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Analysis of Biomarkers in Response to High Intensity Functional Training (HIFT) and High Intensity Interval Training (HIIT): A Systematic Review Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Aerobic training with an acyclic and intermittent character triggers high metabolic stress, responsible for generating alterations in several blood biomarkers. Thus, investigations that clarify understanding of metabolic behavior in response to exercise seem pertinent, when considering the dynamics of prescription of physical training and recovery.
Objective: Demonstrate and discuss the behavior of blood biomarkers in response to High Intensity Interval Training (HIIT) and High Intensity Functional Training (HIFT).
Methods: The PubMed/MEDLINE, Scielo, Lilacs, Bireme, Google Scholar, and Scopus databases were searched from the oldest records available until January 16, 2020. The search was carried

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out by combining descriptors related to the terms: “HIIT”, “HIFT”, and “blood biomarkers”. To be included, studies were required to: 1) have a clinical trial design; 2) evaluate the effects of an HIIT and/or HIFT protocol; and 3) measure blood biomarkers before and after the training protocol. No restrictions were applied to the characteristics of the participants regarding health condition, age, sex, and level of training.

Results: In total, seven studies were included (n=221 participants, aged between 18 and 63 years) that analyzed different population profiles such as athletes, sedentary young people, patients with breast cancer, and diabetics. The biomarkers evaluated included analysis of muscle damage (C Reactive protein and CK); oxidative stress (antioxidant capacity); kidney injury (creatinine and urea); hormones (testosterone and cortisol); cytokines (TNF-α, IL-6, IL-1β, IL-10, IL-4, and IF-γ); and hemogram. In general, the results demonstrated specific patterns for the investigated markers. Thus, there were increases in muscle damage markers, while in the inflammatory markers, there was a reduction in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines. Despite the reduced values of the general blood count, markers such as neutrophils and basophils did not demonstrate statistically significant alterations. Serum testosterone levels were higher and cortisol was lower in the post-exercise period when compared to pre-exercise.

Conclusion: These data are of practical relevance when demonstrating patterns of physiological responses, which also characterize knowledge and understanding essential to determine adequate periodization.

Keywords: Inflammation; sports performance; muscle damage; cytokine; endurance training.

1. INTRODUCTION

High Intensity Functional Training (HIFT) is a method that requires an effort carried out to perform the maximum number of repetitions, in the shortest possible period of time[1]. This model is related to the predominant recruitment of the oxidative aerobic metabolic pathway which, when systematically trained, contributes to improving cardiorespiratory fitness, increasing energy expenditure, and assisting in weight loss[1]. The particularities and advantages mentioned mainly attract young adult audiences, making HIFT an activity with expressive worldwide popularity and a growing number of practitioners [1].

Similarly, high intensity interval training (HIIT) is a modality that involves explosions of short and alternating movements, with a short rest interval, promoting positive functional adaptations in body systems [2]. HIIT also presents significant popularity, with considerable data that include it among the “top 10” of emerging activities, according to the *annual survey of worldwide fitness trends*, for 12 consecutive years [3].

In this scenario, support for the practice of the aforementioned modalities is associated with a series of systemic benefits in the body that include, among others, improvement in physical conditioning, balance, cardiorespiratory resistance, joint mobility and flexibility, body composition, strength, and power [4,5]. In addition, these training protocols are suitable both for maintaining and optimizing good health levels, as well as for the prevention and treatment of chronic conditions, such as diabetes and cancer [5].

In this regard, some authors [4,5] suggest that it is pertinent to include HIIT and HIFT in rehabilitation programs when taking into account the viable physiological benefits as well as the inclusion of diversified methods in groups that motivate patients to remain in treatment, especially in cases of chronic conditions in which patients need to maintain adherence for an indefinite period. In contrast, as in any other sport, studies show a high rate of overload, fatigue, delayed muscle pain, and musculoskeletal injuries resulting from the practice of HIIT and HIFT [6,7], as individual adjustments in training load and rest intervals are required.

Specifically, in the presented modalities, the acyclic and intermittent character demands high intensity, responsible for triggering high metabolic stress, which culminates in the alteration of several blood biomarkers [8] such as TNF–α, C-reactive protein, lactate, creatine kinase, IL-6, creatinine, testosterone, cortisol, lactate, urea, IL-10, IL-1β, IL-4, IF-γ, and blood count [9,10].

Thus, it is essential to understand bioenergetics and metabolism during the practice of each type of exercise to be considered during the prescription of physical strategies in order to

guarantee safe levels of training. In this regard, in the field of sports medicine, the analysis of biomarkers is routinely implemented to identify *overtraining* and stress conditions, and it is possible from these analyses to optimize the dynamics of training prescription based on specific needs for rest or overload [6].

In turn, systematic review studies on methodologies used and validated parameters referring to different biomarkers in HIIT and HIFT practitioners are important to provide standardization in this specific scenario, in addition to allowing subsequent individualized interventions aimed at improving performance and reducing the incidence of musculoskeletal injuries, especially because of the demands required in these sports. In addition, analysis of hematological data is able to demonstrate the condition of the immune system, necessary for good levels of fitness and sports performance [9,10].

Therefore, the objective of this systematic review study was to demonstrate and discuss the behavior of blood biomarkers in response to HIIT.

2. METHODS

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021165233 and all guidelines listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were carried out to ensure the quality of the study [10,11].

2.1 Search Strategy

The included studies were selected from the following databases: Scielo, Medline/PubMed, Lilacs, Bireme, Google Scholar, and Scopus from the oldest records available until January 16, 2020. The search was carried out by combining descriptors related to the terms: “HIIT”, “HIFT”, and “blood biomarkers”. In addition, a manual search was performed in the references of the included studies to complement the electronic searches. As CrossFit™ is classified as a modality of HIFT, studies that evaluated this modality were also included and considered as such. In addition, any modalities that fit the training characteristics of HIFT and HIIT were included.

2.2 Inclusion and Exclusion Criteria

To be included, studies were required to: 1) have a clinical trial design; 2) evaluate the effects of an HIIT and/or HIFT protocol; and 3) measure blood biomarkers in the moments before and after performing the training protocol. No restrictions were applied on the characteristics of the participants regarding health condition, age, sex, and level of training. Case reports, case series, comments, editorials, letters to the editor, and literature reviews were excluded.

2.3 Selection of Studies and Data Extraction

The study selection process was carried out by two independent researchers (DDCS and JSSL) and the exclusions were conducted in stages (duplicates, title, abstract, and full text), as shown in the flowchart in Fig. 1. In cases of disagreement, a third researcher would be contacted to define possible pending issues (CMBA).

All relevant information about the included studies referring to the author/year of publication, sample size, type of study, characteristics of the participants, training protocol used, biochemical markers analyzed, outcome, and classification of the article according to the PEDro scale were extracted and are presented in Table 1.

2.4 Methodological Quality Assessment

The methodological quality of the studies was assessed using the PEDro scale (0-10) by two independent evaluators (DDCS and JSSL). The score obtained on the PEDro scale was not considered as an inclusion criterion. Each study was assessed for: eligibility criteria, random allocation, secret allocation, baseline comparisons, subject, therapist, and evaluator blinding, follow-up with less than 15% loss, appropriate treatment according to allocation or intention to treat, intergroup statistical comparisons, and measures of precision and variability. The total score ranged from zero to 10 points, in which higher scores were considered to be of better methodological quality [10,11].

3. RESULTS

At the end of the data search, a total of 3,026 articles were selected. The exclusion process occurred in stages (duplicates, titles, abstracts, and full text), and was carried out in pairs. Thus,

at the end of the exclusion steps, a total of seven articles met the proposed inclusion criteria and were appropriately analyzed. The detailed selection process is shown in the flowchart in Fig. 1.

3.1 Characteristics of the Studies

The total sum of participants included in the seven studies analyzed was 221 participants (99 men and 122 women). The minimum age was 18 years and the maximum 64 years. The studies were published between the years 2000 and 2019, and were carried out in several countries; Canada [12]; Brazil [13,14]; Iran [15]; Czech Republic [16]; Spain [17]; and Australia [18].

Regarding the sex of the participants, two studies included only men [16,17], one included only women [18], and four included both sexes [12,13,14,18]. With respect to the age group, six studies included adults [13,14,15,16,17,18] and one study included older people [15]. Regarding the level of conditioning and health, the studies varied with one study including sedentary individuals [18]; one study breast cancer patients [15]; two studies included amateur-level athletes [13,16]; one study included elite athletes [17]; and two studies included individuals with diabetes [12,14].

Regarding the duration of the training protocols, it was found that they varied between a single session and 6 months. Thus, one study carried out the test in a single session, however before the experiment, a preparatory protocol of 12 weeks was carried out [12], two protocols lasted for four weeks [14,16], one adopted a duration of nine weeks [18], one lasted 12 weeks [15], one used a 15-week protocol [17], and one lasted six months [13].

The biomarkers evaluated in the studies also varied, with the following biomarkers being investigated: immune system cells [12,13,14,15,17,18], steroid hormones [13], and muscle damage markers [14,17].

The characteristics of the included studies are shown in Table 1.

3.2 Description of the Results of the Analyzed Biomarkers

Due to the diversity in the types of biomarkers investigated, it was decided to present the HIIT and HIFT outcomes separately in order to facilitate understanding of specific behaviors related to blood count, muscle damage, cytokines, and hormones in response to each type of exercise under study. All values of mean and standard deviation referring to the pre and post exercise moments are shown in Table 2.

3.3 Studies that Carried Out HIIT

3.3.1 Hemogram

The included studies evaluated hemogram outcomes referring to monocytes, neutrophils, lymphocytes, eosinophils, granulocytes, basophils, reticulocytes, mean corpuscular volume (MCV), mean corpuscular concentration (MCC), hematocrit, platelets, ferritin, uric acid, CD16 +, CD14 +, Red Blood Cells, Toll-like Receptor 2 (TLR2), Toll-like Receptor 4 (TLR4), and Heat Shock Proteins of 70 kilodaltons (HSP70).

Regarding monocytes, a significant increase was observed in the two studies that evaluated this marker ($p=0.001$ and $p<0.05$, respectively) [12,17]. Two studies analyzed neutrophils, one of which did not observe significant alterations ($p>0.05$) [17] and another observed a significant increase ($p= 0.001$) [12]. With respect to lymphocytes, one study found no significant increase ($p>0.05$) [12]; and two studies showed a significant increase in this marker ($p=0.002$; and $p<0.05$, respectively) [13,17].

One study investigated eosinophils, reticulocytes, basophils, granulocytes, mean corpuscular volume, hematocrit, platelets, ferritin, uric acid, hemoglobin, and transferrin [17] and found no significant differences for eosinophils, basophils, hematocrit, ferritin, granulocytes, and uric acid ($p> 0.05$), while there was a statistically significant increase for reticulocytes ($p<0.05$). In addition, there was a significant reduction in mean corpuscular volume, mean corpuscular concentration, and hemoglobin ($p=0.01$) as well as in platelets, transferrin, and serum ferritin ($p<0.05$).

The study that evaluated CD16+ did not find any statistically significant values ($p> 0.05$) [12] between the pre and post exercise moments for this marker. In addition, there were no statistically significant changes for CD14 ($p>0.05$) [12]. However, there was a significant increase in the values of TLR2 ($p = 0.001$) [15] and TLR4 ($p = 0.04$) [12]. The study that analyzed red blood cells found no significant alterations after exercise ($p=0.07$) [17] for this marker. The study that evaluated HSP70 showed

a statistically significant increase (p = 0.05) [15] in response to exercise.

One study analyzed cellular antioxidant capacity and myoglobin, and found significant increases in both markers after the exercise protocol (p<0.05) [16].

3.3.2 Muscle damage markers

The markers of muscle damage investigated were: lactate, creatine kinase (CK), creatinine, and C-reactive protein.

One study analyzed lactate, and did not show significant alterations in this marker (p> 0.05) [17]. Two studies evaluated CK [16,17], one showing a significant reduction (p <0.05) [16], while the other did not find a significant change (p> 0.05) [17]. One study measured creatinine and found no significant alterations (p>0.05) [17]. Two studies measured C-reactive protein, one of which observed significant alterations (p=0.01) [14], while the other did not (p = 0.08) [18].

3.3.3 Marker of renal function and damage

In one of the included studies, the behavior of the marker of renal function and damage was observed, through the analysis of urea, and did not show a statistically significant change between moments (p> 0.05) [18].

3.3.4 Cytokines

The cytokines evaluated in the included studies were: TNF-α, IL-6, IL-β, IL-10, IL-4, and IL-γ.

With respect to TNF-α, two studies demonstrated a significant reduction between moments for this cytokine (p=0.02 and p=0.001, respectively) [12,15], while two other studies did not find significant alterations in the same marker (p> 0.05 and p = 0.06) [14,18].

With respect to IL-6, one study reported a statistically significant reduction (p=0.007) [15], while another study showed a significant increase (p<0.05) [16]. One study that evaluated IL-β showed no statistically significant alterations (p=0.09) [15], while another study reported that it faced technical problems with equipment, and lost the samples collected, which made any type of analysis unfeasible [18]. One article evaluated IL-10 and did not reveal any statistically significant alterations (p>0.05) [14]. One study evaluated IL-4 (p>0.05) [15] and IL-γ (p=0.66) [15].

3.4 Studies that Analyzed HIFT

3.4.1 Hormones

For cortisol, one study demonstrated a reduction in plasma levels (p=0.002) [13], whereas in another study, levels of statistically significant alterations were not found (p=0.07) [17]. For testosterone, one study revealed a statistically significant reduction (p=0.01) [17] whereas another study observed an increase in the levels of this marker (p=0.001) [13].

3.5 Methodological Quality of Included Studies

The evaluation of the methodological quality of the studies showed an average of 5.7 points on the PEDro scale. Four studies were considered as bad [12,13,16,17], two studies as moderate [14,18], and one study as good [15].

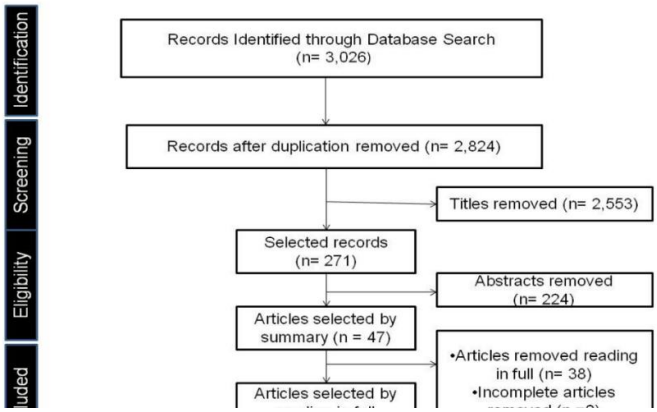

Fig. 1. Study flowchart

Table 1. Characteristics of the included studies

Study	Study design	Characteristics of the participants	Exercise performed	Training protocol	Markers evaluated	Outcomes found	Pedro Score
Iñigo Mujika et al 2000	Analytical Clinical Trial - Controlled – single-blind	n = 8 men Elite runners 19.9 ± 1.8 years	HIIT	The mean (± SD) training distance from the beginning of the season to the reduction was 669.6 ± 235.9 km, of which 88.0 ± 7.3% (584.6 ± 204.4 km) were from the LICT, while 12.0 ± 7.3% (86.2 ± 66.8 km) were from HIIT. In the low volume taper (LVT), on the other hand, the pre-protocol LICT and HIIT values were reduced by 75% (i.e., 85, 70, 55, 40, 25, 25% during tapering days 1 to 6, respectively). The protocol lasted 15 weeks.	Reticulocytes, granulocytes, basophil, lymphocytes, monocytes, creatinine, CK, total and free testosterone, total and free cortisol, Lactate. Red Blood Cells, Mean Corpuscular Volume, Mean Corpuscular Concentration, Hematocrit Platelets Ferritin Uric acid Hemoglobin Transferrin Serum Ferritin Urea	Reticulocytes ↑ NS granulocytes Lymphocytes ↓ Monocytes ↑ Creatinine NS CK ↑ Total Testosterone NS Free Testosterone NS Total Cortisol NS Free Cortisol NS Lactate NS Red blood cells ↓ Mean Corpuscular Volume ↓ Mean Corpuscular Concentration ↓ Hematocrit NS Platelets ↓ Ferritin NS Uric acid NS Hemoglobin ↓ Transferrin ↓ Serum Ferritin ↓ Urea NS Reticulocyte ↑	4
Allen et al. 2017	Clinical Trial - Analytical - Controlled - Randomized	n= 55 (35 women and 20 men) sedentary 49.2 ± 6.1 years.	HIIT	Each participant performed the test on a 25 W cycle ergometer with increments of 25 W per minute until fatigue of the participant. The protocol lasted 9 weeks.	TNF-a and C-Reactive Protein	TNF-α NS C-reactive protein NS	7

Study	Study design	Characteristics of the participants	Exercise performed	Training protocol	Markers evaluated	Outcomes found	Pedro Score
Cipryan 2017	Clinical Trial - Analytical - Uncontrolled	n= 12 men, amateur level athletes 22.8 ± 1.7 years	HIIT	8 mins of warm-up at a speed of 50% of vO2max; interval exercise: duration of 12 min, work/rest ratio = 1, work intensity 100% v O2max, resting intensity 60% vO2max, duration of work and rest of 15 s, 30 s, or 60 s; cool-down: 3 min at 5 km · h-1. The protocol lasted 4 weeks..	IL-6, CK. Antioxidant capacity, Myoglobin	IL-6 ↑ CK ↑ Antioxidant capacity ↑ Myoglobin ↑	4
Durrer et al. 2017	Clinical Trial - Analytical - Controlled	n=19 (9 men and 10 women) Sedentary older adults 57.9 ± 5.4 years	HIIT	HIIT – Warm-up of 4 minutes at 30 W on the cycle ergometer before exercise. 7 × 1 minute intervals at 85% peak power with 1-minute rest periods at 15% peak power between HIIT exercise. The protocol lasted a single session.	TNF-α, monocytes, neutrophils, and lymphocytes CD14 CD16 TLR2 TLR4	TNF-α ↓ Monocytes ↓ Neutrophil ↑ Lymphocytes NS CD14 ↑ CD16 ↑ TRL2 ↑ TLR4 ↑	5
Farinha et al. 2018	Analytical Clinical Trial - Controlled - Randomized	n=28 (15 men and 13 women) Individuals with DMT 1 18 to 40 years	HIIT		TNF-α C-reactive protein IL-10	TNF-α NS C-reactive protein NS IL-10 NS	6
2019 Alizadeh et al.	Controlled Clinical Trial - Randomized	n=52 women with breast cancer ≥ 30 years	HIIT	4 × 4 min walk at 90–95% of HRmax (exercise) and 4 × 3 min uphill. Total duration of each session was 38 min, with 5 min of warm-up, 5 min of cool-down, 16 min of high intensity and 12 min of active recovery between intervals. The protocol lasted 12 weeks. .	TNF-α, IL-6, IL-1β, IL-10 IL-4 IF-γ HSP70	TNF-α ↓ IL-6 ↓ TNF-α/IL-10 ↓ IL-6/IL-10 ↓ IL-β NS IL-4 NS IL- γ NS HSP70 ↑ IL-10 ↑	9

Study	Study design	Characteristics of the participants	Exercise performed	Training protocol	Markers evaluated	Outcomes found	Pedro Score
2019 Poderoso et al.	Clinical Trial - Uncontrolled	n=29 (17 men and 12 women) amateur level athletes 35.3 ± 10.4 years	HIFT	HIFT – 60-minute workout, with an effort between 8 and 10 (OMNI-Resistance Exercise Scale), The protocol lasted 6 months.	Cortisol, testosterone, and Lymphocytes	Testosterone ↑ Cortisol ↓ Lymphocytes (CD8) ↑	5

Legend: HIIT= *High Intensity Interval Training;;* ***EDTA=*** *Ethylenediaminetetraacetic Acid;* ***HIFT =*** *High Intensity Functional Training;* ***ST =*** *Strength Training;* ***HRmax =*** *Maximum Heart Rate;* ***RPM =*** *Rotations per minute;* ***CK =*** *creatine kinase; S**D** = Standard Deviation;* ***LICT =*** *Low Intensity Continuous Training;* ***LVT =*** *Low Volume Taper;* ***CRP =*** *C-reactive protein**; FT:** Free Testosterone;* ***TT:*** *Total Testosterone;* ***NS*** *= Not significant;* ***TNF-a*** *= Tumor necrosis factor alpha;* ***IL-6*** *= Interleukin 6;* ***IL-1****= Interleukin 1;* ***IL-10*** *= Interleukin 10;* ***IL-4*** *= Interleukin 4;* ***IFN-y*** *= Interferon Gama;* ***HSP70*** *= heat shock protein 70;* ***CD14*** *= cluster of differentiation 14;* ***CD16*** *= cluster of differentiation 16;* ***TRL2*** *Toll-like receptor 2;* ***TRL4*** *Toll-like receptor 4; DMT1 = Type 1 diabetes mellitus*

Table 2. Responses of biomarkers between pre and post-exercise (mean ± SD) and percentage change between moments

Study, year	Unit of measurement	Hemogram	Muscle damage	Hormones	Cytokines
2000 Iñigo Mujika et al	$10^3.mm^{-3}$ % $mmol.L^{-1}$ 10 $6.mm^{-3}$ μm^3 $g.dL^{-1}$ $10^3.mm^{-3}$ $mg.dL^{-1}$ $g.dL^{-1}$ $\mu g.dL^{-1}$ $UI.L^{-1}$ $ng.L^{-1}$	Reticulocytes: Pre= 64.5 ± 16.3; Post= 90.6 ± 15.2; granulocytes: Pre= 50.3 ± 6.2; Post= 51.1 ± 8.6; basophils: Pre= 0.4 ± 0.4; Post= 0.3 ± 0.1; lymphocytes: Pre= 40.0 ± 6.7; Post= 37.5 ± 8.3; monocytes: Pre= 9.7 ± 2.1; Post= 11.4 ± 2.2; Lactate: Pre= 15.1 ± 1.8; Post= 15.9 ± 2.9; Red Blood Cells: Pre = 5.04 ± 0.12; Post= 4.94 ± 0;11; Mean Corpuscular Volume: Pre= 91.8 ± 4.0; Post= 92.2 ± 4.4 Mean Corpuscular Hemoglobin Concentration: Pre= 34.0 ± 0.3; Post= 33.5 ± 05 Hematocrit: Pre= 46.4 ± 2.5; Post= 45.6 ± 2.3; Platelets: Pre= 203.7 ± 35.9; Post= 189.8 ± 41.7 Ferritin: Pre= 26.3 ± 13.8; Post= 28.8 ± 13.8; Uric acid: Pre= 5.4 ± 1.4; Post= 5.9 ± 1.6 Hemoglobin: Pre= 15.8 ± 0.9; Post= 15.3 ± 0.8; Transferrin: Pre= 330.0 ± 21.8; Post= 355.8 ± 127.5; Serum Iron: Pre= 75.1 ± 26.3; Post= 60.6 ± 14.8	Creatinine: Pre= 1.15 ± 0.11; Post= 1.16 ± 0.12 CK: Pre= 102.6 ± 63.7; Post= 113.4 ± 108 Urea: Pre= 37.8 ± 6.4; Post= 37.1 ± 9.1	Total testosterone: Pre= 6.82 ± 2.00; Post = 6.56 ± 2.12; Free testosterone: Pre= 29.24 ± 9.21; Post= 28.00 ± 10.62; Total cortisol: Pre 0.37 ± 0.14; Post= 0.40 ± 0.13; Free cortisol: 1.59 ± 0.63; Post= 1.69 ± 0.64	N/A
2017 Allen et al.	mg L^{-1} / pg mL^{-1}	N/A	C-Reactive Protein: Pre=2.36 ± 1.18 Post= 2.30 ± 1.91	N/A	TNF-a: Pre= 4.64 ± 2.39; Post= 3.81 ± 2.18

Study, year	Unit of measurement	Hemogram	Muscle damage	Hormones	Cytokines
2017 Cipryan	$ng \cdot l^{-1}$ / $mmol \cdot l^{-1}$ /($\mu kat \cdot l^{-1}$ / $\mu g \cdot l^{-1}$	Myoglobin: Week 15/15 – Pre = 28.36 ± 7.36; Post = 37.23 ± 9.31; 3h = 35.24 ± 12.09; 24h = 31.92 ± 13.16 Week 30/30 – Pre = 26.38 ± 8.97; Post = 33.94 ± 8.62; 3h = 35.90 ± 13.00; 24h = 30.11 ± 10.82; Week 60/60 – Pre = 24.01 ± 7.09; Post = 32.20 ± 6.24; 3h = 31.91 ± 7.64; 24h = 29.01 ± 10.65.	CK: 15/15 – Pre= 3.12 ± 1.80; Post = 3.81 ± 1.76; 3h = 3.65 ± 1.62; 24h 4.02 ± 1.97 30/30 – Pre = 3.54 ± 2.10; Post = 4.42 ± 2.03; 3h = 4.01 ± 1.97; 24h 4.63 ± 2.05. 60/60 – Pre = 3.72 ± 2.11; Post = 4.61 ± 2.06; 3h = 4.15 ± 2.07; 24h = 4.75 ± 2.17 Antioxidant capacity: 15/15 – Pre = 1.59 ± 0.06; Post = 1.72 ± 0.05; 3h = 1.65 ± 0.05; 24h = 1.61 ± 0.06 30/30 – Pre= 1.59 ± 0.08; Post = 1.71 ± 0.07; 3h = 1.64 ± 0.08; 24h = 1.59 ± 0.08; 60/60 – Pre = 1.58 ± 0.10; Post = 1.72 ± 0.09; 3h = 1.64 ± 0.09; 24h = 1.61 ± 0.07 LDH: 15/15 – Pre = 2.38 ± 0.36; Post = 2.90 ± 0.51; 3h = 2.59 ± 0.40; 24h = 2.47 ± 0.39; 30/30 – Pre = 2.28 ± 0.42; Post = 2.89 ± 0.60; 3h = 2.59 ± 0.49; 24h 2.42 ± 0.41. 60/60 – Pre = 2.35 ± 0.43; Post = 2.96 ± 0.48; 3h = 2.66 ± 0.47; 24h = 2.53 ± 0.53.	N/A	IL-6: 15/15 - Pre = 0.93 ± 0.27; Post = 1.36 ± 0.37; 3h = 1.01 ± 0.24; 24h= 1.08 ± 0.28. 30/30 – Pre = 0.98 ± 0.39; Post = 1.39 ± 0.36; 3h 0.91 ± 0.25; 24h = 0.99 ± 0.24. 60/60 - Pre =0.87 ± 0.26; Post = 1.38 ± 0.41; 3h = 1.02 ± 0.51; 24h = 1.04 ± 0.54.
2017 Durrer et al.	10^5 /ml pg/ml	Monocytes: Pre= 3.2 ± 0.40; Post= 4.5 ± 0.58; 1h= 3.1 ± 0.29; Neutrophils: Pre= 30.6 ± 6.2; Post= 44.1 ± 11.8; 1h= 32.2 ± 5.8; Lymphocytes: Pre= 5.9 ± 4.2; Post= 28.0 ± 7.3; 1h= 16.8 ± 4.7; CD14: Pre= 10 ± 2.5; Post: 7.4 ± 1.8; 1-h Post: 7.2 ± 3.5 CD16: Pre= 4.5 ± 3.5; Post= 5.4 ± 3.7; 1h= 5.3 ± 3.0 TLR2: Pre= 12.5 ± 2.5; Post= 11 ±1.5; 1-h Post= 10.7 ± 4.5 TLR4: Pre= 9.1± 4.1; Post= 9.8 ± 4.5; 1-h Post: 9.5 ± 4.3	N/A	N/A	TNF-α: Pre= 388.5 ± 275.3; Post: 412 ± 198.7; 1h-post: 324 ± 246.9

Study, year	Unit of measurement	Hemogram	Muscle damage	Hormones	Cytokines
2018 Farinha et al.	mg/L pg/mL	N/A	C Reactive Protein: Pre= 2.3 ± 2.4; Post 1.9 ± 2.5	N/A	IL-10: Pre= 38.1 ± 42.2; Post= 24.1 ± 29.2; TNF-α: Pre= 57.9 ± 16; Post= 51.8 ± 9.3
2019 Alizadeh et al.	pg/ml	HSP70: Pre= 130; Post= 150	N/A	N/A	TNF-α: Pre=0.99; Post= 0.50 IL-6: Pre=1.4; Post= 0.8 IL-1β: Pre= 1.19; Post= 1.20 IL-10: Pre=13.000; Post=14.000 IL-4: Pre= 30; Post= 35 IF-γ: Pre= 1.60; Post=1.80
2019 Poderoso et al.	$pg{\cdot}mL^{-1}$ $Cells/mm^3$	Lymphocytes: CD4: Pre (T0)= 1100.5 ± 307.0; Post (T2)= 1026.9 ± 305.6; Post (T4)= 1045.7 ± 275.5; Post (T6)= 1118.8 ± 242.2 CD8: Pre (T0)= 664.9 ± 220.9; Post (T2)= 582.3 ± 226.4; Post (T4)= 623.4 ± 195.4; Post (T6)= 672.4 ± 196.9	N/A	Cortisol: Pre (T0)= 18.0 ± 8.2; Post (T2)= 18.1 ± 9.7; Post (T4)= 15.6 ± 6.3; Post (T6)= 14.6 ± 5.6 Testosterone: Pre (T0) = 261.7 ± 249.3; Post (T2)= 289.5 ± 232.6; Post (T4)= 298.7 ± 258.5; Post (T6)= 346.0 ± 299.7	N/A

Legend: HIFT = *High Intensity Functional Training;* ***ST =*** *Strength Training;;* ***CK =*** *creatine kinase;* ***CRP =*** *C-reactive protein****; FT:*** *Free Testosterone;* ***TT:*** *Total Testosterone;* ***TNF-a*** *= Tumor necrosis factor alpha;* ***IL-6*** *= Interleukin 6;* ***IL-1*** *= Interleukin 1;* ***IL-10*** *= Interleukin 10;* ***IL-4*** *= Interleukin 4;* ***IFN-y*** *= Interferon Gama;* ***HSP70*** *= heat shock protein 70;* ***CD14*** *= cluster of differentiation 14;* ***CD16*** *= cluster of differentiation 16;* ***TRL2*** *Toll-like receptor 2;* ***TRL4*** *Toll-like receptor 4; T0 (Time 0); T2 (Time 2); T4 (Time 4); T6 (Time 6)*

4. DISCUSSION

The purpose of this review study was to identify and describe outcomes of studies that assessed the impact of HIIT and HIFT on different blood biomarkers. The main results found showed increases in the markers of muscle damage. On the other hand, inflammatory markers demonstrated reductions in proinflammatory cytokines and increased values of anti-inflammatory cytokines. Despite the reduced values of the general blood count, markers such as neutrophils and basophils did not show alterations in concentrations. The serum level of testosterone was higher post when compared to pre-exercise. Cortisol, on the other hand, presented a reduction post when compared to pre-exercise.

A point to be highlighted is that only one study evaluated CrossFit™, a modality of HIFT. These data denote that, apparently, with regard to the objectives of this study, it is a little explored modality [13], which may be justified due to the diversity of protocols used in practice and also in the literature, which makes training standards as well as verified responses difficult, also characterizing an important limitation for the elaboration of clinical trials that use HIFT.

Regarding the findings of muscle damage, some studies noted an increase in CK and LDH levels [16,17]. In this regard, the literature shows that muscle damage can assume different proportions related to the type of muscle action as well as the volume and intensity implemented in training [19]. For example, the CK enzyme has a specific function in skeletal muscle tissue, related to assisting the metabolism for the resynthesis of adenosine triphosphate (ATP). In addition, CK is responsible for the hydrolysis of Creatine Phosphate (CP), removing inorganic phosphate (Pi) from creatine for later release of energy [20]. Furthermore, the behavior of endogenous CK levels may be related to physiological variations such as: sex, age, percentage of muscle mass, type of exercise performed, and ethnicity [21]. The set of factors presented, referring to the modulation of CK, justify high levels after training, but these can be adjusted and adapted according to several intrinsic and extrinsic characteristics inherent to training.

In addition, the velocity of eccentric actions can also influence levels of muscle damage. In this sense, studies that investigated different velocities in the eccentric phase reported a greater degree of muscle damage [22,23]. This may be one of the justifications for the CK values found in the included studies, since one of the main characteristics of HIFT is the execution of a large number of repetitions in a short period of time, as previously mentioned.

In addition, indicators of increased cellular permeability resulting from muscle damage have been related to high levels of lactate dehydrogenase (LDH), which is an enzyme responsible for participating in one of the glucose catabolism pathways, converting pyruvate to lactate. When elevated plasma lactate levels are found after exercise, it is possible that increases in LDH levels are also present. In this regard, there was an immediate increase in the LDH marker analyzed in one of the included studies [16]. In this regard, the study of Vieira [24] demonstrates LDH as a key to carbohydrate metabolism, found in most tissues and responsible for acting on the glucose-degrading metabolism that results in lactate, which is a common process during exercise, since in these situations the demand for the production of ATP is higher. This information explains the observed outcomes related to the increase in lactate after exercise.

With regard to inflammatory markers, it was found that for TNF there was a decrease immediately after exercise [12,15,18], while IL-6 expression increased [15,16].

The verification of the increase in IL-10 identified in the present review study leads us to believe that physical exercise increases the production capacity of mononucleated cells and gradually decreases pro-inflammatory cytokines, which have a role in the atherosclerotic framework.

Thus, physical exercise demonstrates importance in modulating adequate levels of some pro-inflammatory cytokines (mainly TNF-α and IL-6) by providing stimulation [20].

These findings demonstrate the anti-inflammatory capacity of IL-10 after exercise, related to the regulation of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, which elevate leukocyte activities such as monocytes and lymphocytes, acting directly on inflammation and reducing the activity of chemotactic factors [25,26].

With regard to the analysis of hormonal concentrations [13,17] different responses were observed in the studies analyzed, characterized

by an increase in testosterone levels after exercise and a reduction in cortisol [13] with non-significant values in testosterone and cortisol levels [17], respectively. However, this inconsistency can be justified by the fact that the cortisol/testosterone ratio may vary according to the duration and intensity of the exercise, for example, which demonstrates the hormonal adaptive capacity in response to exercise. These findings suggest that adequate exercise protocols can trigger positive values in hormonal levels, but it is not clear whether values above those recommended tend to reveal the same result. For this reason, further research is needed to assess the maximum effort in a single HIFT session, in order to observe the behavior of this marker in the acute phase. These data are understandable, since the studies used different training protocols, which can fundamentally justify the differences in the verified hormonal behavior.

In the study that evaluated type 2 diabetes (DMT2) a single session of HIIT led to reductions in circulating TNF-α and also indicated that the modality may be efficient to induce cellular and molecular anti-inflammatory effects.

As there was no increase in the levels of pro-inflammatory cytokines in the parameters measured in patients with DMT2, it is suggested that HIIT may be an adequate option to improve the high concentrations of biochemical components affected by DMT2, since high values of inflammatory markers may be related to the low frequency of physical activity in individuals with DMT2 [12].

In another study that evaluated type 1 diabetes (DMT1), although glycemic values reduced, values of plasma inflammatory markers (TNF-α and IL-10) did not [14].

In addition, the Strength Training (ST), HIIT, or ST + HIIT protocols resulted in improvement in the activity of antioxidant enzymes (analyzed through the total antioxidant capacitye) and in glycemic levels, without alterations in inflammatory markers, indicating that HIIT can be recommended as an adjunct in glycemic and insulinemic control [14]. From a practical point of view, in this specific case, these activities seem to be relevant for reducing insulin dependence in individuals adhering to the protocol used.

It is known that insulin resistance is a silent pathology capable of causing pancreatic failure. The role of inflammatory markers should also not be ruled out, since data show that adipocytes treated with TNF-α reduced insulin signaling, which is associated with a reduction in IRS-1 and GLUT4 [27], causing an increase in insulin resistance. Exercise, in turn, plays a fundamental role in changing this process. In this regard, it is possible to consider HIIT as a tool to reduce TNF-α, improving insulin signaling and adjusting glycemic levels [12].

Regarding the factors involved in the increase or decrease in the expression of TNF-α, some authors have presented *Heat Shock Proteins* (HSP) as reasons for its inhibition, which are highly conserved proteins in primitive beings and humans, which demonstrates their great importance at the evolutionary level [28] emphasizing their value in the analysis of biomarkers involved in inflammatory processes [11].

One possibility for the scarce exploration of TNF-α behavior could be associated with the high cost of analysis or even with the complexity that involves the mechanisms of energy demand in response to the intensity of the exercise, plus the correlation of the interleukin behavior. The fact is that this marker seems to be one of the key points for several physiological processes such as tissue regeneration, taking into account that athletes, amateur practitioners, and sedentary practitioners require adequate recovery, given the fact that they are often exposed to strenuous exercise.

In the study that evaluated the behavior of markers in women diagnosed with breast cancer [15], TNF-α values decreased in comparison with IL-10. This relationship corroborates with study Clarkson & Hubal [21].

These data further reinforce the role that IL-10 plays in the modulation of pro-inflammatory cytokines, since inflammation is a negative indicator in the path of improvement in this framework.

The data presented could be the beginning of an assertive path, regarding the importance of understanding physiological responses to the practice of HIIT and HIFT for training dynamics. Limitations should be reported. Thus, we highlight the fact that the current study did not distinguish between sex, age, and level of conditioning, which could constitute determining factors for checking different parameters in the biomarkers used. In addition, it is suggested that

future review studies investigate injury rates and sports performance in this population profile, so that these data can be correlated with the findings in the present study. Furthermore, new clinical trials are necessary, since the low number of included studies demonstrate the scarcity of research on the investigated methods. Finally, it is reiterated that the results obtained should not be extrapolated to different population profiles or exercises.

5. CONCLUSION

From the findings presented, it is possible to conclude that the impact of HIIT or HIFT exercises on the evaluated biomarkers resulted in specific and different behaviors. Thus, with regard to markers of muscle damage, studies have shown increases in CK concentration, whereas LDH did not demonstrate significant changes. On the other hand, inflammatory markers presented reductions in pro-inflammatory markers (TNF-α, IL-6) while an increase in IL-10 was observed. In turn, the CBC showed a reduction in the values of almost all markers except for some specific ones, such as reticulocytes, monocytes, and neutrophils. Hormonal markers demonstrated an association proportional to the level of training implemented.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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