopted by the authors which did not generate sufficient stimulus to increase IL-6.

Interestingly, Gerosa-Neto et al. (2016) tested the same protocol but with high intensity (90% 1RM) and showed that moderate rest interval allowed a higher workload in terms of volume of repetitions

and subsequently an increase IL-10 levels (1.9-fold) and IL-10/TNF-a ratio (2.3-fold) compared with the short rest interval condition, but only 30 min after the cessation of exercise. The differences in volume protocols during the strength exercise session may explain the discrepancy in results between protocols in Rossi et al. (2016) and Gerosa-Neto et al. (2016) which were not equalized.

Abd El-Kader and Al-Shreef evaluated elderly volunteers after 6 months of chronic aerobic exercise training (40 min running on a treadmill at 60-80% maximal heart rate index-HRmax) versus resistance exercise training (three sets of 8-12 repetitions with 60 s of rest between each set, 60 and 80% 1-RM) and provide evidence that aerobic exercise is more appropriate in modulating the immune system and inflammatory markers among the elderly population-observed by decrease in TNF-α, IL-6 and CRP levels and increase in IL-10 level. Since the lower metabolic cost of strength exercise compared with aerobic is less pronounced, this justify the insignificant increase in IL-10 levels in the studies analyzed.

4.3 | Effects of duration

Our results indicate there is a linear relationship between exercise duration and changes in plasma IL-10 (Figure 3). The average IL-10 levels in the strenuous group showed significantly increased up to five-fold whereas less dramatic increase was more frequent in the other protocols. Thus, the duration of the exercise is the single most important factor determining the magnitude of the exercise-induced increase of plasma IL-10 (48%).

Krzemiński et al. (2016) showed that well-trained young men who completed a 100 km ultra-endurance exercise reported significant increases in plasma IL-6, IL-10, IL-18, and TNF-α concentrations immediately after the event. At 90 min of the recovery period, plasma concentrations of IL-6 and IL-10 were still higher ($p < 0.05$) than before exercise, whereas plasma TNF-α did not differ significantly from the resting pre-exercise values.

The IL-10 response in this study follows that previously reported for Nickel et al. (2012) which showed significantly upregulated levels in all groups compared with their respective baseline levels (10–20-fold) after marathon running and that IL-10 values return to baseline values 24 hr after that. It could be argued that this occurrence could prevent potential inflammation and tissue damage. There was an increase in circulating IL-6 secreted by T-cells and macrophages immediately after exercise (seven-fold) and remains elevated until 24 hr after marathon compared with baseline, whereas the increase in TNF-α and CRP was delayed for 24 hr (seven-fold).

Kaoru et al. (2013) assessed triathletes after a duathlon race comprising 5 km of running, 40 km of cycling, and 5 km of running. There were significant increases in plasma concentrations of IL-6 (30-fold) and IL-10 (50-fold) immediately after the race whereas TNF-α did not change. The authors also reported subsequent acute inflammatory responses by increased in IL-8 and monocyte chemoattractant protein-1 (MCP-1); both cytokines are potent neutrophil and monocyte chemokines and stimulate cell extravasation into inflammatory tissue immediately after the race. This may mediate exercise-induced pathogenesis as muscle inflammatory damage, exertional rhabdomyolysis and heat-related multiple organ failure (Kaoru et al., 2013).

Comassi et al. (2015) compared the effect between Ironman (3.8 km swim, 180 km cycling, and 42.197 km running without interruption) and Half Ironman competitions on the inflammatory profile in male triathletes. The authors also reported an increase in plasma IL-6 and IL-10 levels (four and five-fold respectively) whereas plasma TNF-α did not differ significantly from resting pre-exercise values in both groups. In addition, the authors reported increases in MCP-1 levels and increased white blood cells count, attributed to cell mobilization in response to the increase in mechanical and metabolic stress observed in both groups. This study reported a marked increase in IL-6 and IL-10 levels provoked by exercise and direct anti-inflammatory effects by limiting of TNF-α and IL-1β signaling.

Regarding the differences in training status from individuals, Pedersen and Febbraio (2008) have reported a negative association between the amount of regular physical activity and plasma IL-6 levels release and suggest a downregulation of IL-6, partially counteracted by an enhanced expression of IL-6 receptors whereby the sensitivity to IL-6 by trained muscle is increased. Accordingly, Monteiro et al. (2017) observed in fact that 8 weeks of concurrent program (5-km intermittent run on a treadmill at 100% sVO_2max plus strength training with four sets at 80% 1RM) lead to training-induced downregulation of IL-10 peak levels after one acute exercise session only compared with pre-training condition, suggesting an immune system adaptation. Thus, we speculated the trained skeletal muscle may not explain the release amount of IL-6 and IL-10 found in trained versus an untrained subjects during exercise instead of duration of exercise.

However, studies indicate the pronounced inflammatory response induced by prolonged and exhaustive exercise could lead to transient suppression of several immune components and increase the risk of upper respiratory symptoms, potentially due to the cross-regulatory effect of interleukin-4 on interferon-γ production and immunosuppressive action of IL-10 (Gleeson, 2007; Shaw, Merien, Braakhuis, & Dulson, 2018). To prevent the transient suppression of the immune system and in illness-prone athletes, those negaged in strenuous training programs might need to adopt effective strategies to support the immune function.

4.4 | Overall completeness and applicability of evidence/implications for practice

Physical activity represents natural anti-inflammatory effects. Due the methodological heterogeneity in the protocols identified, our review shows that manipulations in the duration of the exercise exert direct inflammatory effects in magnitude on release IL-10.

Although the duration of exercise appears to be the single most important factor, currently, data lead to hypothesize that additional influence of intensity could determine this magnitude. Although the intensity was not significantly associated with circulating levels of IL-10, there was a linear relationship.

4.5 | Risk of bias

Some potential limitations could affect the interpretation of our findings. First, the sample size in these studies was small, so the distribution of the data was not normal. Second, the analysis was based on unadjusted data and did not control for confounding factors including gender, age, previous physical conditioning, and therefore cannot exclude the influence of mixed factors.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

RZP, JSRN, NCB, and FSL designed the study protocol. CCS, IMCF, and EALJ conducted the search and screening of titles, abstracts, full-text articles, the study selection, data extraction and quality, screened the full-text articles, and assessed the eligibility of the studies. CCS and EALJ conducted the analysis and interpretation of data and contributed to the writing of the manuscript. All authors read the final version of the manuscript.

ORCID

Edson Alves Lima Junior http://orcid.org/0000-0002-8816-4573
Rafael Zambelli Pinto http://orcid.org/0000-0002-2775-860X
Fábio Santos Lira http://orcid.org/0000-0002-9645-1003

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APPENDIX 1

Search algorithm

- *Outcome*

1. inflamm$ OR
2. biomarkers OR
3. immune$ OR
4. inflammatory mediators OR
5. inflammatory biomarkers OR
6. serum mediators OR
7. interleukin-10 OR
8. IL-10 AND

- *Population*

1. health$ OR
2. healthy individuals AND

- Intervention

1. physical exercise [MeSH Terms],
2. physical training OR,
3. continuous exercise OR,
4. high intensity interval exercise OR,
5. high intensity interval training OR,
6. sprint interval training OR,
7. sprint interval exercise OR,
8. resistance exercise OR,
9. endurance exercise OR,
10. aerobic exercise OR,
11. strength exercise.