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Systematic Review

Do nonsteroidal anti-inflammatory drugs affect responses to resistance training in elderly and middle-aged individuals?

Anti-inflamatórios não esteroides afetam as respostas ao treinamento resistido em indivíduos idosos e de meia-idade?

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most popular drugs in the world for treating pain and inflammation. Although the long-term use of NSAIDs is associated with adverse renal, cardiovascular, hepatic, and other effects, it has also been suggested that may cause impairing neuromuscular adaptations promoted by exercise. **Objective:** The objective of this systematic review was to compare the effects of NSAIDs use in neuromuscular adaptations, such as hypertrophy and muscle strength in middle-aged and elderly practitioners of resistance training. **Methods:** The databases included Bireme, Pubmed e Science Direct. Meta-analyses were conducted using the robust variance estimation of correlated effects with small-sample adjustments. **Results:** Six studies were included for meta-analytical analysis. No statistical differences were found for hypertrophy (ES: 0.000531 ± 0.0424, 95%CI: -0.123 – 0.124; P = 0.991) and muscle strength (ES: 0.323 ± 0.213, 95% CI: -0.417 – 1.06; P = 0.258). **Conclusion:** The findings of this review do not support the hypothesis that the use of NSAIDs combined with resistance exercise negatively influences the hypertrophy and muscle strength.

Key-words: Non-steroidal anti-inflammatory agents, Resistance training, Hypertrophy, Muscle strength, Aged.

RESUMO

Introdução: Os anti-inflamatórios não esteroides (AINEs) estão entre os medicamentos mais populares do mundo para o tratamento da dor e inflamação. Embora o uso a longo prazo de AINEs esteja associado a efeitos adversos renais, cardiovasculares, hepáticos e outros, também foi sugerido que ele pode causar comprometimento nas adaptações neuromuscular promovida pelo exercício. **Objetivo:** O objetivo desta revisão sistemática foi comparar os efeitos do uso de AINEs nas adaptações neuromusculares, como hipertrofia e força muscular em pessoas de meia-idade e idosos praticantes de treinamento resistido. **Métodos:** As bases de dados pesquisadas incluíram Bireme, Pubmed e Science Direct. As meta-análises foram conduzidas usando o método de estimativa de variância robusta de efeitos correlacionados com ajustes de pequenas amostras. **Resultados:** Seis estudos foram incluídos para análise meta-analítica, nenhuma diferença estatística foi encontrada para hipertrofia (ES: 0,000531 ± 0,0424, IC 95%: -0,123 - 0,124; P = 0,991) e força muscular (ES: 0,323 ± 0,213, 95% CI: -0,417 - 1,06; P = 0,258). **Conclusão:** Os achados desta revisão não sustentam a hipótese de que o uso de AINEs combinado com exercícios resistidos, influencie negativamente a hipertrofia e a força muscular.

Palavras-chave: Anti-inflamatórios não esteroides, Treinamento de resistência, Hipertrofia, Força muscular, Envelhecimento.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most popular drugs in the world for treating pain and inflammation [1]. Because of the ease of obtaining these substances, since they are sold without a prescription, consumption of high prevalence in different populations are found, but more used in the elderly [2].

Although the long-term use of NSAIDs is associated with adverse renal, cardiovascular, hepatic, and other effects [1], it has also been suggested that is capable of impairing neuromuscular adaptations promoted by exercise [3]. The negative influence of the drugs in adaptive responses to training may be linked to its mechanism of action since it is proposed to inhibit the activity of cyclooxygenase (COX), thereby decreasing the production of prostanoids pro-inflammatory, such as prostaglandins these pathways, which have been documented as necessary for the development of maximum muscle hypertrophy in response to the overload imposed on training [5,6]. It is of utmost importance to understand the actions of NSAIDs during exercise since resistance training is effective and widely applicable to reverse or control changes in the neuromuscular system, such as loss of muscle mass and strength, associated with aging [7-10]. These changes result in annual reductions of 1% in muscle mass and between 2-4% in strength [11-13], leading to increased morbidities, disability, loss of autonomy, decreased quality of life, and mortality [14].

Regarding scientific literature, the use of NSAIDs in neuromuscular responses appears to be conflicting. Studies conducted in rodents induced to mechanical overload by synergic ablation [5,15] demonstrated a reduced hypertrophic response when supplemented with NSAIDs, however, a positive effect was found after a protocol of 450 eccentric repetitions, in the recovery of muscle strength for a single dose of NSAIDs [16]. In humans, Lilja *et al.* [3] observed a decrease in responses when used in high doses of anti-inflammatory drugs. However, studies are showing no significant difference [17,18], or the use of NSAIDs potentiates hypertrophic responses [19].

Thus, the objective of this systematic review was to summarize the effects of NSAID use in neuromuscular adaptations, such as hypertrophy and muscle strength in middle-aged and elderly individuals practicing resistance training.

Methods

This systematic review with meta-analysis was performed according to the declaration of preferential reports for protocols of systematic review and meta-analysis (PRISMA-P) [20], under the prospective international registry of systematic reviews PROSPERO (CRD42018110375).

Eligibility criteria

For inclusion of studies on the qualitative assessment were required: 1) randomized clinical trials, 2) assess subjects aged ≥ 50 years, 3) were performed resistance exercises, 4) there was a group making use of NSAIDs compared to a placebo group, 5) had a minimum duration of 4 weeks, 6) measured hypertrophy and muscle strength as a primary or secondary outcome. For meta-analytical evaluation, the studies should present the effect size for the outcomes of interest or provide the information for the calculation manually. Studies that were in progress were excluded.

Search strategy

The databases included Bireme, Pubmed e Science Direct, the first searches were carried out until October 10, 2020. The search strategy employed the use of Medical Subject Headings (MeSH) descriptors associated with free terms as shown in the supplementary files. Searches through the references of each article were also used as secondary searches for retrieval of appropriate studies. After the final selection of the included studies, the general search precision was calculated, dividing the number of articles included by the number of relevant articles found, in addition to the number needed for reading (number needed to read, "NNR"), calculated by the inverse of precision [21].

Data collection

Independently, two researchers (C.P and M.T) selected articles by titles and subsequently by abstracts, thus identifying possible studies for full reading, excluding manuscripts that did not deal with the proposed content. In case of divergence, a third evaluator was asked (C.S).

The extraction of data on characteristics of participants, interventions and outcome measures were obtained independently by two reviewers (C.P and M.T). The percentage of pre- and post-training change was adopted. Studies that did not present the data in % are manually calculated using the following formula: pre = average of the pre-intervention moment and post = average of the post-training moment: %▲ = (post - pre / pre) X 100.

Risk of bias

To assess the risk of bias, the Cochrane Collaboration tool, the Risk of Bias Tool 1.0 (RoB 1.0) was adopted [22]. The RoB 1.0 instrument, consists of seven evaluation domains and was applied by two evaluators independently (C.P and N.C), in cases of divergence, a third evaluator (M.T) was consulted.

The seven domains of Rob 1.0 were: a) selection bias due to the generation of random sequence, b) selection bias due to concealment of allocation, c) performance bias, d) detection bias, e) attrition bias, f) reporting bias, and g) other bias.

Statistical analysis

The effect size (ES) was calculated for each outcome of hypertrophy and muscle strength, such as the difference between the posttest - pretest, divided by the standard deviation of the pretest, with adjustments for small sample bias [23]. The variance of each ES was calculated using the sample of each study [24]. Meta-analyses were conducted using the robust variance estimation of correlated effects with small-sample adjustments [25,26], using the robot package in software R version 3.5.2 (The R Foundation for Statistical Computing). Heterogeneity was assessed using I^2 statistics, with I^2 <50% low, ≥50% substantial, and> 75% high heterogeneity [27].

Results

Study selection

After searching the databases and eliminating duplicates, 831 studies were identified for selection by titles and abstracts, of which only 21 (3%) articles were selected for reading the full text. Six studies were included for the qualitative and quantitative assessment [18,19,28-31], as shown in figure 1. All studies included for qualitative analysis were quantitatively incorporated for the hypertrophy outcome

and only four articles for muscle strength. The overall accuracy of the survey was 0.007, while the NNR was 139.

Among the studies excluded for not satisfactorily meeting the inclusion criteria are: Three studies due to inadequate design; two studies by the studied population; four studies by intervention; three studies for the measured outcome and four studies for evaluating the same sample.

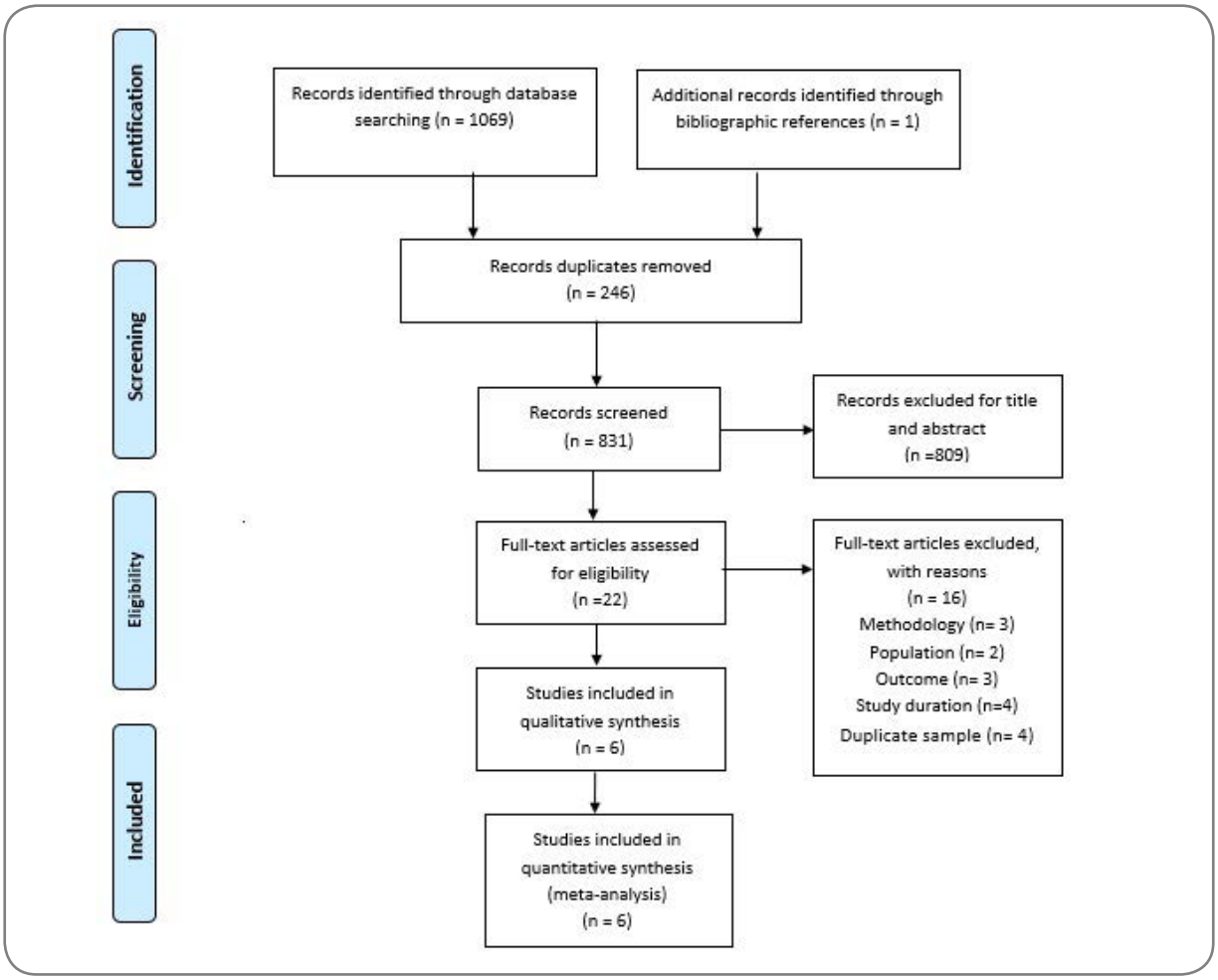

Figure 1- Flowchart.

Assessment of risk of bias

According to the RoB 1.0 tool, most studies were classified as unclear risk of bias (figure 2).

Regarding the selection bias, three studies [18,29,31] were considered as low risk and the rest were classified as an unclear risk for generating a random sequence. However, none of them were clear whether the allocation concealment was properly performed, thus indicating an unclear risk.

For performance bias, all included studies reported adequate methods to blind participants and staff and were considered as low risk of bias. In the assessment of the detection bias, the risk was classified as unclear in all included studies, since no study clearly detailed the blinding of the outcomes.

Attrition bias was considered at high risk by four studies [18,28,29,31]. Only two studies were classified as low risk for reporting bias. All articles included were classified as an unclear risk for other biases.

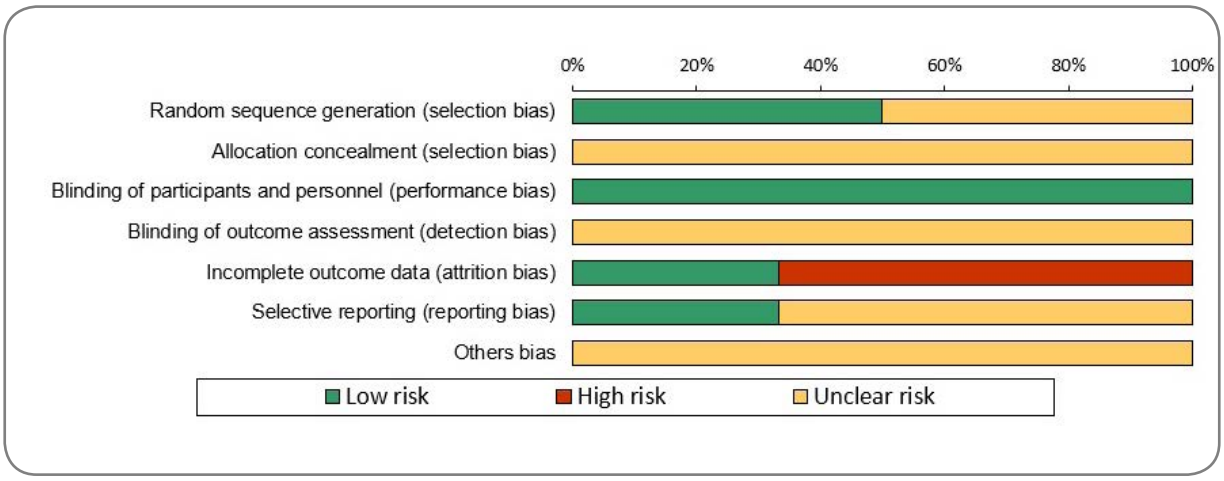

Figure 2 - Graph of risk of bias.

Study characteristics

The general characteristics of each study are described in Table I. The included studies were published between 2011 and 2016, all in English, in journals reporting the impact factor between 3.077 to 12.511. All studies reported sources of funding.

Regarding endpoints hypertrophy and / or muscle strength, five studies assessed as primary objective and only one secondary [29]. The methods for evaluating the outcomes of interest were magnetic resonance imaging (MRI), dual energy x-ray absorptiometry (DXA) and ultrasound. Interventions lCSAed from 6 to 36 weeks. The number of groups in the included studies ranged from 2 to 4 groups under investigation.

Subjects characteristics

Regarding the demographics of the samples, two studies evaluated North Americans [19,29], two in Danes [18,30], and two in Canadians [28, 31]. The age ranged from 50 to 80 years. Presented age, weight, height, body mass index means of 64.8 ± 2.3 years, 78.4 ± 14.1 kg 167.7 ± 6 cm, 27.2 ± 4.7 kg/m2, respectively.

In the qualitative analysis, the studies recruited 348 participants in 17 groups, with 67% of the sample consisting of women, distributed in seven groups for ibuprofen plus exercises, six for the placebo group, and four for other interventions. However, according to the inclusion criteria, meta-analytical analysis of hypertrophy and muscle strength were measured in 299 participants, 177 in 7 groups of NSAIDs and 112 in 6 placebo groups.

All studies evaluated sedentary individuals, including three with menopausal women [28,29,31], one study included people with osteoarthritis [18].

Characteristics of interventions

Interventions are reported in table II. Five included studies reported general warm-up and the activity was based on cycling lCSAing between 5 and 10 minutes, describing them as low intensity. A study performed specific warm-up [19], described as 2 sets of 10 repetitions, however, the authors did not report the quantification of the intensity used in the warm-up period. Only one study used intensities self-suggested by the participants [28].

Table I – General demographic characteristics of the sample of included studies.

Study	Year	Country	Age	Weight	Height	% Woman	Status of sample	Clinical condition	Assessment of	
									Hypertrophy	Strength
Trappe *et al.* [19]	2011	USA	65 ± 1.9	84 ± 7.7	172.5 ± 3.9	33.4	N.R	Healthy	MRI	1RM
Petersen *et al.* [18]	2011	DNK	62.3 ± 4.3	80.9 ± 15.4	169.6 ± 9.5	55.5	N.R	Osteoarthritis	MRI	5RM
Candow *et al.* [28]	2013	CAN	57.2 ± 4.7	74.5 ± 9.6	164.6 ± 6.1	100	Sed	Menopause	DEXA UTS	ID 1RM
Jankowski *et al.* [29]	2015	USA	64.6 ± 4	78.6 ± 16	170 ± 0.09	63	Sed	Healthy	DEXA	N.R
Duff *et al.* [31]	2016	CAN	64.8 ± 4.3	75.68 ± 13.5	161.3 ± 5.9	100	Sed	Menopause	DEXA	1RMpred
Dideriksen *et al.* [30]	2016	DNK	69 ± 7	80.4 ± 3.7	N.R	0	N.R	Healthy	MRI DEXA	MIVC

1RM = One-repetition maximum; 1RMpred = Submaximal prediction of one-repetition maximum; 5RM = five-repetition maximum; CAN = Canada; MIVC = Maximum isometric voluntary contraction; DEXA = Dual emission x-ray densitometry; ID = Isokinetic dynamometer; DNK = Denmark; MRI = Magnetic resonance image; N.R = Not reported; Sed = Sedentary; USA = United States of American; UTS = Ultrasound.

Table II - Characteristics of the interventions of the studies.

Study	Goups sample (M/F)	% Dropout	Dosage (mg/day)	Volume x Repetitions	Intensity (% or RM)	Recovery interval (seconds)	Weekly Frequency	Outcome	
								Hypertrophy	Strength
Trappe *et al.* [19]	IBU: 13 (9/4)	N.R	1200	3 X 10	% 1RM (73 ± 1; 74 ± 1 for IBU and PLC)	120	3	CSA: ↑↑ (10.9%)	1RM: ↑↑ (27.9%)
	PLC: 12 (8/4)	N.R	1200					CSA: ↑ (8.6%)	1RM: ↑ (21%)
	ACT: 11 (7/4)	N.R	4000					CSA: ↑↑ (12.8%)	1RM: ↑↑ (26.7%)
Petersen *et al.* [18]	IBU: 11 (4/7)	8.3	1200	Wk: 1-7: 4 X 12 a 15; Wk: 8-12: 4-5 X 8	% 1RM (70 to 80%)	N.R	3	CSA_{10cm}: ↔(4.4%) CSA_{20cm}: ↑ (5.7%)	$ID_{iso:}$ ↑↑ (18%) $ID_{con:}$ ↑↑ (12.7%) $ID_{exc:}$ ↑↑ (18.8%) 5RMlg: ↑ (49.2%) 5RMKe: ↑ (36.9%)
	PLC: 12 (5/7)	26	1200					CSA_{10cm}: ↔(6.1%) CSA_{20cm}: ↑ (4.3%)	$DIS_{iso:}$ ↔ (18%) $DIS_{con:}$ ↔ (12.7%) $DIS_{exc:}$ ↔ (18.8%) 5RMlg: ↑ (53%) 5RMke: ↑ (58.5%)
	GLC: 12 (5/7)	0	1500					CSA_{10cm}: ↔(6,3%) CSA_{20cm}: ↑ (4,8%)	$ID_{iso:}$ ↑ (13.6%) $ID_{con:}$ ↑ (11.6%) $ID_{exc:}$ ↔ (2.4%) 5RMlp: ↑ (33.8%) 5RMke: ↑ (37.3%)
Candow *et al.* [28]								FFM: ↓ (2.8%) MTke: ↑ (9.1%) MTkf: ↔ (2%) MTee: ↔ (5.6%) MTef: ↔ (-3.2%) MTapf: ↑ (8.7%) MTad: ↑ (12.1%)	1RMlp: ↑ (21.7%) 1RMbp: ↑ (13%)
	PLC: 13 (0/13)	N.R	400					FFM: ↓ (1.8%) MTke: ↑ (5.7%) MTkf: ↔ (-1.9%) MTee: ↔ (5.4%) MTapf: ↔ (24%) MTapf: ↑ (11.9%) MTad: ↑ (3%)	1RMlp: ↑ (21.1%) 1RMsp: ↑ (24.5%)
Jankowski *et al.* [29]	IBUb: 51 (19/32)	7.2	400	3 X 5 to 12	% 1RM (60 to 80%)	N.R	≥3	FMM: ↔ (0.8%)	N.R
	IBUa: 42 (15/27)	22.20	400					FMM: ↔ (1.2%)	N.R
	PLC: 37 (14/23)	N.R	440					FMM: ↔ (1.2%)	N.R
Duff *et al.* [31]	IBU: 23 (0/23)	21.70	400	2 X 8 to 12	N.R	N.R	3	FMM: ↔ (0%)	1RMb: ↑ (22%) 1RMs: ↑ (129%)
	PLC: 22 (0/22)	13.60	400					FMM: ↔ (2,3%)	1RMb: ↑ (25%) 1RMs: ↑ (88%)
	IBS: 23 (0/23)	26.09	400					FMM: ↔ (0%)	1RMb: ↔ (0%) 1RMs: ↔ (13%)
	CON: 22 (0/22)	31.82	0	Did not perform training				FMM: ↔ (0%)	1RMb: ↔ (13%) 1RMs: ↔ (15%)
Dideriksen *et al.* [30]	IBU: 8 (8/0)	N.R	1200	Wk 1: 3-4 X 12	RM	N.R	3	CSA: ↑ (5%)	MVIC: ↑ (11.8%)
		N.R	1200	Wk 2-4: 3-4 X 10; Wk 5-6: 3-4 X 8	wk1: 15RM wk2-4:12RM; wk5-6: 10RM			CSA: ↑ (1.4%)	MVIC: ↑ (5.2%)

1RMb = One repetition maximum in the biceps; 1RMbp = One repetition maximum in the bench press; 1RMle = One repetition maximum in the leg extension; 1RMlp = One repetition maximum in the leg press; 1RMs = One repetition maximum in the squat; 5RMke = Five repetition maximum in the leg extension; 5RMlp = Five repetition maximum in the leg press; 10 RM = Ten repetition maximum; 12RM = Twelve repetition maximum; 15RM = Fifteen repetition maximum; ACT = Acetaminophen; CSA = Cross-sectional area; CSA10cm = Cross-sectional area measured at 10 cm; CSA20cm = Cross-sectional area measured at 20 cm; FFM = Fat-free mass; GLC = Glucosamine; IBS = Ibuprofen and stretching; IBU = Ibuprofen; IBUa = Ibuprofen after training; IBUb = Ibuprofen before training; IDcon = Concentric evaluation on the isokinetic dynamometer; IDexc = Eccentric evaluation on the isokinetic dynamometer; IDiso = Isometric evaluation on the isokinetic dynamometer; MIVC = Maximum isometric voluntary contraction; MTad = Muscle thickness of the ankle dorsiflexors; MTapf = Muscle thickness of the ankle plantar-flexors; MTee = Muscle thickness of the elbow extensors; MTef = Muscle thickness of the elbow flexors; MTke = Muscle thickness of the knee extensors; MTkf = Muscle thickness of the knee flexors; N.R = Not reported; PLC = Placebo; RM = Repetition maximum; WK = Week; ↑ = Significant increase $p > 0.05$ in relation to the pre-moment; ↑↑ = Significant increase $p > 0.05$ in relation to the placebo group; ↓ = Significant reduction $p > 0.05$ in relation to the pre-moment; ↔ = No significant difference.

Regarding the choice of resistance training, they were composed of 64.3% of single-joint. The number of machines and / or free weights used in the studies ranged from 1 to 12, with knee extension, leg press and elbow flexion being the most prescribed, corresponding to 71, 57 and 57%, respectively. Complementary jumping jacks exercises, climbing and descending stairs, as well as medicine ball exercises were used.

The reported sets numbers were 2 to 4 between studies, with 6 to 15 maximum repetitions or 60 to 80% of 1RM. Only two studies reported conducting training until concentric muscle failure [28,31]. The interval between sets ranged from 1 minute and 30 seconds to 2 minutes. The reported weekly frequency was 2-3 days. The NSAIDs doses used were 400 mg to 1200 mg / day, single or divided into 2 to 3 times per day.

NSAIDs in the muscle hypertrophy

Qualitatively, six studies evaluated muscle hypertrophy. They involved 270 individuals, of which 163 (71.6%) were women, allocated to the NSAIDs group and 107 participants (64.4%) women in the placebo group. The findings for changes in muscle hypertrophy ranged from -2.8% to 10.9%.

In the meta-analytical analysis were assessed 14 ES for 6 studies. By analyzing the overall effect was observed a low heterogeneity (I^2 = 0%), but did not show significant difference between hypertrophy NSAIDs group and placebo group (ES: 0.000531 ± 0.0424, 95%CI: -0.123, 0.124; P = 0,991).

NSAIDs in muscle strength

In the qualitative analysis, five studies assessed muscle strength. Involving 163 subjects, 93 (77.4% women), allocated in the NSAIDs group. The placebo group consisted of 70 participants, 65.7% were women. Gains ranged from 5% to 128,9%.

Ten ES of four studies, evaluating 121 participants (78.5% women) were included in the meta-analysis for the outcome of muscle strength. By analyzing the overall effect, it was reported substantial heterogeneity (I^2 = 67.8%). However, there was no statistical difference between the groups (ES: 0.323 ± 0.213, 95%CI: -0.417, 1.06; P = 0.258).

Discussion

Based on current evidence, after a qualitative and meta-analytical assessment, the findings do not allow to state that the use of NSAID ibuprofen, combined with RT negatively results in the outcomes of hypertrophy and muscle strength.

Diverging from the results found in this research, a recent systematic review evaluated 28 articles, including randomized and nonrandomized clinical trials, cross-over, cohort, and cross-sectional studies that evaluated the effects of anti-inflammatory drugs in humans and animals. The authors concluded that the use of NSAIDs had a protective effect on age-related muscle mass [32]. However, it is worth noting that these findings should be evaluated with caution, since the inclusion of observational studies may lead to a potential risk of bias compared to randomized trials [33].

By observing the individual statistical of the studies regarding the changes from baseline for muscle hypertrophy, only three showed significant increases. However, only the study of Trappe *et al.* [19] demonstrated statistical superiority of NSAIDs group of 26.7% compared to the placebo.

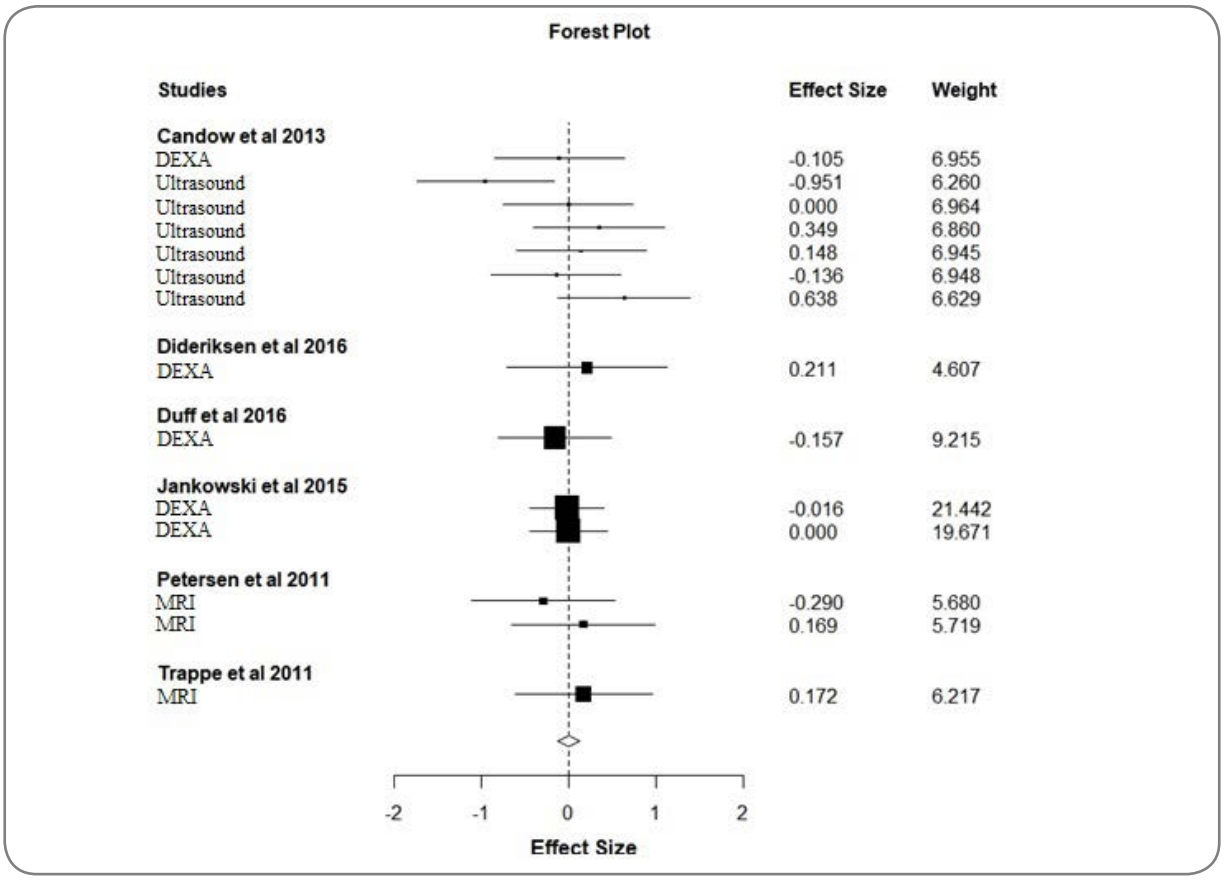

Figure 3 - Forest plot of the effect of NSAIDs on muscle hypertrophy.

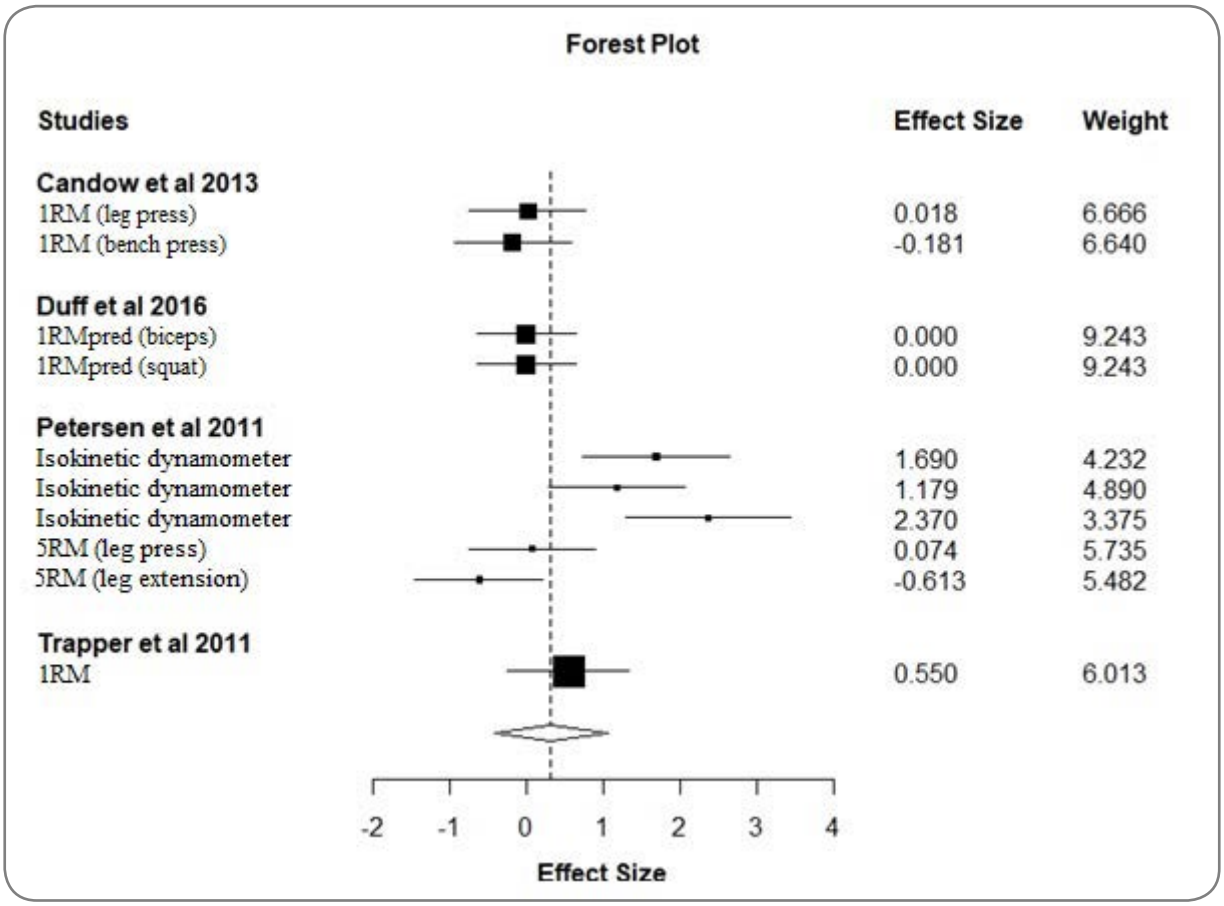

Figure 4 - Forest plot of the effect of NSAIDs on muscle strength.

The promising findings in hypertrophy and muscle strength, found by Trappe *et al*. [19], are not entirely clear in the literature. However, they appear to be partially explained by an increase in prostaglandin F2α receptors (PGF2αR), and suppression of production of prostaglandin E2 (PGE2), thereby controlling the production of interleukin-6 (IL-6) and the activation of muscle RING-finger protein-1 (MURF1) [34,35]. It is worth noting that this hypothesis has a priori the actions of PGF2a and PGE2, as an important regulator of protein turnover of musculoskeletal [36-39].

The regulation of IL-6 by suppressing PGE2 should be observed with caution, since this cytokine is suggested as an important triggering the hypertrophic process through induction of satellite cells [40]. The role of satellite cells in the myogenic process is well documented as in the key process of the myonuclear domain [40,41]. However, the role of NSAIDs on satellite cells is not clear, studies have reported a decrease [42,43], increase [44] or no difference in the number of cells after the use of drugs [45]. In addition, a recent review of myogenic regulation brings emerging evidence in studies with rodents pointing out that the contribution of satellite cells to the regulatory process of muscle mass can change with aging [41].

Despite this, Lilja *et al*. [3] found decreased responses in muscle hypertrophy after eight weeks of training in young people using ibuprofen in higher doses compared to low doses of aspirin. These findings may suggest that the dose of NSAIDs is influenced by the individual's age, since aging is associated with chronic inflammation [46,47] and a higher production of PGE2 than in young people [48]. However, it is noteworthy that the lack of a control group only with resistance exercises make impossible to claim that the NSAIDs are harmful to hypertrophy, since the study compared with another group using NSAIDs.

Krentz *et al*. [17] evaluated 18 individuals young people (12 men and 6 women) with a mean age of 24 years in a crossover, double-blind study, randomizing their arms for use of ibuprofen (400mg/day) or placebo after the training. They performed exercises for the left and right biceps on alternate days, performing six sets of four to ten repetitions, with a frequency of five days a week for six weeks. The authors found no differences in gains in strength and muscle hypertrophy compared to placebo side. Suggesting that the use of anti-inflammatory does not cause damage to neuromuscular adaptations.

Only the study by Candow *et al*. [28] demonstrated a reduction in the free fat mass in both groups evaluated (NSAID x Placebo). Importantly, the decrease in muscle mass in this study may have masked, if any, real influence of the anti-inflammatory since both groups had reduced. These findings may be associated with lack of food control, even after the authors suggest participants to refrain from feeding at 1pm after training during the study. This orientation may have influenced the participants to keep the restriction of caloric intake for longer, thus creating a negative energy balance and enabling moderate weight loss found in the study.

Regarding muscle strength, it is worth highlighting its prominence in the literature as a strong predictor of mortality [49-51], since older people with low muscle strength levels have 2.34 times more likely to die from any cause [52]. By observing the magnitude of the reported earnings by the studies included, one can notice a great heterogeneity in the results, ranging from 5-129%. About statistical significance, only two included studies reported increases higher than the placebo group. These differences in the findings may be associated with the inflammatory state of the evaluated, since they were not evaluated in individual studies, since high levels of IL-6 are correlated with greater decline and attenuation in gains in muscle strength [53,54]. However, in the meta-analytical evaluation, although we found an increase

(TE: 0.323), no statistical superiority was found for the NSAIDs group.

There are limitations present in this review that need to be evaluated with caution. First, studies have low sample size, this may entail an increased risk that the results being influenced by a type II error. Second, the small number of studies found made it impossible to investigate a possible influence of publication bias.

Conclusion

Based on current evidence, after qualitative and meta-analytical assessment, the findings do not confirm the hypothesis that the use of NSAID ibuprofen combined with resistance exercise negatively influences muscle strength and hypertrophy. Due to the discrepancies in the quality of the articles included, further studies with greater methodological rigor are needed to elucidate whether there is a negative influence on the use of NSAIDs on neuromuscular adaptations promoted by exercise.

Potential conflict of interest
No conflicts of interest have been reported for this article.

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There were no external sources of funding for this study.

Authors' contributions
Conception and design of the research: Paz CLSL, Tenório MCC. **Data collection:** Paz CLSL, Tenório MCC. **Analysis and interpretation of data:** Paz CLSL, Tenório MCC. **Statistical analysis:** Paz CLSL, Júnior NC, Tenório MCC. **Obtaining financing:** None. **Writing of the manuscript:** Paz CLSL. **Critical revision of the manuscript for important intellectual content:** Sá CKC, Tenório MCC.

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