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Systematic Review

Biomarkers of tissue injury in high-intensity interval running: a systematic review

Biomarcadores de lesão tecidual em corrida intervalada de alta intensidade: uma revisão sistemática

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ABSTRACT

Introduction: The improvement of aerobic and anaerobic capacity in athletes of different sports is related to high-intensity exercise performance, which causes cellular microlesions and leads to an inflammatory process necessary for muscle adaptation. Biochemical markers, such as creatine kinase (CK) and lactate dehydrogenase (LDH), have been used to measure muscle and inflammatory damage to identify the physiological response and improving sports performance. **Objective:** To describe the changes in the CK and LDH biomarkers after high intensity interval running. **Methods:** It was conducted a systematic review following the PRISMA guidelines and registered on PROSPERO (CRD42020201678), with a literature search, in February 2021, in the Medline, Lilacs, Scopus, SPORTDiscus, CINAHL, Web of Science, ScienceDirect, Cochrane, and Scielo databases. We used the descriptors "HIIT", "L-Lactate Dehydrogenase", "Creatine Kinase" and their synonyms, available in the *Descritores em Ciências da Saúde* (DeCS) and Medical Subject Headings (MeSH). **Results:** From the 80 studies found, 6 met the inclusion criteria. Of these, four studies showed significant increases in CK and LDH simultaneously, while one study observed a significant increase only in CK and the other study only in LDH. The increases in biomarkers occurred at different magnitudes. The studies' protocols and the sample characteristics showed high heterogeneity. **Conclusion:** High-intensity interval running can acutely elevate CK and LDL levels, making them excellent markers for injury risk and exercise load dosing.

Keywords: high-intensity interval training; creatine kinase; lactate dehydrogenase.

RESUMO

Introdução: A melhora da capacidade aeróbia e anaeróbia em atletas de diferentes modalidades esportivas está relacionada à realização de exercícios de alta intensidade, que causam microlesões celulares e levam a um processo inflamatório necessário para adaptação muscular. Marcadores bioquímicos, como creatina quinase (CK) e lactato desidrogenase (LDH) vêm sendo utilizados para a mensuração de danos musculares e inflamatórios a fim de identificar a resposta fisiológica e auxiliar na melhora do desempenho esportivo. **Objetivo:** Descrever as alterações nos biomarcadores CK e LDH após a execução de corrida intervalada em alta intensidade. **Métodos:** Foi realizada uma revisão sistemática, seguindo as recomendações do PRISMA e registrada na PROSPERO (CRD42020201678), com uma busca na literatura em fevereiro de 2021, nas bases *Medline*, *Lilacs*, *Scopus*, *SPORTDiscus*, *CINAHL*, *Web of Science*, *ScienceDirect*, *Cochrane* e *Scielo*, utilizando os descritores "*HIIT*", "*L-Lactate Dehydrogenase*", "*Creatine Kinase*" e seus sinônimos, disponíveis nos Descritores em Ciências da Saúde (DeCS) e *Medical Subject Headings* (MeSH). **Resultados:** Dos 80 estudos encontrados inicialmente, 6 atenderam aos critérios de inclusão. Destes, quatro estudos apresentaram aumento significativos de CK e LDH simultaneamente, enquanto 1 estudo observou aumento significativo apenas de CK e o outro estudo apenas de LDH. Os aumentos nos biomarcadores ocorreram em magnitudes diferentes. Os protocolos dos estudos e as características da amostra mostraram alta heterogeneidade. **Conclusão:** A corrida intervalada de alta intensidade pode elevar os níveis CK e LDL de forma aguda, o que torna os mesmos excelentes marcadores para o risco de lesão e dosagem das cargas do exercício.

Palavras-chave: treinamento intervalado de alta intensidade; creatina quinase; lactato desidrogenase.

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Introduction

High-intensity interval training (HIIT) is a widely used and effective training method in many sports, including endurance and sprint/power events [1]. According to different combinations of work intensity and session length, HIIT uses different work interval protocols, including long interval (2-4 min of work/session at submaximal intensity, LI-HIIT), short interval (< 45 s of work/session at submaximal intensity, SI-HIIT), sprint interval (> 20-30 s of work/session close to maximum intensity, SIT), and repeated sprint exercises (≤ 10 s of work/session close to maximum intensity, RST). When the number of repetitions is increased, HIIT protocols can be implemented with high (16 min work) or low (4 min work) session volume (HV-HIIT or LV-HIIT) [2].

HIIT requires an integration of several physiological systems. The contributions of ATP-phosphocreatine (PCr) and the glycolytic metabolic pathway are necessary to achieve high exercise intensity, while an oxidative metabolic pathway is predominant to maintain high exercise intensity as long as possible [3].

High-intensity exercises have benefits for athletes of different modalities [4] and are related to a series of aerobic and anaerobic adaptations, such as the increase in the dimensions of mitochondria, greater tolerance to blood pH, and increased anaerobic capacity [5]. However, strenuous, high-intensity exercise can have unfavorable effects when the workload is not controlled [6], which can cause severe damage to muscle tissue. Some enzymes are used as indicators of tissue damage. Among these enzymes, creatine kinase (CK) and lactate dehydrogenase (LDH) are capable of stimulating inflammation and muscle damage because of the physical stimulus suffered by the body [7].

CK is an intramuscular enzyme that accelerates the resynthesis of ATP and its increases are noticed in blood dosages after strenuous activities [8]. Generally, the peak concentration occurs between 24 and 48 hours after exercise and returns to baseline values between 48 and 120 hours, depending on the peak magnitude [9].

LDH is an enzyme that is in the cytoplasm of most cells and is responsible for catalyzing the reaction that results in the conversion of pyruvate to lactate [10]. Like CK, LDH is associated with muscle injuries [11].

The time of detection of CK in the blood is dependent on the level of training, type, intensity, and duration of the exercise. CK values vary widely between individuals and may change according to sex, age, amount of muscle mass, race, level of training, and climatic condition. Likewise, LDH has post-exercise variations and can also change with the training level of the individual [12].

The understanding of the dynamics of expression of these biochemical markers and its functional criteria can help in the training load adjustments, and thereafter to adaptations in the athletes' organism facing this type of exercise [13]. Thus, studies that investigate the acute effects of physical exercise on inflammatory markers, usually done with blood collection before and immediately after physical

activity, are important for the relationship between training and performance [14].

Therefore, the present study aimed to describe the changes in CK and LDH biomarkers after high-intensity interval running.

Methods

Protocol and registration

This systematic review it was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [15] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) as number CRD42020201678.

Inclusion criteria

We included studies that met the following inclusion criteria [16]: Population: running practitioners; Exposure of interest (independent variable): high-intensity interval running; Outcome (dependent variable): biomarkers of tissue damage CK and LDH in individuals of both sexes. We excluded studies of systematic reviews, meta-analyses, case studies, and studies with a publication date before the year 2011, considering a systematic review published on this issue in 2012 [17].

Search strategy

A systematic literature search was conducted in February 2021, without a language filter, in the databases National Library of Medicine (Medline), Lilacs, Scopus, SPORTDiscus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, ScienceDirect, Cochrane, and Scielo. We used the descriptors "HIIT", "L-Lactate Dehydrogenase", "Creatine Kinase" and their synonyms, available in *Descritores em Ciências da Saúde* (DeCS) and Medical Subject Headings (MeSH). The following search phrase was obtained using the Boolean operators "AND" between descriptors and "OR" between synonyms: ("High Intensity Interval Training" OR "High-Intensity Interval Trainings" OR "Interval Training, High-Intensity" OR "Interval Trainings, High-Intensity" OR "Training, High-Intensity Interval" OR "Trainings, High-Intensity Interval" OR "High-Intensity Intermittent Exercise" OR "Exercise, High-Intensity Intermittent" OR "Exercises, High-Intensity Intermittent" OR "High-Intensity Intermittent Exercises" OR "Sprint Interval Training" OR "Sprint Interval Trainings") AND ("Creatine kinase" OR "Kinase, Creatine" OR "ATP Creatine Phosphotransferase" OR "Creatine Phosphotransferase, ATP" OR "Phosphotransferase, ATP Creatine" OR "Creatine Phosphokinase" OR "Phosphokinase, Creatine" OR "ADP Phosphocreatine Phosphotransferase" OR "Phosphocreatine Phosphotransferase, ADP" OR "Phosphotransferase, ADP Phosphocreatine" OR "Macro-Creatine Kinase" OR "Macro Creatine Kinase") AND ("L-Lactate Dehydrogenase" OR "Dehydrogenase, L-Lactate" OR "L Lactate Dehydrogenase" OR "Lactate Dehydrogenase" OR "Dehydrogenase, Lactate").

Additionally, references of the selected studies and other sources were explored to maximize the search. Two independent evaluators selected the studies. A third researcher resolved the disagreements between the evaluators. This procedure was performed in all phases of the present study.

Data collection process

We extracted the following data from the studies: profile of participants, sex, age, height, total body mass (TBM), body fat percentage (BF%), body mass index (BMI), maximum oxygen consumption (VO_{2max}), assessment protocols, biochemical analyzes of CK and LDH, and study results.

Methodological quality analysis

Methodological quality was assessed through the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX). This tool has a 15-point scale, each item equals 1 point. The following domains were evaluated: 1) Eligibility criteria specified; 2) Randomization specified; 3) Allocation concealment; 4) Groups similar at baseline; 5) Blinding of evaluator; 6) Withdrawals from the study <15%; reported adverse events; reported session attendance; 7) Intention-to-treat analysis; 8) Primary and secondary between-group statistical comparisons reported; 9) Point measures for all results; 10) Activity monitoring in control groups; 11) Relative exercise intensity remained constant; 12) Exercise energy expenditure reported [18].

Risk of bias analysis

The A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) was used to assess the risk of bias of the included studies. This tool analyzes seven domains: 1) Bias due to confounding; 2) Bias in selection of participants into the study; 3) Bias in measurement of interventions; 4) Bias due to departures from intended interventions; 5) Bias due to missing data; 6) Bias in measurement of outcomes; 7) Bias in selection of the reported result [19]. For each domain, the studies were classified as uninformed, low, moderate, severe, or critical risk of bias. For a study to be classified as "low risk", it should be classified as low risk in all domains. A study is classified as "critical risk" if it presents a critical risk in at least one of the seven domains of the tool.

Results

Initially, 80 articles were identified in the searched databases (Medline = 19; Lilacs = 2; Scopus = 0; CINAHL = 31; SPORTDiscus = 0; Web of Science = 22; ScienceDirect = 0; Cochrane = 6; SciELO = 0). Four studies were included manually. After using the eligibility criteria, six studies were included in this review (Figure 1).

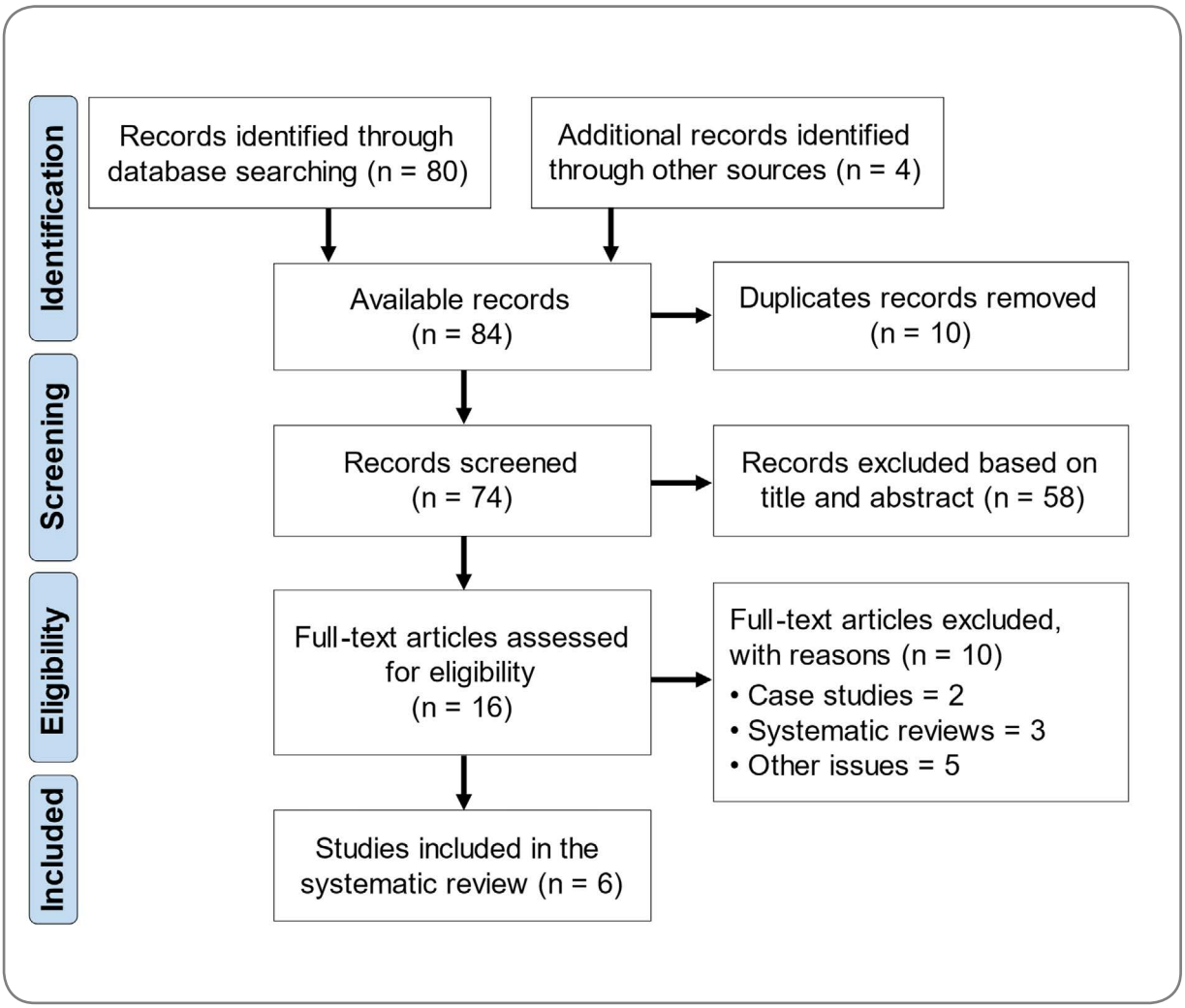

Figure 1 - Flow diagram of the studies included in the systematic review

The sample characteristics and protocols of the included studies are summarized in Table I. The sample had a total of 84 participants, 64 male and 20 not informed. Among the characteristics of the subjects, all six studies showed age, total body mass, and height. Only Cipryan [20] did not present the BMI. Three studies showed aerobic capacity (VO_{2max}) [20-22]. Only Cipryan [20] and Santos *et al.* [23] presented the body fat percentage (BF%). Four studies used HIIT protocols [19-22,24] and two used tests that resemble HIIT protocols [23,25].

Table II presents the biochemical variations and the results of the included studies. The protocols were slightly different concerning the times when data were collected in each study and the number of collections performed. Two studies collected only pre and post-test [23,25], Aloui *et al.* [25] performed pre and post measurements twice, each at a different time of the day (morning and afternoon). Another three studies [21,22,24] checked CK levels in 3 periods, Farias-Junior *et al.* [21] and Brandão *et al.* [22] in pre, 24, and 48 h, and Dorneles *et al.* [24] in pre, post, and 30 min. Cipryan [20] collected data in four phases: pre, post, 3, and 24h.

Table I - Sample characteristics and protocols

Study	Participants	VO_{2max} ($mL \cdot kg^{-1} \cdot min^{-1}$)	Protocol
Dorneles *et al.*, 2016 [27]	22 M (10 N, 12 O) Age.: N: 26.5 ± 6.11; O: 27.41 ± 9.20 Height: N: 1.73 ± 0.06; O: 1.75 ± 0.04 TBM: N: 66.07 ± 7.61; O: 98.82 ± 13.15* BMI: N: 22.00 ± 1.63; O: 31.99 ± 3.93*	NI	HIIE: 10 × 60 s (85–90% PMax)/75 s (50% PMax)
Aloui *et al.*, 2017 [28]	111 students Age: 21.00 ± 0.48 Height: 1.81 ± 2.28 TBM: 72.75 ± 1.79 BMI: 22.15 ± 0.54	NI	Intermittent test (YYIRT) in two hours of the day (07:00 and 17:00), with rest ≥ 36 hours between tests, in random order
Cipryan, 2017 [23]	12 M Age: 22.8 ± 1.7 Height: 1.84 ± 0.78 TBM: 77.0 ± 8.4 BF%: 9.9 ± 4.0	57.2 ± 6.3	3 × 12min, effort/rest; effort at 100% VO_{2max}, rest at 60% VO_{2max}, with: HIIT1: 15/15s; HIIT2: 30/30s; HIIT3: 60/60s
Farias-Junior *et al.*, 2019 [24]	15 M Age: 28.9 ± 5.0 Height: 1.7 ± 0.1 TBM: 87.1 ± 16.2 BMI: 29.2 ± 3.8	39.0 ± 4.1	HIIE: (10 × 1 min a 100% VO_{2max}/1 min recovery)
Santos *et al.*, 2018 [26]	9 A Age: 16.5 ± 1.5 Height: 1.7 ± 0.1 TBM: 59.2 ± 11.4 BF%: 12.6 ± 4.0 BMI: 19.6 ± 2.5	NI	Teste Rast = 6 maximum sprints of 35m with 10s interval between them
Brandão *et al.*, 2020 [25]	15 M Age: 28.0 ± 8.0 Height: 1.7 ± 0.1 TBM: 73.9 ± 17.5 BMI: 24.9 ± 4.8	51.4 ± 5.7	HIIT1: 15s effort (130% vVO_{2max})/15s passive rest, until exhaustion HIIT2: 30s effort (130% vVO_{2max})/30s passive rest, until exhaustion

M = men; N = normal weight; O = overweight; A = athletes; Age in years; Height in meters; TBM = total body mass (kg); BMI = body mass index (kg/m2); BF% = body fat percentage (%); min = minutes; HIIE = high intensity interval exercise; HIIT = high intensity interval training; YYIRT = Yo-Yo intermittent recovery test; CK = creatine kinase; LDH = lactate dehydrogenase. *difference between groups; NI = not informed

All 6 studies, each with a different exercise protocol and time of collection, evaluated CK. Five of these studies showed a significant increase in CK [21-25]. Only Cipryan [20] did not observe a significant difference in this biomarker at any time. Three studies observed a significant increase immediately after exercise [23-25]. Dorneles *et al.* [24] also found a significant increase 30 min after the test. Farias-Junior *et al.* [21] and Brandão *et al.* [22] found changes 24 and 48 hours after the work performed, with variation at 48 hours only in the 30/30 protocol.

In the studies by Cipryan [20], Farias-Junior *et al.* [21], and Brandão *et al.* [22], the increase in CK peaked 24 hours after exercise, while the peak occurred in 30 minutes in Dorneles *et al.* [24].

As for LDH, 5 of the 6 studies [20,22-25] found a significant increase after high-intensity interval running, and 4 studies [20,23-25] observed increases only immediately after the test. Brandão *et al.* [22] found a significant increase in LDH only 24 h after exercise. Farias-Junior *et al.* [21] found no significant difference in LDH at any time.

Farias-Junior *et al.* [21] and Brandão *et al.* [22] found an LDH peak 24 h after the protocol was performed. Dorneles *et al.* [24] and Cipryan [20] observed LDH peak immediately after exercise.

Tabela II - Biochemical variations and main results

Study	Biochemical variations	Results
Dorneles *et al.* [24]	3 moments (Pre, Post, and 30min) CK pre (U/L) HIIE: N= 135 ± 15*; O= 188 ± 17* CK post (U/L) HIIE: N= 180 ± 25#; O= 225 ± 30# CK 30min (U/L) HIIE: N= 185 ± 25#; O= 230 ± 30# LDH pre (U/L) HIIE: N= 238 ± 12; O= 226 ± 7 LDH post (U/L) HIIE: N= 270 ± 13#; O= 275 ± 9# LDH 30min (U/L) HIIE: N= 251 ± 9; O= 253 ± 9	This type of exercise was well tolerated and may have important implications for the generation of anti-inflammatory effects through a low-volume session, helping to control chronic low-grade inflammation in obesity.
Aloui *et al.* [25]	2 moments (pre and post); Periods (morning and afternoon) CK (U/L) pre: morning = 170.63 ± 16.01; afternoon = 222.27 ± 1.81 CK (U/L) post: morning = 268.18 ± 27.09#; afternoon = 320 ± 15.64*# LDH (U/L) pre: morning = 264.54 ± 24.27; afternoon = 363.18 ± 6.21 LDH (U/L) post: morning = 420.90 ± 28.61#; afternoon = 458 ± 23.30*#	Performance was impaired in the morning compared to the afternoon, associated with an oxidative response of patent variation, as well as biochemical measures.
Cipryan [20]	4 moments (Pre, Post, 3h, and 24h) CK (µkat/L) pre: 15/15 = 3.12 ± 1.80; 30/30 = 3.54 ± 2.10; 60/60 = 3.72 ± 2.11 CK (µkat/L) post: 15/15 = 3.81 ± 1.76; 30/30 = 4.42 ± 2.03; 60/60 = 4.61 ± 2.06 CK (µkat/L) 3h: 15/15 = 3.65 ± 1.62; 30/30 = 4.01 ± 1.97; 60/60 = 4.15 ± 2.07 CK (µkat/L) 24h: 15/15 = 4.02 ± 1.97; 30/30 = 4.63 ± 2.05; 60/60 = 4.75 ± 2.17 LDH (µkat/L) pre: 15/15 = 2.38 ± 0.36; 30/30 = 2.28 ± 0.42; 60/60 = 2.35 ± 0.43 LDH (µkat/L) post: 15/15 = 2.90 ± 0.51#; 30/30 = 2.89 ± 0.60#; 60/60 = 2.96 ± 0.48# LDH (µkat/L) 3h: 15/15 = 2.59 ± 0.40; 30/30 = 2.59 ± 0.49; 60/60 = 2.66 ± 0.47 LDH (µkat/L) 24h: 15/15 = 2.47 ± 0.39; 30/30 = 2.42 ± 0.41; 60/60 = 2.53 ± 0.53	The results indicated that the 15/15 and 60/60 protocols can be preferred to the 30/30 protocols to maximize the training stimulus. LDH showed post-exercise changes with 90% confidence intervals for HIIT 15/15, 30/30, 60/60.

Table II - Continuation

Study	Biochemical variations	Results
Farias-Junior *et al.* [21]	3 moments (Pre, 24h, and 48h) CK pre (U/L) HIIE: 147.3 ± 48.5 CK 24h (U/L) HIIE: 206.1 ± 76.6# CK 48h (U/L) HIIE: 198.0 ± 76.4# LDH pre (U/L) HIIE: 323.4 ± 62.0 LDH 24h (U/L) HIIE: 330.5 ± 60.9 LDH 48h (U/L) HIIE: 318.1 ± 43.6	Inactive overweight men expressed displeasure during the performance of HIIE, particularly at the end of the exercise session when the metabolic and perceived exertion were greater and self-efficacy was less than MICE.
Santos *et al.* [23]	2 moments (Pre and Post) CK (U/L) pre: 278.1 ± 78.64; post: 983.62 ± 339.49# LDH (U/L) pre: 326.0 ± 72.65; post: 758.72 ± 135.09#	The Rast Test promoted oxidative stress and muscle damage, with a significant increase in muscle damage markers (LDH and CK) in young athletes.
Brandão *et al.* [22]	3 moments (Pre, 24h, and 48h) CK (U/L) pre: 15/15 = 210 ± 170; 30/30 = 220 ± 170 CK (U/L) 24h: 15/15 = 370 ± 180*; 30/30 = 340 ± 160* CK (U/L) 48h: 15/15 = 310 ± 230; 30/30 = 230 ± 140# LDH (U/L) pre: 15/15 = 200 ± 60; 30/30 = 190 ± 70 LDH (U/L) 24h: 15/15 = 270 ± 80*; 30/30 = 250 ± 60* LDH (U/L) 48h: 15/15 = 240 ± 60; 30/30 = 230 ± 50	The performance values were similar in the H15 and H30 protocols. The difference between the relative changes (1%) was greater for H15 in relation to H30 in the activity of the CK enzyme, an important finding, since H15 had a similar performance in relation to H30.

H = men; N = normal weight; O = overweight; A = athletes; CK = creatine kinase; LDH = lactate dehydrogenase; HIIE = high intensity interval exercise; HIIT = high intensity interval training; MICE = moderate intensity continuous exercise; NI = not informed. *difference between groups; #difference between moments

Table III presents the assessment of methodological quality, using the TESTEX tool. The main methodological flaws observed were related to the reported randomization criteria and the blinding of the evaluators. These items were not scored in any of the included studies since all studies had a quasi-experimental design.

Table III - Methodological quality of selected studies

Study	1	2	3	4	5	6	7	8	9	10	11	12	Total
Dorneles *et al.* [24]	1	0	0	0	0	3	1	2	1	1	1	1	11
Aloui *et al.* [22]	1	0	1	1	0	2	0	2	1	1	1	1	11
Cipryan [20]	0	0	0	1	0	2	0	2	1	0	1	1	8
Farias-Junior *et al.* [21]	1	1	1	1	0	3	1	2	1	1	1	1	14
Santos *et al.* [23]	1	0	0	0	0	2	0	2	1	1	1	1	9
Brandão *et al.* [22]	1	0	0	1	0	3	1	2	1	1	1	1	12
Total	8	0	4	7	0	33	5	28	14	8	14	14	mean 10,83

1 - Eligibility criteria specified; 2 - Randomization specified; 3 - Allocation concealment; 4 - Groups similar at baseline; 5 - Blinding of evaluator; 6 - Withdrawals from the study < 15%; reported adverse events; reported session attendance; 7 - Intention-to-treat analysis; 8 - Primary and secondary between-group statistical comparisons reported; 9- Point measures for all results; 10 - Activity monitoring in control groups; 11 - Relative exercise intensity remained constant; 12 - Exercise energy expenditure reported

The main sources of bias in the present review were related to the measurement of results and the selection of the reported result, because, according to the ACROBAT-NRSI tool, the possibility of influencing the measurement of results due to the non-blinding of the researchers is sufficient for the risk of bias is at least moderate [19]. Thus, all included studies had a moderate risk of bias (Table IV).

Table IV - Risk of bias analysis of selected studies

Study	1	2	3	4	5	6	7	Risk
Dorneles *et al.* [24]	L	L	L	L	L	M	M	M
Aloui *et al.* [25]	L	L	L	L	NI	M	M	M
Cipryan [20]	L	M	L	L	NI	M	M	M
Farias-Junior *et al.* [21]	L	M	L	L	L	M	M	M
Santos *et al.* [23]	L	M	L	L	L	M	M	M
Brandão *et al.* [22]	L	L	L	L	L	M	M	M

1 - Bias due to confounding; 2 - Bias in selection of participants into the study; 3 - Bias in measurement of interventions; 4 - Bias due to departures from intended interventions; 5 - Bias due to missing data; 6 - Bias in measurement of outcomes; 7 - Bias in selection of the reported result. L = low; M = moderate; NI = not informed

Discussion

The present systematic review described the changes in the tissue injury biomarkers (CK and LDH) after high-intensity interval running. The heterogeneity of the methods and the characteristics of the samples of the included studies indicate that the results found must be analyzed with caution. It was observed that, despite the different protocols used, four of the six studies found a significant increase in CK and LDH concentrations simultaneously [22-25]. However, the extent of these changes has not always occurred to the same magnitude.

The CK results were consistent in terms of the behavior observed immediately after exercise, since five of the six studies showed an increase in CK levels [21-25]. The cause of this increase is pointed to the damage caused to the muscle fiber structures [26], more specifically to the sarcolemma membrane [27].

Furthermore, the changes depend on the protocol used, intensity, volume, frequency, time of post-test collection, number, and physical conditioning of the samples [28]. Moghadam-Kia *et al.* [29] mention that the type and duration of exercise are the main factors for variation in CK levels. Strenuous exercises are responsible for the highest elevation. Gender and race also have a significant contribution to the variation of this biomarker, with CK levels higher in men than women and in black people when compared to white people [29,30].

The increase in CK, observed in studies whose protocols involved running, can be explained by the mechanism of the stretching-shortening cycle, which generates muscle microlesion in the lower limbs during running [31]. Another explanation for the increase in CK levels may be the characteristic of the exercises to generate tension, which promotes muscle damage and results in the increase of this enzy-

me [32]. Besides, the eccentric muscle action implies greater muscle damage [27,30]. Such changes may take a week to return to baseline levels [33].

The CK peak occurs 24 to 96 hours after the onset of activity [27,34,35], which was observed in three [20-22] of the six included studies, although the Cipryan's study [20] presented the interval 90% confidence, which requires careful analysis of this result. However, as in Cerqueira *et al.* [36], another three studies did not show such a pattern or did not collect at that time [23-25]. At rest, CK levels tend to be higher in athletes when compared to healthy individuals, despite after exercise, the increase in CK levels tends to be lower in athletes [3].

Although LDH shows a difference in CK regarding metabolic adaptations to exercise [27], a similar behavior was observed between the indicators of muscle damage CK and LDH in four [22-25] of the six studies included. This finding can be explained by the biochemical adaptation to the physical load because when CK levels remain high, individuals also have an altered LDH [37]. As with CK, the increase of LDH levels depends on the duration and intensity of the effort [12]. Also, van de Vyver *et al.* [35] reported a strong correlation between VO_{2max} and the peak values of the biomarkers CK and LDH.

According to Brancaccio *et al.* [34], LDH activity seems to be correlated with the individuals' training levels and sports performance. A short interval training can increase the activity of glycolytic and oxidative muscle enzymes, resulting in a slight increase in LDH. This was found in the study by Klapcińska *et al.* [37], who verified that the lack of adaptation to training in untrained people can be observed by the higher concentration of LDH after a single stimulus. However, the levels of this biomarker showed to be higher in athletes at rest [36,37].

Callegari *et al.* [31] reported that aerobic exercise, such as running, can cause an increase in LDH from 12 to 24 hours. Bessa *et al.* [38] observed a significant increase between 3 and 6 hours after intense exercise. As in the previous study [38], another study showed that the increase in LDH levels, in moderate to intense physical activity, begins to be noticed from 1 to 3 hours after the end of the exercise, with a peak of 3 to 6 hours and returning to baseline levels in 24h [39].

Such statements confirm the results presented by most of the studies included in the present review and contradict Delsmann *et al.* [40], who observed that the increase in LDH can occur for up to 14 days after exercise, with the peak between the third and fourth days after stimulation. Concomitantly, Shin *et al.* [41] report that CK and LDH can help as markers for assessing the degree of muscle damage since such enzymes demonstrate skeletal muscle deficit, muscle damage, and cell necrosis.

The present systematic review has some limitations. The different moments of evaluation of the biomarkers, as well as the difference in the HIIT protocols used in the included studies, hinder a comparative analysis with greater depth. The studies included in this systematic review were related to healthy individuals. Thus, it is not possible to declare whether the same results would be valid for unhealthy populations. Moreover, all studies conducted the experiment with a small number of parti-

cipants, which may have contributed to greater individual variability. Therefore, the data evaluated needs to be observed with caution.

Conclusion

Based on the observed evidence, the present study pointed out that the CK and LDH biomarkers have high levels with high-intensity interval running. It was found that the measurement of these biomarkers can be a strategic tool for assessing the exercise load, accumulation of exercise, and intensity of physical activity, risks, and injury degree.

More research is needed to examine the impact of other types of exercise on inflammation. It is important that future studies carefully evaluate the intensity associated with the type and duration of exercise since these aspects influence inflammation during intense exercise.

Conflict of interest
The authors declare no conflict of interest with relevant potential.

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Author's contributions
Conception and design of the research: Sales TD, Mello DB, Romão WS, Castro JBP, Nunes RAM, Neves EB, Vale RGS. **Data collection:** Sales: TD, Mello DB, Romão WS, Castro JBP, Vale RGS. **Data analysis and interpretation:** Sales TD, Mello DB, Castro JBP, Nunes RAM, Neves EB, Vale RGS. **Writing of the manuscript:** Sales TD, Mello DB, Romão WS, Castro JBP, Vale RGS. **Critical review of the manuscript regarding important intellectual content:** Sales TD, Mello DB, Romão WS, Castro JBP, Nunes RAM, Neves EB, Vale RGS.

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