

Responses of myokines concentrations from exercise stimulus: a systematic review

Respostas das concentrações de miocinas a partir do estímulo do exercício físico: uma revisão sistemática

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ABSTRACT

Introduction: The skeletal muscle is the largest endocrine organ of human body, and have this role trough peptides and proteins known as myokines. The myokines are citocines that are produced and secreted by the skeletal muscle in response to the stimulus of contraction, acting locally and/or be released in the circulation and influence other distant tissues. Physical exercise is a potent stimulus for molecular adaptations in the organism, and when practiced with regularity, promotes structural and functional adaptations in skeletal muscle. Therefore, physical exercise has a direct action on the concentrations of myokines.

Objective: Based on this, this research investigated, through a systematic literature review, the responses of myokines concentrations from the stimulus of physical exercise.

Methods: Searches were carried out by two researchers independently, in the Scielo, Pubmed and Virtual Healthy Library databases, analyzing articles published between 2009 and 2020, after a careful selection process in four stages, the works that reached the third stage were read in full and submitted to quality analysis using a critical review form.

Results: At the end of the process, 12 articles were selected to compose the discussion.

Conclusion: The analyzed articles shows that physical performance, both acute and chronic, is capable of significantly modulating the concentration of several myokines, promoting an increase in many such as IL-6, IL-15, BDNF and Apelin, in addition to a significant decrease in muscle myostatin.

Key-words: exercise, skeletal muscle fibers, cytokines.

RESUMO

Introdução: O músculo esquelético é o maior órgão endócrino do corpo humano e possui esse papel a partir de peptídeos e proteínas conhecidos como miocinas. As miocinas são citocinas que são produzidas e secretadas pelo músculo em resposta ao estímulo das contrações, podendo agir localmente e/ou cair na circulação e influenciar outros tecidos distantes. O exercício físico é um potente estímulo para adaptações moleculares no organismo e, quando regularmente executado, induz adaptações estruturais e funcionais no músculo esquelético. Sendo assim, o exercício físico possui ação direta nas concentrações dessas miocinas.

Objetivo: Baseado nisso, essa pesquisa teve como objetivo investigar, através de uma revisão sistemática de literatura, as respostas das concentrações de miocinas a partir do estímulo do exercício físico.

Métodos: As buscas foram realizadas por dois pesquisadores de forma independente, nos bancos de dados do Scielo, Pubmed e BVS, analisando artigos publicados entre 2009 e 2020. Após processo de seleção criterioso em quatro etapas, os trabalhos que chegaram até a terceira etapa foram lidos na íntegra e submetidos a uma análise de qualidade por via formulário de revisão crítica.

Resultados: Ao final do processo, foram selecionados 12 artigos para compor a discussão.

Conclusão: Os artigos revisados demonstram que o exercício físico, tanto de forma aguda quanto de forma crônica, é capaz de modular de forma significativa a concentração de diversas miocinas promovendo o aumento da concentração das mesmas, por exemplo da IL-6, IL-15, BDNF e Apelina, além de diminuição significativa de miostatina muscular.

Palavras-chave: exercício físico, fibras musculares esqueléticas, citocinas.

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Introduction

Skeletal muscle (SM) has a great adaptative potential, being the intracellular signaling promoted by muscle contraction a strong mechanism to molecular and functional adaptation to muscle itself. Through stimulus caused by regular exercise training is possible to increase protein synthesis into SM, promoting higher functional capacity and performance [1].

Exercise is largely recommended both in prevention and as treatment to metabolic diseases by its anti-inflammatory (AI) role and as a metabolism regulator. In this scenario, the SM has an important role due the production and release of many cytokines and another peptide, called myokines by Pedderon *et al.* [2] in 2003.

These myokines can, in several cases, have AI role not only inside the muscle, but may be released into bloodstream and be transported to another organs and tissues. It can stimulate immunological responses and contrast with the deleterious effects of some cytokines produced by adipose tissue (AT), for example the tumor necrosis factor (TNF) [3,4]

Beyond that, the scientific literature shows evidences indicating that exercise training has the potential to directly alter the circulating levels of myokines, increasing production and release of many myokines, as interleukins (IL), IL-15 and IL-6 [4,5].

Although the importance of myokines be notable, taking into account that it allow communication between SM and other tissues, is still unclear how is their responsiveness to different exercise stimulus, as type, intensity and volume of exercise training. The knowledge of these responses can help to build a better exercise prescription aiming specific benefits promoted by higher myokines concentrations.

Besides that, there are some studies analyzing the effects of exercise into myokines concentrations, leading us to consider this review relevant, summarizing systematically the actual evidences in this field. Based in the knowledge of myokines responses, the professional of exercise prescription can be more specific to prescribe the exercise aiming to modulate properly one or more myokines. Based in these rational, the aim of this systematic review was to verify the responses of myokines concentration from exercise stimulus.

Methods

Determination of databases, research strategy and combinations

A systematic review was carried out based on bibliographic research of studies that analyzed the biological responses of myokines from the exercise stimulus. The research of the articles was performed by two independents researchers in December 2019, in the following electronic databases: Pubmed, Scielo and Virtual Health Library (in portuguese Biblioteca Virtual em Saúde [BVS]).

The selection of the descriptors used was made based on health science descriptors. In the searches for the articles the terms “myokines” and “effects of exercise” were used in the following combinations in English and Portuguese languages “skeletal muscle” AND “myokines”, “effects of exercise” AND “production of myokines”.

Was performed the PICO strategy: P – Participants in studies with exercise who dosed myokines; I - Interventions with systematic exercise of any type; C – Comparisons of results with theirselves pre and posts results; O – Outcomes of exercise concentrations of circulating myokines.

To better organization of references, we organized than in an Excel spreadsheet 2013.

Search plan steps

Search plan was divided in four steps (stages). In the first step was identified 197 publications potentially eligible to review. Then, in second step, the “2009 to current” and “human” filters were used to find studies closer to the proposed theme, resulting in 45 studies.

In third stage, the titles, abstracts and conclusions were read in order to verify their suitability for the purpose to this review. In addition, was applied the inclusion criteria established for the paper’s selection. Were included the papers that: a) original cross-sectional or longitudinal work; b) with at least one physical exercise session; c) reporting the effects of exercise on myokines concentrations. After analyzing the studies, 18 publications were selected and analyze in the next step.

In the fourth stage of article selection, the established exclusion criteria were performed. To begin, the papers were fully read by two independent researchers and were excluded papers that: were duplicated; b) those that did not reached 10 points or more in the critical review of Law *et al.* [6], and c) myokines that were not be analyzed at least in two different papers.

Results

At the end of the fourth stage, 12 papers were selected to compound this review. Is important to note that in all steps of search the papers and its analyzes was conducted by two independents researchers using the statistical software SPSS 22.0 and the Kappa concordance test [7] to check the level of agreement between the researchers. As a result, values was always above 0.80 and $P < 0.001$, indicating almost perfect concordance between researchers. In this analysis, values up to 0.19 indicate poor agreement, between 0.20-0.39 mild agreement, 0.40-0.59 moderate agreement, 0.60-0.79 substantive agreement and between 0.80-1.00 indicates almost perfect agreement [7]. For a better understanding of the results, Figure 1 shows the number of studies during all the pre-established stages.

Table I shows the score obtained by the studies selected using the instrument proposed by Law *et al.* [6]. It aims to classify the quality of studies and has 15 items.

However, item 4 does not score, as it is only to distinguish the type of study, so item 4 was removed from our analysis and item 5 became 4 and so on, totaling 14 items that were scored below in the table. A quality cut-off point of 10 points was defined, that is, the article that did not score at least 10 items would be eliminated from the review. The items that were scored were marked with an “x” while those that were not scored were left blank.

The profile of the 12 selected studies that met the inclusion and exclusion criteria was described in Chart 1. The total number of participants was 224 individuals, 74.2% (166) of whom were male and only 13.8% (31) women. Two studies did not report the gender of the sample. The age range of study participants ranged between 18 and 65 years.

Regarding study designs, 75% (9) were cross-sectional, while only 25% (3) evaluated biological responses in a longitudinal way. The response of myokines by stimulating resistance exercises (RE) was evaluated in 50% (6) studies. In turn, 50% (6) studies analyzed aerobic exercises (AE). Finally, the Elisa Kit was the most used enzymatic method of analysis in research.

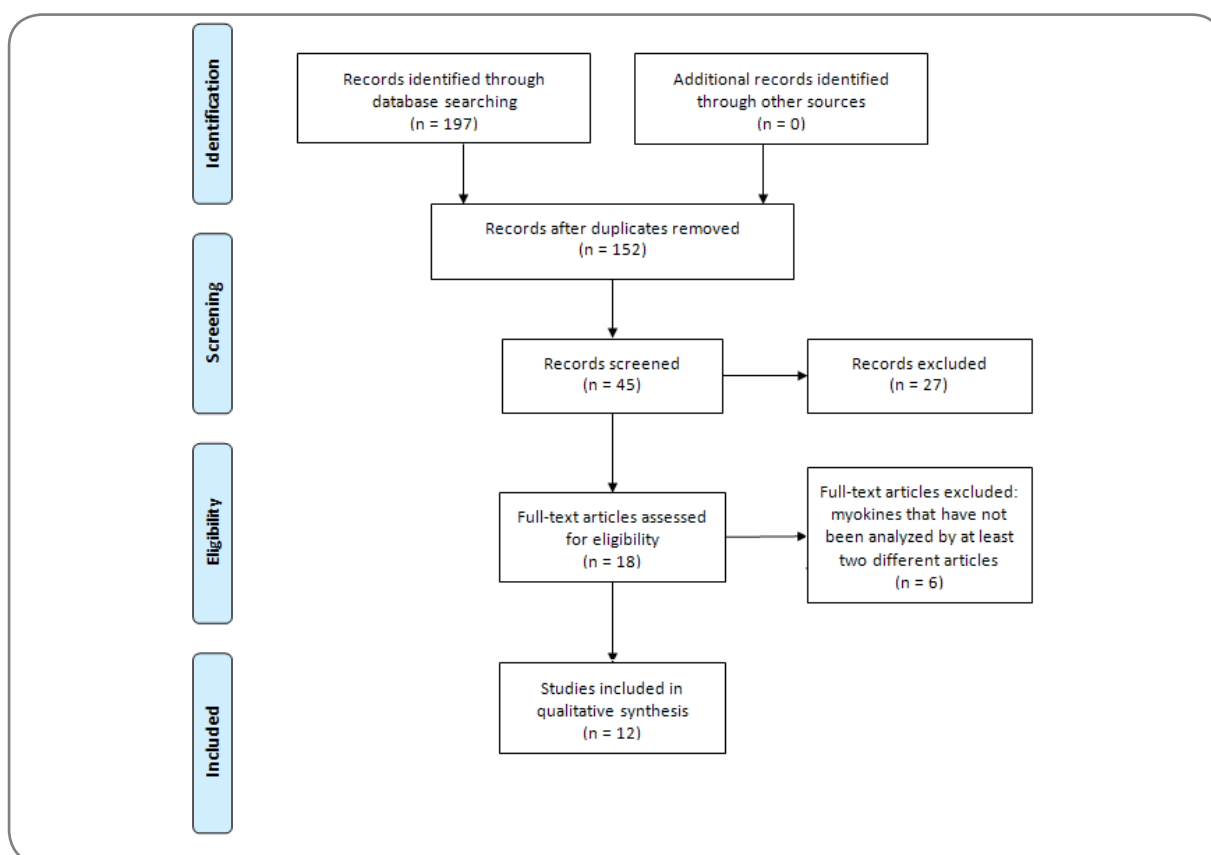


Figure 1 - Flowchart of the steps of the systematic review.

Table I - Score of studies in the critical review form by Law et al. (1998).

Author	1- Clear objective?	2- Revised literature?	3- Detailed sample?	4- Calculation Sampling	5- Confidence Measures	6- Measures validity	7- Description intervention	8- Contamination avoided?	9- Co-intervention avoided?	10- Report results	11- Statistical analysis	12- Clinic Relevance	13-Drop out	14-Conclusions	Total
Bugera et al. (2018)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	14
Oliver et al. (2016)	X	X	X		X	X	X	X	X	X	X	X	X	X	13
Sanchis-Gomar et al. (2015)	X	X	X	X	X	X	X	X	X	X	X	X		X	13
Wahl et al. (2015)	X	X	X	X	X	X	X	X	X	X	X	X		X	13
Carvalho et al. (2018)	X	X	X		X	X	X	X	X	X	X	X		X	12
Fortunato et al. (2018)	X	X	X		X	X	X	X		X	X	X	X	X	12
Hittel et al. (2010)	X	X	X		X	X	X	X		X	X	X	X	X	12
Pérez - López et al. (2018)	X	X	X		X	X	X	X	X	X	X	X		X	12
Zembron-Lancy et al. (2010)	X	X	X		X	X	X	X	X	X	X	X		X	12
Hjorth et al. (2016)	X	X	X		X	X	X		X	X	X	X		X	11
Kerschman-Schindl et al. (2015)	X	X	X		X	X	X		X	X	X	X		X	11
Tamura et al. (2011)		X	X		X	X	X		X	X	X	X	X	X	11

Chart 1 - Profile of the selected studies.

Author / year	Sample (N and sex)	Analysis method	Myokines analyzed / Type of exercise
Bugera <i>et al.</i> (2018)	N = 9 M; 18-35 years old; physically active, (at least 1 year in resistance training).	Human ELISA Kit KHC0061, Thermo Fisher Scientific, Waltham, WA, EUA;	IL-15 Bilateral knee extension Exercise with and without blood flow restriction
Oliver <i>et al.</i> (2016)	N = 10 W; 27 ± 4 years old; healthy, trained in resistance training.	R&d custom Premixed magnetic bead-based multiplex kit, fcstm14-02 (r&d systems inc., minneapolis, mn).	IL-6 e IL-15 Squat
Sanchis-Gomar <i>et al.</i> (2015)	N = 15 H; 27 ± 5 years old; Professional Soccer Players.	CSB-EL007669HU, Cusabio, Wuhan, China and EIAAPC, RayBiotech, Norcross, GA, EUA; respectively.	Alepin A soccer session.
Wahl <i>et al.</i> (2015)	N = 13; 24,8 ± 3,7 years old; healthy, non-smokers.	Quantikine HS ELISA-HS600B, R & D Systems, EUA.	IL-6 e BDNF Cycloergometer
Carvalho <i>et al.</i> (2018)	N = 61 (30W; 31M); 20-45 years old; Sedentary with BMI and obese individuals.	Enzyme-linked immunosorbent assay (ELISA); Quantikine human immunoassays (r&d systems, inc. Minneapolis, usa).	Myostatin Maximum treadmill test; Evaluation of strength and resistance in isokinetic equipment
Fortunato <i>et al.</i> (2018)	N = 20 M; Healthy; 18-35 years old; TG and UTG in resistance training.	Hmyomag-56k milliplex® map and luminex®	Apelin e BDNF Leg press, knee extension and leg flexion
Hittel <i>et al.</i> (2010)	N = 10 M; 40-60 years old; overweight and hyperinsulinemic (BMI = 27.9).	ELISA Kit	Myostatin Moderate aerobic exercise
Pérez - Lopez <i>et al.</i> (2018)	N = 14; 18-35 years old; trained in resistance training (at least one year).	ELISA kit (r&d systems, minneapolis, mn, usa)	IL-15 Leg press
Zembron-Lacny <i>et al.</i> (2010)	N = 16 M; 20,7 ± 0,9 years old; Not trained, physically active.	Enzyme immunoassay commercial kits (r&d systems, usa)	IL-6 Treadmill + Treadmill 10% inclined
Hjorth <i>et al.</i> (2016)	N = 24 M; 40-65 years old; Sedentary, CG (n = 13) normal blood glucose and dysglycemic (n=11).	Taq- man assays applied biosystems	Myostatin Cycloergometer; Resistance Training
Ker - schan-Schindl <i>et al.</i> (2015)	N = 19 (18M; 1W); 41-48 years old; ultramarathon athletes.	Colorimetric competitive immunoassay, immundiagnostik; bensheim, Germany.	Myostatin ultramarathon
Tamura <i>et al.</i> (2011)	N = 13 M; Healthy, untrained, physically active.	Human IL-15 quantiglo ELISA Kit, R&D systems, Minneapolis, MN, USA.	IL-15 Treadmill

BMI = body mass index; CG = Control Group; DG = Dysglycemic group; M = men; MR = maximum repetition; VO₂ = maximum oxygen consumption; TG = Trained Group; UTG Untrained Group = Grupo não treinado); W = women.

Chart 2 shows the myokines response concentrations from the exercise stimulus. It is observed that IL-6, IL-15 and myostatin were the target of 4 studies each one, standing out, as the myokines of greatest interest in literature when it comes to response through exercise.

Chart 2 - Biological responses to physical training.

Author / year	Exercise applied / Training	Weekly frequency	Biological responses to exercise / training	Conclusion
Bugera <i>et al.</i> (2018)	Bilateral knee extension. BFR-RE:30 reps at 30% 1MR + 3 sets of 15 reps, with 30s of interval HL-RE: 4 sets of 7 repetitions com 1' interval between series at 80% of 1 ME LL-RE: replication of BRF-RE but without blood flow restriction.	1 session; cross-sectional study.	IL-15 did not show* difference between exercise protocols neither 1h and 23 post exercise	There was no difference in the concentration of IL-15 post-exercise in any of the groups.
Oliver <i>et al.</i> (2016)	4 sets of 10 reps at 70% of 1 MR. TRD: 180s intra ser interval. Cluster: 30s interval intra reps and 150s intra sets.	1 session; cross-sectional study.	There was no \uparrow^* to IL-15 or IL-6 under any conditions and at any time	There was no \uparrow^* of myokines IL-15 and IL-6
Sanchis-Gomar <i>et al.</i> (2015)	A competitive soccer session (from January to May)	6 months; longitudinal study;	In the competitive period (January-March) there was \uparrow^* of apelin from 341.8 ng / mL to 433.3 ng / mL. However, on returning from vacation (May-July) no changes * were found.	The follow-up to a season of professional football showed \uparrow^* of apelin only in the competitive period and there was no correlation with performance
Wahl <i>et al.</i> (2015)	3 Conditions: A = Cycling (C); B = cycling and electrostimulation (C + E); C = electrostimulation (E). 60 Min / 70% of peak power.	1 session; cross-sectional study	C+E and E \uparrow^* IL-6 levels at times, 0', 30' and 60' after EF. 30' after C + E the values of IL-6 \uparrow^* compared to C. The levels of IL-6 \downarrow^* at moments 0', 30' and 60' after E compared to C + E and C. C+E and C \uparrow^* BDNF at 0' after exercise compared to pre. BDNF levels \uparrow^* at times 0' and 30' after E compared to C + E and C. 240' after exercise C + E \uparrow^* compared to C.	IL-6 showed higher \uparrow after C + E followed by C and E. Serum BDNF levels were * higher in C and C + E, while E induced non-changes *.
Carvalho <i>et al.</i> (2018)	1 min concentric knee extension and 5 sec isometric extension in a dynamometer. Isokinetic test set at 70° with a speed of 60°/s, for the isometric test the fixed position was 60°.	1 session; cross-sectional study	Normal weight group; Obese healthy group; Obese unhealthy group. Myostatin was considered elevated only in unhealthy obese individuals, Women had higher values than men for myostatin myostatin had a weak positive * correlation with metabolic syndrome (r = 0.26); Insulin levels (r = 0.25) and TNF α (r = 0.39), and negative associations with adiponectin (r = 0.40 and insulin sensitivity (r = 0.27)	Myostatin levels can be used to identify unhealthy phenotypes in young adults with obesity
Fortunato <i>et al.</i> (2018)	4 sets of leg press, knee extension and leg flexion at 65% of 1MR, with 90s of recovery	1 session; cross-sectional study	Two groups: (GNT) and the trained group (GT). Strength training \uparrow^* levels of apelin in the GNT at the times 2 hours after and 24 hours after, the brain-derived neurotrophic factor (BDNF) \uparrow^* only in the GT at the time immediately after.	An acute session of strength training increased * levels of apelin and BDNF levels

Chart 2 - Continuation.

Author / year	Exercise applied / Training	Weekly frequency	Biological responses to exercise / training	Conclusion
Hittel <i>et al.</i> (2010)	Moderate aerobic training 40-55% VO ₂ máx (treadmill, elliptical and bicycle) 9 months total (3 months of adaptation and 6 of training)	9 months; longitudinal study	A negative correlation was found in the pre-workout between myostatin and insulin sensitivity ($r^2 = -0.82$). After training, this correlation was ($r^2 = 0.49$) Myostatin ↓ * from 28.7 ± 3.1 to 22.8 ± 2.0 ng / mL with aerobic exercise	Myostatin levels decreased after 6 months of aerobic training.
Pérez-López <i>et al.</i> (2018)	Bilateral leg resistance exercise: 4 sets of leg press and 4 sets of knee extension in the extension chair at 75% of 1RM until concentric failure.	1 session; cross-sectional study	Serum IL-15 ↑ * at ~ 5.3 times after EF. IL-15 concentration was negatively correlated with muscle strength in the leg press ($r = -0.80$) and the extension chair ($r = -0.63$)	The signaling of IL-15 and its IL-15 receptor is activated in response to a single session of ER, increasing * the concentration of IL-15 post-exercise.
Zembron-Lacny <i>et al.</i> (2010)	Ex.1: 90' running at 65% VO ₂ máx and then at Ex.2: 90' running at 65% VO ₂ máx, 15' eccentric phase. The period between Ex.1 and Ex.2 was 3 months.	1 session; cross-sectional study	↑* IL-6 in the eccentric phase. IL-6 correlated with NO concentration after Ex.2 ($r = 0.66$).	Eccentric contraction is an important factor in increasing the concentration of cytokines considering that in the eccentric phase, IL-6 levels increased *.
Hjorth <i>et al.</i> (2016)	12 weeks of training in healthy individuals with supervised dysglycemia with 2 sessions / week of interval cycling (60') and 2 sessions / week of full body strength training (60'). Before and after the 12 weeks of training, a test was performed on the bicycle, lasting 45 minutes at 70% of VO ₂ máx measured before, shortly after and 2h after the two tests	Longitudinal study Aerobic training 2x / week; Resistance training 2x / week; 12 weeks;	Plasma concentration of myostatin ↓ * in 7.5% after 12 weeks of training Myostatin expression correlated positively with fast-acting fibers ($r = 0.53$) and negatively with slow-acting fibers ($r = -0.52$) There was a negative correlation between myostatin expression in the muscle and insulin sensitivity ($r = -0.53$)	Myostatin expression in muscle correlated with impaired insulin sensitivity
Kerschán-Schindl <i>et al.</i> (2015)	Ultramarathon (246 km); Venous blood collection 3 times: the day before the test, 15' after the end of the test and 3 days after the test.	Ultramarathon; cross-sectional study	Average levels of myostatin ↑ * post-test compared to pre-test levels. Average pre-test levels: 23.73 (ng / ml); Average post-test levels: 26.73 (ng / ml)	Increased serum myostatin levels appear to reflect muscle catabolism induced by extreme exercise.
Tamura <i>et al.</i> (2011)	30 min on the treadmill at 70% of HRmax.	1 session; cross-sectional study	The serum concentration of IL-15 ↑ * in 10' after the 30' run on the treadmill compared to pre-exercise levels. IL-15 concentration returned to baseline after 3 hours.	Extreme high-intensity exercise does not seem to be necessary to increase circulating levels of IL-15.

*Significant differences; BFR = Blood flow resistance; BFR-RE = exercise with blood flow restriction; BDNF = Brain derived neurotrophic factor; BMI = body mass index; C = Cycling CLU = Cluster Test; E = Electro-stimulation; GNT = group non-trained; HL-RE = High load resistance exercise; HRmax = maximum heart rate; IL-6 = Interleukin-6; IL-15 = Interleukin-15; LL-RE = low load resistance exercise; pg/ml = Picogram per milliliter; ng/mL = Nanogram per milliliter; NO = Nitric Oxide; TNF- α = Tumor Necrosis Factor alpha; VO₂ = oxygen consumption. HRmax = maximum heart rate; YAU = Yukon arctic ultra.

Discussion

The aim of the present study was to systematically review the response of myokines after exercise training. To better understanding the data, we will initially address the actions of the myokines that will be discussed, to later describe the effects of exercise on them.

Myokines actions

IL-6, the first myokine described, was showed by Steensberg *et al.* [8] in 2000. In addition to being produced by SM as a result of muscle contraction, is also produced in other tissues, as liver, for example. There is evidence that IL-6 acts stimulating the proliferation of satellite cells after acute damage in the SM, and, therefore, having a role in muscle hypertrophy [9].

When in physical exercise, the release of IL-6 occurs independently of release of TNF- α [10], possessing, thus, AI capacity. In this conditions, IL-6 acts inhibiting the production and secretion of TNF- α and its soluble receptors, as well, blocking IL-1 and IL-10 receptors [11]. Chronically, the levels of IL-6 are lowed after an exercise program, however, is also reported a better AI state in individuals that practiced exercise [12]. A possible explanation to this paradox, may be the fact that exercise modulates the release of IL-6 in other tissues, as in the immune system, consequently, lowering the release of IL-6 associated to TNF- α . The scientific literature shows that higher circulating levels of IL-6 are associated with physical inactivity and higher risk of metabolic syndrome [3,11,13].

Another myokine that has been studied in recent years is the IL-15. This myokine, similar with many others molecules produced in the body, promotes several effects in different organs. These effects include signaling to muscle hypertrophy, in additional to acting on lipidic metabolism [14], reducing the deposition of lipids and reducing the mass of white adipocytes cells. In the immune system, IL-15 acts mobilizing natural killer (NK) cells, that in its turn, act reducing tumor growth [15]. In bone tissue, associated with fibroblast growth factor (FGF) 21, IL-6 helps with bone mineralization, consequently aiding bone formation and repair after fracture [3,16].

We know that not all substances produced by muscular secretome assists in synthesis of other tissues, and myostatin is a good example of a myokine that acts limiting the muscle hypertrophy. Myostatin belongs to the family of transforming growth factor and with higher plasma levels of this myokine being observed in obese and sedentary individuals [17,18]. In addition to this limiting effect on muscle growth, myostatin has an important role in bone tissue and adipose tissue. In bone tissue, myostatin has acts opposite to IL-15, making mineralization and post-fracture repair difficult. In adipose tissue, therefore, evidence shows that myostatin triggers the signaling to hypertrophy of adipose tissue cells [16].

When performed acutely and chronically, the exercise downregulates myostatin levels in the tissues previously mentioned [19]. Evidence points to a large reduction of myostatin levels after one single session of exercise (56%), and in a longitudinal way, exercise training can reduce 34% of myostatin levels. In addition, a reduction of 48% was observed in elderly after an exercise program of training [20].

Another important myokine modulated by exercise is the brain-derived neurotrophic factor (BDNF), which in central nervous system, acts to maintain or improve cognitive activity by regulating neuronal survival, facilitating synaptic plasticity,

neurogenesis and improving the memory process. BDNF also has a role in neuroprotection against anxiety and depression [16,21].

Finally, apelin is a myokine that has receptors in various organs, as the kidneys, lungs, adrenal gland, heart, pancreas and brain. It is important to increase the cardiac inotropism and is associated with insulin metabolism. Apelin also improves the mitochondrial capacity in SM and reduces muscle damage [22].

Myokines and exercise

Interleukin 6 (IL-6)

The study conducted by Oliver *et al.* [14] evaluated myokines acute late responses after traditional squat and in the cluster squat (with 30s intra-series interval and 150s interval between sets), both at 70% of a maximum repetition (1MR). This study demonstrated a significant increase in the IL-6 concentration after exercise, but there were no significant differences between the kinds of squat. These findings can be partially explained by the fact that IL-6 can both acts as an anti-inflammatory factor and as an energy sensor in the cell [24]. Once having a bigger energy demand and increased gluconeogenesis, IL-6 is released, and both, the intensity and volume of exercise, affect its releasing.

In a study conducted by Wahl *et al.* [25], when analyzed the responses of three different situations 1) cycling with an effort at 70% of peak power, over a period of 60 minutes, 2) cycling plus electrostimulation and 3) only electrostimulation. The authors observed that the concentration of IL-6 increased significantly during cycling both with, and without electrostimulation, but not in isolated electrostimulation. These findings corroborate with the idea that the production and release of IL-6 is related to the mechanotransduction stimulus triggered by muscle contraction.

In a study conducted by Zembron-Lacny *et al.* [26] related the late acute response of IL-6 in a normal running and running with eccentric emphasis. They found higher IL-6 concentrations after running with eccentric emphasis. These findings can be explained to complementary factors. First, in eccentric contractions there a bigger tendency to muscle damage. In second, IL-6 also acts in muscle repair, inducing the proliferation of satellite cells [9]. In this way, exercise with eccentric emphasis can increase the expression of IL-6 messenger ribonucleic acid (mRNA) in the muscle.

Bugera *et al.* [27] evaluated bilateral knee extension with and without blood flux restriction in low intensity and without blood flux restriction in high intensity in strength training experienced individuals. The researchers did not find serum detectible levels of IL-6. Since there is little time of exposure to exercise and that the fact that IL-6 together with AMP-activated protein kinase (AMPK) are the most powerful energy sensors in the cell. Increasing its expression when there is a high metabolic demand compatible with cyclic training of greater volume, in resistance training there is a greater activation of Phosphoinositide 3-kinases-Protein Kinase B-mammalian target of rapamycin (PI3K-AKT-mTOR) pathway, that, which, in addition to signaling for protein synthesis, inhibits AMPK pathway [28].

The studies described above corroborate with the literature about the fact that IL-6 acts as a metabolic sensor and its concentration increases while the glycogen concentrations drop both in the muscle as in the liver. In another hand, chronically, evidences point, to decrease in plasma concentration levels of IL-6 decrease after physical exercise [12].

IL-15

We found studies analyzing IL-15 myokine only acutely. In the study conducted by Perez-Lopez *et al.* [29] was found a significance increase in IL-15 levels after leg press and in bilateral knee extension. IL-15 was more than 5 folds higher after exercise. This finding can be explained due to the mediating role of IL-15 in the elevation of myofibrillar protein synthesis observed in SM after a single session of a resistance training. This finding corroborates the study by Oliver *et al.* [23] who also found a significant post-EF increase for lower limbs.

On the other hand, Bugera *et al.* [27] when evaluating the resistance training with and without blood flow restriction, found no significant difference in IL-15 concentrations after exercise. Contrary to the two researches previously mentioned, Bugera *et al.* [27] adopted a submaximal exercise protocol and the total exercise volume was also lower. In our opinion, these results point to the need for high volume application to stimulate the response of this myokine. In addition, fatigue appears to play an important role in IL-15 secretion, as in the studies by Oliver *et al.* [23] and Perez-Lopez *et al.* [29], since this myokine plays a role in the response to muscle fatigue.

Tamura *et al.* [30] evaluated the acute response of IL-15, 30 minutes after an exercise performed on the treadmill at 70% of maximum heart rate, finding a significance increase in IL-15 levels after 10 minutes of recovery. The aforementioned studies indicate that regardless of the type of exercise, whether aerobic or resistance training, the contractile activity of the SM can triggers the production and release of IL-15, which may influence the mediation of systemic and local benefits from the exercise. From these studies, it seems to us that volume is a more important variable in resistance training than in aerobic training for the release of IL-15.

Miostatin

In an interesting study conducted by Carvalho *et al.* [18] the myostatin response was acutely evaluated after a maximal treadmill test and isokinetic exercise for lower limbs in three distinct groups composed of eutrophic individuals (EI), metabolically healthy obese individuals (MHOI) and obese individuals metabolically unhealthy (OMUH). Being classified as OMUH individuals who had insulin resistance and at least three of the five criteria for Metabolic Syndrome according to Panel III of adult treatment of the National Cholesterol Education Program [31].

The results showed that myostatin was elevated only in OMUH, because unhealthy obesity was associated with events such as insulin resistance, metabolic syndrome, TNF- α and low muscle mass. In addition, and perhaps more importantly, the authors also determined in this study the ideal cutoff point for myostatin concentration, which is > 505.1 pg / ml. These findings may prove to be useful in future studies and also in the monitoring of cardiometabolic disorders.

Myostatin response was evaluated in a longitudinally way by Hitel *et al.* [32] in a program of moderate exercise, where after each exercise session was measured myostatin levels. The authors analyzed myostatin levels after a 9 months exercise program in sedentary hyperinsulinemic individuals, using two different methods: western blotting and ELISA. In the western blotting method was found 37% reduction in myostatin levels, however, through the ELISA method, a 21% reduction in these levels was found. In our view, this discrepancy in values should be observed with caution, because most of the studies reviewed here adopted the ELISA method as a way of quantifying myokine concentrations.

Hjorth *et al.* [33] evaluated the myostatin concentrations during 12 weeks of exercise, both resistance and aerobic training in healthy individuals and in individu-

als with dysglycemia. The authors found a significant drop of 7.5% in the group with dysglycemia that was in the exercise training. However, acutely, the myostatin levels was found increased, in addition, a moderate positive correlation was found with glycolytic fiber, indicating that the greater the glucose consumption, more myostatin is produced and released. This find is corroborated by the moderated negative correlation for myostatin concentration and slow contraction oxidative fibers.

Kerschan-Schindl *et al.* [34] evaluated myostatin levels after 246 km marathon, the authors found a 12% increase in myostatin levels in the post-race compared to the pre-race. Despite this study finding higher levels of myostatin after exercise, possibly due to the level of effort required in an ultramarathon, the trend shown in the studies cited above is that myostatin appears reduced after physical training performed chronically. Still, the scientific literature is not clear when explaining the reason for this reduction, but it is known that there is a crosstalk between the skeletal muscle and the liver, where, in this case, the release of follistatin is increased by the liver and this substance acts by inhibiting the production and release of myostatin by the SM, which could chronically lead to these findings [3].

Brain Derived Neurotrophic Factor (BDNF)

In the study by Fortunato *et al.* [35], there was an increase in BDNF expression only for the group trained in resistance training, compared to the control group. In the study by Wahl *et al.* [25], the authors found greater increases in BDNF concentration after 60 minutes on the isolated cycle ergometer, followed by the cycle ergometer plus electrostimulation condition. These findings contribute to the notion that muscle contraction is a potent stimulator of BDNF release. Recently, the functioning of two pathways of crosstalk between muscle-brain has been discussed.

In the first pathway, moderate to high intensity exercise stimulates the secretion of cathepsin B, which manages to cross the blood-brain barrier (BBB) and stimulate the production of BDNF messenger ribonucleic acid (mRNA) [36]. In the second pathway, exercise stimulates the release of irisin into the bloodstream and irisin, in turn, would be able to cross the BBB and stimulate the production of BDNF in the hippocampus region [37].

Apelin

In the study by Fortunato *et al.* [35] it was shown that resistance training was able to increase plasma levels of apelin in the group with people not trained in resistance exercises, 2 hours and 24 hours after the end of session. In the study by Sanchis-Gomar *et al.* [38] apelin was evaluated longitudinally during a professional football season, with a significant increase in its concentration in the first three months of the season. However, although this myokine is related to the improvement of mitochondrial capacity [39], this increase was not correlated with the players' sports performance. Based on that, the authors consider that this myokine should not be considered as a performance biomarker. In our opinion, more studies need to be carried out with this theme, not only in football, but in other sports.

Taking into account the acute results of the studies above. We consider important to highlight the hypotensive effect of apelin already demonstrated in the literature and how its secretion can benefit hypertensive individuals. This is due to phosphorylation of the enzyme nitric oxide synthase endothelial, consequently causing an increase in the production of nitric oxide [40]. In hypertensive subjects, the levels of apelin are decreased, mainly due to hemodynamic changes caused by the pathology [41]. Longitudinally, the study by Izadi *et al.* [42] demonstrated that hi-

gh-intensity interval training has the ability to increase the secretion of apelin and nitric oxide in hypertensive individuals.

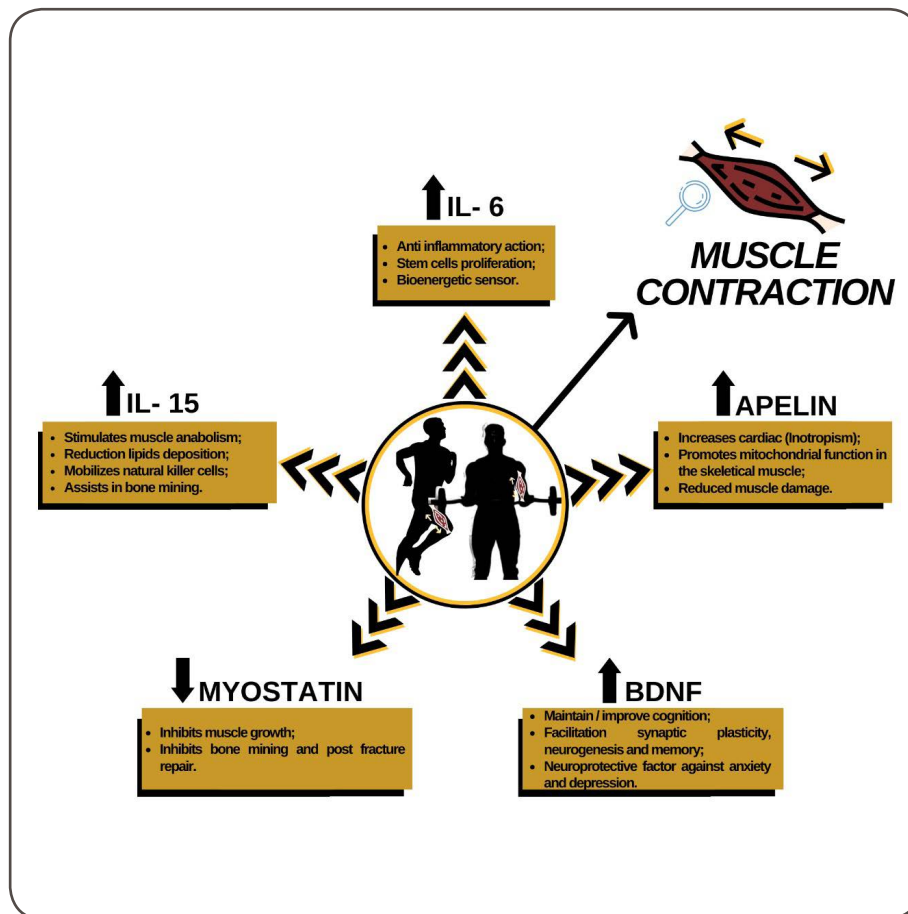


Figure 2 - Summary of myokine responses and actions.

Limitations and future directions

We highlight as limitations, the fact that of the selected articles, a small number of studies (only three), evaluated the responses of myokines to exercise in a chronic way and that different intervention methodologies resulted in difficulty in comparing the findings. As future directions, we suggest that a pattern in the intervention methodology, with respect to volume and intensity, be replicated in different studies, with the aim of verifying whether there is a difference between the results, and that studies investigating the effect of different environmental temperatures are produced and exercise conditions in the responses of myokines to increase the external validity and application of the exercise prescription considering the concentrations of myokines.

Conclusion

Based on the findings of this review, the ability of both aerobic training and resistance training to stimulate changes in the concentrations of different myokines is evidenced. It is also observed that the volume and intensity of exercise play a regulatory role in the production and secretion of myokines.

In addition, it was possible to observe that, both acutely and chronically, the practice of exercise provided significant changes in the release of myokines and that not all respond in the same way, such as IL-6 and BDNF, which increases after the exercise session, however, on the other hand, myostatin tends to decrease.

It was also possible to verify that most studies analyzed IL-6, IL-15 and myostatin, which suggests a specific interest in the literature to investigate the concentrations of these myokines. On the other hand, this creates a gap in the study of other myokines that should be further investigated, such as apelin and BDNF.

Potential conflict of interest

No conflicts of interest with potential potential for this article have been reported.

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