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Photobiomodulation in human muscle tissue: an advantage in sports performance?

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Abstract

Photobiomodulation (PBM) describes the use of red or near-infrared (NIR) light to vstimulate, heal, and regenerate damaged tissue. Both pre-conditioning (light delivered to muscles before exercise) and PBM applied after exercise can increase sports performance in athletes. This review covers the effects of PBM on human muscle tissue in clinical trials in volunteers related to sports performance and in athletes. The parameters used were categorized into those with positive effects or no effects on muscle performance and recovery. Randomized controlled trials and case-control studies in both healthy trained and untrained participants, and elite athletes were retrieved from MEDLINE up to 2016. Performance metrics included fatigue, number of repetitions, torque, hypertrophy; measures of muscle damage and recovery such as creatine kinase and delayed onset muscle soreness. Searches retrieved 533 studies, of which 46 were included in the review (n=1045 participants). Studies used single laser probes, cluster of laser-diodes, LED-clusters, mixed clusters (lasers and LEDs), and flexible LED arrays. Both red, NIR, and red/NIR mixtures were used. PBM can increase muscle mass gained after training, and decrease inflammation and oxidative stress in muscle biopsies. We raise the question of whether PBM should be permitted in athletic competition by international regulatory authorities.

Keywords

photobiomodulation; LLLT; LEDT; fatigue; creatine kinase; delayed onset muscle soreness

INTRODUCTION

Photobiomodulation (PBM) is also called low-level laser therapy (LLLT) and light-emitting diode therapy (LEDT). PBM can provide several benefits to muscle tissue as evidenced by a plethora of studies that have been carried out *in vitro*, *in vivo* and in clinical trials. This review will cover these effects that have been reported up to now in the current literature,

concentrating on: i) prevention of muscle damage after exercise, including delayed onset muscle soreness (DOMS); and ii) increasing capacity for muscle workload, improving fatigue resistance, functional and athletic activity, and hastening recovery after exercise. We summarize studies with different levels of evidence such as randomized clinical trials (level 1b) and case-control studies (level 3b) published up to September 2016 that have aimed to increase muscle performance, recovery after exercise or prevent muscle damage by photobiomodulation using LLLT and/or LEDT applied to the upper limbs (*biceps brachii*) and lower limbs (*quadriceps femoris* muscles, hamstrings and *triceps surae*) in healthy volunteers/athletes.

The rationale for using PBM on muscles relies on the well-known stimulation of mitochondrial activity that occurs after red or near-infrared photons delivered to the tissue have been absorbed by cytochrome c oxidase. Muscles rely heavily on adenosine triphosphate (ATP), which is the biological source of energy needed for muscle work, and therefore robust increased ATP levels are the most popular hypothesis to explain the extraordinary effects that PBM appears to exert on muscle tissue. Moreover, there are several mechanisms of action to explain the effects of PBM on muscle tissue, and consequently improvement in sports performance. Several of these mechanisms have been described previously [1]: i) increases in energy metabolism and ATP synthesis; ii) stimulation of defenses against oxidative stress; iii) prevention and repair of muscle damage; iv) modulation of gene expression by activation of transcription factors; v) possible increase in the excitability of muscle fibers. For more details, see the review [1].

The use of PBM to prevent muscle damage was first demonstrated in animal models, usually by irradiating skeletal muscles before a bout of intense exercise (known as muscular pre-conditioning) and by assessing the severity of muscle damage by measuring creatine kinase (CK) levels in the bloodstream. To the best of our knowledge, the first study that used photobiomodulation to prevent muscle damage in animal models was carried out by Lopes-Martins et al. [2] in rats. These authors investigated the effects of different doses of light (wavelength 655 nm, 0.5 J/cm²; 1.0 J/cm² and 2.5 J/cm²) to prevent muscle fatigue and muscle damage (CK) induced by neuromuscular electrical stimulation. This study reported a dose response with the delivered fluence and its ability to decrease CK levels.

Another experimental study used training of rats on a treadmill running in decline (downhill running) and measured inhibition of inflammation, reduction of CK activity and lowering of oxidative stress. They also found increases in defense against oxidative stress (increased activity of superoxide dismutase - SOD) 24 h and 48 h after exercise [3]. These previous studies and other similar ones [2–7] were important to establish a scientific bridge to clinical trials for prevention of muscle damage in humans by photobiomodulation.

Regarding improved muscle performance and exercise recovery in clinical trials, the first published studies were looking at delayed onset muscle soreness (DOMS) [8–11] and resistance to muscle fatigue [12,13] during one or only a few bouts of exercise; and measuring muscle strength [14] and resistance to muscle fatigue [15] after exercise training programs combined with PBM.

The primary objective of the present review was to determine the effects of PBM in the form of LLLT or LEDT on muscle tissue in clinical trials that enrolled both untrained and trained healthy subjects, or athletes who were treated with muscular pre-conditioning (PBM before bouts of exercises), or PBM irradiation delivered after exercise/training sessions. The outcomes assessed in this review aimed to identify the effects (no effects, or positive effects) on muscle performance/recovery in upper and lower limbs when effective PBM was compared with control groups and/or placebo (sham) PBM therapy in humans regarding: i) number of repetitions, ii) torque, iii) torque in maximum voluntary contraction (MVC) or maximum voluntary isometric contraction (MVIC), iv) 1-repetition maximum test (1-RM), v) fatigue by surface electromyography analysis or time to exhaustion, vi) prevention of muscle damage (creatine kinase-CK), vii) reduction of DOMS, viii) blood lactate, and ix) muscle recovery. Finally, as a secondary objective, this review aimed to cover all the parameters used in the included studies in order to show which parameters “worked” (produced positive effects) and which did not “work” (produced no effects) when PBM was combined with exercise for upper and lower limbs. However, this review did not aim to conduct comparative (statistical) analyses (meta-analysis) regarding all outcomes of interest.

MATERIAL AND METHODS

Data Source and Searches

The effects of photobiomodulation (PBM) using low-level laser therapy (LLLT) and/or light-emitting diode therapy (LEDT) on muscle tissue in humans were determined through a review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [16] recommendations. However, risk of bias, quality of evidence (GRADE or PEDro approach), and comparative (statistical) analysis (mean differences, 95 % confidence intervals, effect sizes - meta-analysis) regarding all outcomes assessed from all included studies were not evaluated in this review.

The strategy to identify the studies to be included in the present review was accomplished by searching the current literature on MEDLINE (via Pubmed). The time window used for the search was from January 1960 to September 2016. All retrieved studies were analyzed to determine their eligibility according to the inclusion criteria. Potential studies were assessed by two authors that screened independently all titles and abstracts. Disagreements between review authors (CF and YYH) were resolved with decision from the third review author (MRH). We used only full-text papers, written in English, to determine the final inclusion in the review. There were no restrictions regarding gender, age, physical training condition of the healthy participants (athletes or untrained subjects) in each study included.

Randomized controlled trials (RCTs) and crossover trials (level of evidence 1b), as well as case control studies (level 3b), were eligible to be included in this review. Inclusion criteria were that the effective PBM, or placebo (sham) PBM should be applied before (muscular pre-conditioning) a bout of exercise or training programs, and/or after a bout of exercise or training programs in RCTs and/or case-control studies. Control groups were required as a mandatory criteria for study inclusion excluding those where PBM had no other kind of control therapy such as placebo (sham). Studies assessing PBM effects on exercises for upper or lower limbs, as well as exercises performed on treadmills were also considered

eligible. All terms used to search all studies were described in Table 1. Filters for article types, text availability, publication dates or species were not applied during search procedures in MEDLINE via Pubmed.

Data extraction (PBM parameters and outcomes) and quality assessment

Two review authors (CF and YYH) extracted study characteristics, PBM parameters and outcomes measured. They also qualified PBM effects as positive (providing an advantage) or without effect (no effect) according to the statistical results and statements in each included study. All studies were classified as acute (< 7 exercise sessions repeated with or without washout period plus PBM), and chronic (>7 consecutive exercise sessions without a washout period plus PBM). Calculations were done when PBM parameters were not fully or correctly provided in the study. A flowchart of this review is presented in Figure 1. All PBM parameters and outcomes from each study are summarized in tables 2, 3 and 4 and 5.

RESULTS

The database search retrieved 993 studies. After further selection based on the title and abstract, a total of 50 studies were screened and considered eligible to be included in this review taking into account the objectives and inclusion criteria. One study was excluded due to lack of a control group [17] and three studies [18–20] were excluded due to PBM being applied during exercise. Therefore, this review included in total 46 studies [Figure 1], comprising 1045 participants enrolled in the included trials. Risk of bias and comparative (statistical) analysis (meta-analysis) were not conducted in this review.

All 46 studies included in this review were allocated into 4 subsections according to their similarity regarding the number of exercise sessions (acute or chronic), combined or not with PBM, exercise or test used, and muscle or muscle groups subjected to such tests or exercises:

- A. Acute photobiomodulation (PBM) response in exercise using upper limb muscles;
- B. Acute photobiomodulation (PBM) responses in exercise using lower limb muscles;
- C. Acute photobiomodulation (PBM) responses in exercise on a treadmill;
- D. Chronic responses in clinical trials and case control studies.

A. Acute photobiomodulation (PBM) response to exercise using upper limb muscles

To our best of knowledge, the first randomized clinical trial (RCT) was conducted by Craig et al. [10] (level 1b). The authors investigated the efficacy of three different frequencies (2.5 Hz, 5 Hz, 20 Hz) of pulsed PBM using low-level laser therapy (LLLT) at 660 nm and 950 nm to mitigate DOMS induced by repeated eccentric contractions of the elbow flexor muscles with free weights until exhaustion in a randomized, placebo-controlled trial. The subjects received LLLT on the *biceps brachii* exercised for 3 days. However, DOMS increased for all groups treated with different LLLT pulse frequencies, as well as for the control and placebo groups. Range of motion was impaired and pain increased for all

groups. The authors reported no effect of PBM in DOMS assessed by visual analogue scale (VAS) and mechanical pain threshold/tenderness (MPT).

Years later, the same research group [11] (level 1b) conducted a very similar study to investigate the effectiveness of LLLT on DOMS during a treatment period of 7 days in a randomized, placebo-controlled trial. DOMS induction, as well as LLLT device used were similar to previous study [10], consisting of elbow flexion exercises with free weights and laser diodes at (660 nm and 950 nm, 73 Hz), respectively. After complete DOMS induction, subjects were treated with placebo, or LLLT, or control (rest in supine position) on 1 point over the *biceps brachii* for 5 consecutive days, plus 2 days in the following week. The authors reported no effect of LLLT to mitigate DOMS assessed by VAS and MPT.

Vinck et al. [9] (level 1b) investigated the effects of LEDT (cluster of 32 LEDs, 950 nm) on DOMS after induction of fatigue in the *biceps brachii* muscle using an isokinetic dynamometer. The authors reported no significant difference between the LEDT group and the placebo group regarding elbow flexor peak torque exerted and pain in this randomized, single-blind, placebo-controlled trial. However, using similar methodology, Douris et al. [8] (level 1b) in a randomized, double-blind placebo-controlled trial applied LEDT (cluster of 36 LEDs, 880 nm and 660 nm) on the *biceps brachii* muscles after elbow flexion/extension bearing free weights, and found a significant reduction in DOMS after 48 h when comparing LEDT to the control and placebo groups.

Using a muscular pre-conditioning protocol, Leal Junior et al. [13] (level 1b) applied LLLT (655 nm) on the *biceps brachii* muscle before elbow flexion/extension until exhaustion on a Scott bench in a randomized, double-blind, placebo-controlled trial. The PBM was applied on 4 points located on the muscle, and then maximum voluntary contractions (MVC) were applied with a load of 75%. The number of repetitions and total time to accomplish the exercise increased significantly in all the volunteers that received muscular pre-conditioning PBM compared to the placebo group. However the results of blood lactate were not significantly different. Moreover, similar studies have been conducted by the same research group, investigating a muscular pre-conditioning regimen with LLLT (830 nm) applied on 4 points of the *biceps brachii* [21] (8/10, level 1b). They also compared red (660 nm) and near-infrared (830 nm) wavelengths applied on the *biceps brachii* muscle before MVC on a Scott bench [22] (level 1b). These authors found significant differences between the placebo group and both groups irradiated with LLLT, but without significant difference between the two different wavelengths regarding the mean and peak force developed by each group irradiated.

Applying a muscular pre-conditioning protocol on 2 sites on the *biceps brachii* during 30 sec, Leal Junior et al. [23] (level 1b) in a randomized, double-blind, crossover, placebo-controlled trial reported an increased number of repetitions could be achieved, and found decreased lactate levels in blood as well as lower CK and C-reactive protein. The PBM used in this study was delivered by a cluster of 5 laser diodes (810 nm). Similar results were reported by the same research group [24] (level 1b) using a cluster of 69 LEDs (850 nm and 660 nm) applied on 1 site of the *biceps brachii* muscle in a muscular pre-conditioning protocol using elbow flexion/extension with a load of 75% of MVC on a Scott bench. The

LEDT group increased the number of repetitions and the duration of exercise compared to placebo group in this randomized, double-blind, crossover, placebo-controlled trial. LEDT also decreased blood levels of lactate, CK and C-reactive protein compared to placebo group.

Investigating the effects of PBM by LEDT (630 nm) applied after an exercise protocol to induce muscle damage by eccentric elbow flexion/extension, Borges et al. [25] (level 1b) reported a reduction in DOMS, and a slower decay in the isometric force able to be exerted by the LEDT group when compared to the placebo group in a randomized, double-blind, placebo-controlled trial. The authors also reported less restriction or a smaller decrease in the range of motion possible in the LEDT group 24 h, 48 h, 72 h and 96 h after induction of muscle damage. In a similar study Felismino et al. [26] (level 1b) applied LLLT (808 nm) on the *biceps brachii* muscle between 10 sets of 10 repetitions with a load corresponding to 50% of the 1-repetition maximum test (1-RM) during exercise consisting of elbow flexion/extension on a Scott bench. The results of this randomized, double-blind, placebo-controlled trial pointed to a significant reduction in muscle damage (measured by CK) only at 72 h after the exercise test compared to the placebo group. However, there was no significant difference in muscle performance (load) between groups.

Rossato et al. [27] (level 1b) compared the effects of large cluster probe (33 diodes; 30.2 cm²) versus small cluster probe (9 diodes; 7.5 cm²) on elbow flexor muscle fatigue in a randomized, crossover, double-blind, placebo-controlled trial. The authors reported an increased time to exhaustion when active PBM by LEDT with large and small cluster probes were used as muscular pre-conditioning to increase fatigue resistance assessed in an isokinetic dynamometer through maximum voluntary isometric contraction (MVIC). Both cluster probes induced an increase in time to exhaustion compared with respective placebo therapies, but there was no difference between both active cluster probes. Moreover, there were no significant differences among placebo, large and small cluster probes groups regarding maximum peak torque and electromyography analysis in the *biceps brachii*.

Some other studies did not report significant benefits of PBM on the *biceps brachii*, such as that by Higashi et al. [28] (level 1b) who used an exercise protocol on a Scott bench. These authors used a muscular pre-conditioning protocol with LLLT (808 nm) on 8 sites of irradiation on the *biceps brachii*. There was no significant increase in the number of repetitions and reduction in lactate levels in the blood, or reduction in fatigue assessed by surface electromyography in this randomized, triple-blind, crossover, placebo-controlled trial. Finally Larkin-Kaiser et al. [29] (level 1b) in a randomized, double-blind, crossover, placebo-controlled trial enrolling both men and women, applied a muscular pre-conditioning protocol with LLLT (800 nm and 970 nm) on the *biceps brachii* muscle at 15 points of irradiation. Although only a very small difference was found compared with placebo group, the LLLT group had an improvement in MVIC assessed by isokinetic dynamometer, and no significant effect on muscle point tenderness.

Figure 2 shows an example of the sites of irradiation on the muscles and exercise test for upper arms. Table 2 presents all parameters of photobiomodulation used for testing acute response in exercises with upper arm muscles.

B. Acute photobiomodulation (PBM) responses in exercise using lower limb muscles

One of the first studies published in this area was conducted by Gorgey et al. [12] (6/10, level 1b). The authors performed a muscular pre-conditioning protocol applying photobiomodulation (PBM) by LLLT (808 nm) for 5 minutes (scanning mode) comparing low energy (3 J) with high energy (7 J) on the *quadriceps femoris* muscles before induction of fatigue by neuromuscular electrical stimulation. Although apparently less fatigue in the LLLT groups compared to control, there was no significant difference among all groups.

Leal Junior et al. [30] (level 1b) in randomized, double-blind, crossover, placebo-controlled trial irradiated the *rectus femoris* muscle before Wingate tests with a muscular pre-conditioning protocol. These authors reported no significant effects of the LLLT (830 nm) on muscle performance, but the levels of CK and lactate in bloodstream were decreased when compared to the placebo group. Leal Junior et al. [31] (level 1b) conducted another randomized, double-blind, crossover, placebo-controlled trial using the Wingate test and compared the effects of LLLT (single diode, 810 nm) to LEDT (cluster of 69 LEDs, 850 nm and 660 nm) on the muscle performance of athletes. LLLT or LEDT was applied on 2 sites on the *rectus femoris* muscle in a muscular pre-conditioning protocol. LEDT decreased CK levels in blood compared to placebo and LLLT groups. However, there was no improvement in muscle performance or reduction in lactate levels in the bloodstream of the LEDT group compared to placebo and/or LLLT groups. Similar results were reported by Denis et al. [32] (level 1b) who also did not find positive results when LEDT (cluster of 69 LEDs, 950 nm and 660 nm) was applied during the rest intervals of the Wingate tests. These authors reported no significant differences in muscle peak power, fatigue index and blood lactate levels when compared to the placebo group in this randomized, single-blind, crossover, placebo-controlled trial.

In another randomized, double-blind, crossover, placebo-controlled trial using Wingate test, Leal Junior et al. [33] (level 1b) also compared the effects of photobiomodulation by LEDT (cluster of 69 LEDs, 850 nm and 660 nm) to the use of cold-water immersion (cryotherapy) in order to promote muscle recovery. Six athletes performed 3 Wingate tests on non-consecutive days and received either LEDT or cold-water immersion of the lower limbs (5°C for 5 minutes) as a therapy. LEDT was applied on 2 sites on the *quadriceps femoris* muscles, 2 sites on the hamstrings and 1 site on the *triceps surae*. Comparing both groups, LEDT significantly decreased levels of CK and lactate in the blood but was not able to increase muscle work in the Wingate test and did not reduce C-reactive protein.

In a similar study, de Paiva et al. [34] (level 1b) investigated the effects of cryotherapy on DOMS and muscle damage (CK) as a single treatment, or combined with PBM by a cluster with 1 infrared laser diode (905 nm), 4 red LEDs (640 nm) and 4 infrared LEDs (875 nm) in a randomized, double-blinded, placebo-controlled trial. The authors induced muscle damage in subjects with eccentric contractions of knee extensor muscles in an isokinetic dynamometer. Three minutes after, the subjects received either placebo, or PBM, or cryotherapy, or PBM + cryotherapy, or cryotherapy + PBM. Post-exercise assessments consisted of measuring CK in blood, visual analogue scale for pain (VAS) and maximum voluntary isometric contraction (MVIC) at 1 h, 24 h, 48 h, 72 h and 96 h. Treatments were repeated at 24 h, 48 h and 72 h. PBM improved MVIC, decreased DOMS and CK from 24 h

to 9 h when compared to placebo, cryotherapy and cryotherapy + PBM. The combination of PBM + cryotherapy reduced the efficacy of PBM. Finally, cryotherapy as a single treatment, and cryotherapy + PBM were similar to placebo, showing the superiority of PBM as a single treatment.

Assessing muscle performance by an exercise protocol using eccentric exercise in an isokinetic dynamometer, Baroni et al. [35] (level 1b) used a muscular pre-conditioning protocol with LLLT (cluster of 5 laser diodes, 810 nm) applied on 6 sites of the *quadriceps femoris* muscles in a randomized, double-blind, placebo-controlled trial. The authors reported an improved MVIC immediately and 24 h after the exercise protocol, and increased lactate dehydrogenase (LDH) activity at 48 h after exercise, and the CK levels in blood decreased after 24 h and 48 h when compared to the placebo group. However, the DOMS was not improved by LLLT. In addition, this same research group [36] (level 1b) also investigated the effects of the same LEDT cluster (69 LEDs, 850 nm and 660 nm) applied on 3 sites of the *quadriceps femoris* muscles before a fatigue protocol performed in an isokinetic dynamometer for knee flexion/extension. The authors reported that LEDT was able to decrease the decay of the knee extensor peak torque exerted compared to placebo group in this randomized, double-blind, crossover, placebo-controlled trial.

With a similar protocol of exercise in isokinetic dynamometer of previous study [36], Antonialli et al. [37] (level 1b) used laser diodes (905 nm) and LEDs (640 nm and 875 nm) assembled in the same device to stimulate muscle recovery when applied as a muscular pre-conditioning protocol on the *quadriceps femoris* muscles before a fatigue protocol with eccentric contractions and MVIC in an isokinetic dynamometer. Muscular pre-conditioning using lasers and LEDs was performed 3 minutes before the exercise protocol in a randomized, double-blind, placebo-controlled trial. The authors reported that light energies of 10 J, 30 J and 50 J per site of irradiation increased the percentage of knee extensor peak torque of maximum voluntary isometric contraction (MVIC) immediately and the effect lasted until 96 h after the muscular pre-conditioning. DOMS was reduced significantly using light energies of 30 J and 50 J when compared with the placebo group. Finally, this study reported a significant reduction of CK with light energies (doses) of 10 J, 30 J and 50 J.

On the other hand, the same aforementioned research group conducted another randomized, double-blind, placebo-controlled trial with soccer athletes and assessed also the effects of PBM using LLLT on the knee extensor peak torque of MVIC, DOMS, CK and interleukin-6 expression [38] (level 1b). This study applied LLLT on 6 sites of irradiation on the *quadriceps femoris* muscles similar to Antonialli et al. [37], but interestingly found different effects for light energies (doses) of 10 J, 30 J and 50 J. Light energies (doses) of 10 J and 50 J per site of irradiation were more effective to decrease CK levels in blood and interleukin 6 (IL-6), with better results in favor of 50 J. Moreover, MVIC was improved immediately after exercise up to 24 h after exercise with 50 J, and from 24 h to 96 h with 10 J. However, 30 J per site of radiation had no effect on MVIC, CK, IL-6 and DOMS. The main difference from this study [38] and the previous study [37] was the device used for photobiomodulation. While Antonialli et al. [37] used a cluster of lasers and LEDs, this study [38] used a cluster of 5 lasers diodes (810 nm) similar to used in previous study [35] that found positive effects with 30 J per site of irradiation.

In another study looking at dose-response, Hemmings et al. [39] (level 1b) developed a randomized, double-blind, crossover, placebo-controlled trial with 34 subjects to investigate the effects of PBM with LEDT on *quadriceps femoris* muscle performance in an isokinetic dynamometer. LEDT was applied as muscular pre-conditioning with light energies of 41.7 J, 83.4 J, 166.8 J, or placebo. Compared to placebo therapy, the authors reported a higher number of repetitions when LEDT was applied 83.4 J and 166.8 J per site of irradiation. However, there was no effect on blood lactate levels or torque exerted by knee extensor muscles in MVIC.

Toma et al. [40] (level 1b) in a randomized, triple-blind, crossover, placebo-controlled trial used a muscular pre-conditioning protocol with LLLT (808 nm) on the *quadriceps femoris* muscles and assessed muscle fatigue by surface electromyography during 60 seconds of leg extension exercise, also measuring the maximum number of repetitions. The authors reported an increased number of repetitions in the LLLT group compared to the placebo, but surface electromyography showed no statistical difference. In a similar study, Dos Santos Maciel et al. [41] (level 1b) used a muscular pre-conditioning protocol with LLLT (780 nm) applied on the *tibialis anterior* muscle and investigated fatigue in an isokinetic dynamometer combined with surface electromyography analysis. This double-blind controlled trial reported an increased torque exerted by the *tibialis anterior* muscle after muscular pre-conditioning, but muscle fatigue analyzed by surface electromyography was not reduced, and lactate levels in blood were not significantly different between groups.

On the other hand, de Brito Vieira et al. [42] (level 1b) in a randomized, double-blind, crossover, placebo-controlled trial applied a photobiomodulation by LLLT (808 nm) on 5 sites of the *quadriceps femoris* muscles between 3 sets of 20 maximum voluntary repetitions in an isokinetic dynamometer at a single training session. Two days after the training session, all volunteers were evaluated through the number of maximum repetitions of knee flexion/extension in the isokinetic dynamometer in conjunction with surface electromyography to measure muscle fatigue. The authors reported increased number of repetitions in the LLLT group and less muscle fatigue compared to the placebo group. Similarly, aiming to investigate the responsiveness of elderly woman to photobiomodulation, Vassao et al. [43] (level 1b) applied LLLT (808 nm) on 8 sites of the *rectus femoris* before a fatigue protocol in an isokinetic dynamometer in conjunction with surface electromyography and blood lactate analysis in a randomized, double-blind, crossover, placebo-controlled trial. The LLLT group had decreased blood levels of lactate, and reduced muscle fatigue assessed by surface electromyography, but were not able to improve their muscle performance in an isokinetic dynamometer.

da Silva Alves et al. [44] (level 1b) investigated the effects of PBM on cardiopulmonary exercise testing in conjunction with electromyography analysis performed on a cycle ergometer in a randomized, double-blind, crossover, placebo-controlled trial. The authors applied a muscular pre-conditioning protocol with a cluster of 7 laser diodes (850 nm) on three sites of the *quadriceps femoris* muscles (1 *vastus lateralis*, 1 *vastus medialis*, 1 *rectus femoris*) and 1 site on the gastrocnemius muscles. Compared to placebo, LLLT increased the peak O₂ uptake, cardiovascular efficiency, but had no effect on time of running, and fatigue in electromyography analysis.

Zagatto et al. [45] recently developed a randomized, double-blind, placebo controlled-trial to investigate the effects of PBM by LLLT on performance, muscle damage and inflammatory markers in water polo players. LLLT (810 nm) was applied on 8 points of the adductor muscle region immediately after each one of the 5 training days. The authors reported a moderate improvement in the 30-s crossbar jump test (performance) in the group treated with LLLT compared to placebo, but without further improvements in performance (200 m maximal swim). In addition, there was no significant differences between groups regarding muscle damage measuring lactate dehydrogenase (LDH) and CK, or inflammatory markers measuring interleukin 1 beta (IL-1 β), interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF- α).

In an attempt to find the best time point to apply PBM on muscles, Dos Reis et al. [46] (level 1b) compared the effectiveness of LLLT (830 nm) applied on the *quadriceps femoris* muscles as muscular pre-conditioning, or after an exercise protocol using leg extension with 75% of 1-RM until muscle fatigue in a randomized, double-blind, placebo-controlled trial. The authors reported that there was no significant difference regarding the number of maximum repetitions performed by all groups. However, lactate and CK levels in blood were lower in the group that was treated with LLLT after the exercise protocol when compared to placebo and LLLT delivered before the exercise.

Fritsch et al. [47] (level 1b) investigated the effects of photobiomodulation by LLLT (810 nm) on plyometric exercises, muscle damage (ultrasonography), soreness (visual analogue scale - VAS), torque in maximum voluntary contraction (MVC), as well as the best moment of irradiation: muscular pre-conditioning *versus* irradiation after a bout of exercise. This randomized, double-blind, placebo-controlled trial reported that both irradiation time points (muscular pre-conditioning and after exercise) promoted significant reduction in muscle damage compared to placebo (contralateral limb), but did not produce positive effects on VAS and MVC.

Recently Pinto et al. [48] (level 1b) investigated the effects of photobiomodulation using laser diodes and LEDs on muscle performance of rugby athletes in a randomized, crossover, double-blinded, placebo-controlled trial. These athletes received a muscular pre-conditioning protocol with laser diodes (905 nm) and LEDs (640 nm and 875 nm) assembled in the same device, or placebo therapy, before assessment in the Bangsbo Sprint Test at the training field, and blood lactate collection at 3, 10, 30 and 60 minutes after the Bangsbo Sprint Test. Compared to placebo therapy, the authors reported an improved average time for the sprints, lower fatigue index and lower percentage of blood lactate when athletes received the muscular pre-conditioning. However, PBM was not able to improve the best time for all the seven sprints performed in the Bangsbo Sprint Test.

Regarding the use of photobiomodulation in the sports field in real life competition, and trying to translate laboratory findings to clinical practice, Ferraesi et al. [49] (level 1b) used an array of 200 LEDs (100 LEDs at 850 nm and 100 LEDs at 630 nm) to test the effectiveness of PBM by LEDT for prevention of muscle damage in a randomized, double-blind placebo- controlled trial. The authors applied muscular pre-conditioning with LEDT on the *quadriceps femoris*, hamstrings and *triceps surae* muscles of professional volleyball

players before each official match during a national championship to prevent muscle damage measured by CK. In addition, this study tested 4 light energies (doses): 105 J, 210 J and 315 J and placebo. The authors reported that the effective light energies (210 J and 315 J) could prevent a statistically significant rise in CK while 105 J and placebo allowed significant increases in CK to occur in the blood 24 h after each official match.

Table 3 presents all parameters of PBM used in acute response to exercises with lower limbs. Figure 3 shows an example of the sites of irradiation on the *quadriceps femoris* muscles and an exercise test for lower limbs in isokinetic dynamometer in conjunction with surface electromyography analysis.

C. Acute photobiomodulation (PBM) responses in exercise on a treadmill

There have been several studies in the literature looking at the acute effects of PBM on muscles when used in muscular pre-conditioning regimens, and testing exercise performed on a treadmill. De Marchi et al. [50] (level 1b) in a randomized, double-blind, crossover, placebo-controlled trial used a cluster of 5 laser diodes (810 nm) applied on the *quadriceps femoris* muscles, hamstrings and *triceps surae* before a protocol of progressive and maximum effort on a treadmill. This study showed that LLLT increased both the relative and absolute oxygen uptake as well as the maximum time of running on the treadmill when compared with the placebo group. In addition, LDH, CK and lipid peroxidation (TBARS - thiobarbituric acid reactive substances) were significantly higher in the placebo group showing the PBM had protected against muscle damage. Finally, superoxide dismutase enzyme activity was lower in the placebo group after the exercise compared to the PBM group suggesting that PBM can protect against oxidative stress.

Analyzing the kinetics of oxygen uptake, Ferraesi et al. [51] (level 3b) conducted a randomized, double-blind, crossover, placebo-controlled trial with a single elite runner athlete. The authors applied a muscular pre-conditioning protocol on the lower and upper limbs and the trunk muscles using an array of 50 LEDs (850 nm) before high-intensity constant workload running exercise on a treadmill. Compared to placebo therapy, LEDT improved the speed of muscular VO_2 adaptation, decreased O_2 deficit, increased the VO_2 from the slow component phase, and increased the time limit of exercise. LEDT also decreased CK in blood (muscle damage) and reduced other markers of muscle damage and fatigue, which were alanine and lactate levels in the urine analyzed by proton nuclear magnetic resonance spectroscopy (1H NMR).

Miranda et al. [52] (level 1b) also conducted a randomized, double-blind, crossover, placebo-controlled trial to investigate the effects of PBM using a cluster probe with laser diodes (905 nm) and LEDs (640 nm and 875 nm) on cardiopulmonary exercise tests. The authors reported increases in the distance covered, time to exhaustion, ventilatory rate and less dyspnea when active PBM was applied on 9 sites of the *quadriceps femoris* muscles, 2 sites of the hamstrings and 2 sites on *gastrocnemius* muscles immediately before (muscular pre-conditioning) the cardiopulmonary exercise test.

However, recently a double-blind, crossover, placebo-controlled trial conducted by Malta et al. [53] (level 1b) investigated the effects of LEDT applied as muscular pre-conditioning to

improve high-intensity running effort in health subjects. This study used a cluster with 56 red (660 nm) and 48 infrared (850 nm) LEDs applied on the *quadriceps femoris* and *biceps femoris* muscles and between *soleus* and *gastrocnemius* region. The authors reported no effect of LEDT on maximal accumulated oxygen deficit, or contributions of the three different types of muscle metabolism (aerobic or glycolytic or phosphagen), time to exhaustion, peak lactate concentration, exhaustion perceived and heart rate at exhaustion. Moreover, the authors reported a possible negative effect of LEDT on maximal accumulated oxygen deficit and lactate based on the magnitude inference of effect size.

Table 4 presents all parameters of PBM used in acute response to exercises performed on treadmill. Figure 4 shows an example of the sites of irradiation on the *quadriceps femoris* muscles and a cardiopulmonary exercise testing on treadmill.

D. Chronic responses in clinical trials and case control studies

Ferraresi et al. [14] (level 1b) in a randomized clinical trial studied the effects of photobiomodulation (PBM) by LLLT (cluster with 6 laser diodes, 808 nm) on volunteers undertaking a strength training program using a load of 80% of 1-RM, twice a week during 12 weeks. Immediately after each training session, the LLLT was applied on 7 regions of the *quadriceps femoris* muscles. The authors reported an increased load in the 1-RM test achieved by the LLLT group compared to the control group and the groups undergoing training without any LLLT. In addition, only the LLLT group increased the knee peak torque extensor assessed by an isokinetic dynamometer.

Investigating resistance to muscle fatigue, Vieira et al. [15] (level 1b) in a randomized clinical trial measured the effects of LLLT (cluster with 6 laser diodes, 808 nm) on moderate training using a cycle ergometer performed 3 days per week during 9 weeks. LLLT was applied on 5 sites of the *quadriceps femoris* muscles immediately after each training session. The authors reported that only the LLLT group showed a reduced fatigue index of the knee extensor muscles in an isokinetic dynamometer.

Ferrerasi et al [54] (level 3b) recently conducted a randomized, double-blind, placebo controlled study in which a pair of identical twins were treated with a flexible 850 nm LED array (real or placebo delivered to different twins) applied on the *quadriceps femoris* muscles immediately after each strength training session (3X/week for 12 weeks). Real PBM (compared to placebo) increased the maximal load, muscle hypertrophy, expression of genes for hypertrophy and defense against oxidative stress; and decreased fatigue, markers of muscle damage and DOMS, expression of genes related to inflammation and muscle atrophy in muscle biopsies.

Baroni et al. [55] (level 1b) in a randomized clinical trial assessed the effects of LLLT (cluster with 5 laser diodes, 810 nm) applied as muscular pre-conditioning on the *quadriceps femoris* muscles during an eccentric training program in an isokinetic dynamometer, twice a week for 8 weeks. The thickness of the knee extensor muscle increased in the LLLT group compared to placebo assessed by ultrasonography, as well as significant increases in isometric knee extensor peak torque and eccentric knee extensor peak torque in an isokinetic dynamometer.

Recently other studies have investigated the effects of training programs combined with PBM. Kakihata et al. [56] (level 1b) assessed the effects of LLLT (single probe, 660 nm) on vertical jump performance and delayed onset muscle soreness in healthy subjects during 2 weeks. Vertical jump performance was assessed at the first, fifth, eighth, twelfth and fifteenth days. Group 1 (control group) did not receive LLLT irradiation on the *triceps surae* before or after vertical jump assessments; group 2 received active LLLT between or before two vertical jump assessments and two days after for muscle recovery (6 sessions/days of LLLT); and group 3 received LLLT between or before two vertical jump assessments and six days after for muscle recovery (10 sessions/days of LLLT). The authors reported no improvement in vertical jump performance (muscle power and fatigue) and decay in delayed onset muscle soreness among all the groups.

Toma et al. [57] (level 1b) conducted a randomized, double-blind, placebo controlled trial with elderly women submitted to a strength training program in a leg extension chair twice a week for 8 weeks, combined or not with PBM by LLLT (single probe, 808 nm). The irradiation was applied on the *quadriceps femoris muscles* immediately after each training session. The authors reported that PBM increased work, peak torque and power in an isokinetic dynamometer in the training + LLLT group compared to the control group; there were no changes in fatigue index, lactate concentration, 6-min walk test and surface electromyography among all the groups (training + LLLT, training, control) as well as further differences between training + LLLT and training group.

Finally, a comparison between the effects of PBM on muscle performance when applied as muscular pre-conditioning and/or after a bout of exercise [46] or training program [58] was also investigated by Vanin et al. [59] (level 1b). The authors used laser diodes (905 nm) and LEDs (640 nm and 875 nm) assembled in the same device, such as used by the same research group in previous study [37]. The strength training program was based on their previous study [14], but adding leg extension exercises [54]. This study measured the peak torque in the maximum voluntary isometric contraction (MVIC), load in a 1-repetition maximum test (1-RM) and also measured thigh circumference (perimetry). The authors reported significant increases in MVIC, 1-RM in leg press and in 1-RM in leg extension when PBM was applied before (muscular pre-conditioning) each training session. PBM before (pre-conditioning) and after, or only PBM after each training session added no effect to muscle performance. Thigh perimetry was not increased with any type of PBM.

Figure 5 shows an exercise training program and an example of the sites of irradiation applied to the muscles of lower limbs after each training session. Table 5 presents all parameters of PBM in chronic response studies with exercise of lower limb muscles.

Discussion

The foregoing summary of the clinical results that have been obtained with PBM of muscles, will raise some interesting questions that remain to be answered by further research.

1. What is (are) the best wavelength(s) to use?

2. When is the best time to apply PBM on muscles? Before or after exercise? If before or after exercise, how long should the time interval between light and exercise be?
3. What are the best PBM parameters (irradiance, fluence, pulse structure)?
4. How many points or sites of irradiation should be used on each muscle group?
5. How exactly does PBM interact with muscle tissue on a biochemical level to increase sports performance?
6. Does the well-known biphasic dose response that is typical of PBM apply to muscles? In other words is it possible to use too much light?

There are several questions, such as those raised above, that a health professional or a sports physiologist will certainly require to be answered before PBM is widely adopted to improve sports performance. Based on the present literature review, the wavelengths employed have been mainly in the red (630–660 nm) and near-infrared (808–950 nm) spectral regions. However, although a previous study did not find any significant difference between red and NIR LLLT for improved muscle performance in upper limbs [22], there appears to be a preference for NIR wavelengths in published studies, possibly due to its better penetration into muscle tissue. Possibly motivated by the desire to “get the best of both worlds” there has been an increased use of mixed red and NIR wavelengths recently made possible by newly developed clusters and arrays of laser diodes or LEDs for PBM. See tables 2, 3, 4 and 5.

It is important highlight the scientific rationale for the use of red and NIR wavelengths at the same time. Our research group already reported previously [58,60] that irradiations with red and NIR wavelengths at the same time possibly offer advantages based on the absorption bands of the chromophores in the cells that absorb light [61–64], in special cytochrome c oxidase in the mitochondrial electric transport chain, resulting in even more synthesis of ATP than either red or NIR used alone [65,66].

One of the key questions is what is the appropriate time point to irradiate muscle tissue? The current literature shows there are two main strategies concerning the use of PBM to increase muscle performance and exercise recovery in clinical trials aiming at sports performance. The first strategy is a muscular pre-conditioning protocol, i.e., irradiation of muscle tissue usually about 3–5 minutes before the bout of exercise. There are several pieces of scientific evidence in favor of a muscular pre-conditioning protocol [1,67,68], when the purpose is to increase sports performance, reduce muscle damage and prevent pain developing after a single bout of exercise. This strategy deals with acute response simulating an athletic competition. This strategy generally seems to be effective for this purpose; however recent studies have suggested that in fact short times before the exercise such as 5 minutes may not in fact be the best time. Therefore, a recent study conducted by our research group reported a wide time window (time-response) for PBM to produce highly significant increases in mitochondrial metabolism and synthesis of ATP, with a best time occurring between 3–6 hours after irradiation [60].

Another study also conducted by our research group corroborated these aforementioned results, Ferraesi et al. [69] applied a muscular pre-conditioning protocol with PBM in mice, and measured the performance (ladder climbing carrying a load) after different time intervals. They found that the muscle performance increased more than 300–600% (compared to sham) after waiting for 3–6 hours. However a group that received PBM only 5 minutes before exercise did not show any significant difference to the sham group. In this context, other studies also reported a time-response for PBM to increase cytochrome c oxidase activity in rats with red and/or NIR wavelengths [70,71].

The effects of time-response with PBM on biological tissues is not new [72,65], but requires further investigation *in vitro*, *in vivo* and in clinical trials. In this perspective, a muscular pre-conditioning protocol delivered to professional volleyball players, 40–60 minutes before official matches was able to prevent statistically significant muscle damage measured by CK levels in the bloodstream [49], showing that muscular pre-conditioning applied 3–5 minutes before a bout of exercise may not actually be the best time point. Moreover, it is very important to note that several studies (see tables 2, 3 and 4) applied a muscular pre-conditioning PBM protocol using LLLT or LEDT, or both together, and in general showed positive effects in preventing muscle damage and increase muscle performance from 1 h until 72–96 h. These results reinforce previous results *in vitro* [60,72,65] and *in vivo* [69–71] regarding the best time window or time-response for PBM to maintain its beneficial effects on biological tissues, may also apply to skeletal muscles in humans.

The second strategy is to apply PBM using LLLT or LEDT immediately after each bout of exercise in order to accelerate muscle recovery [1,46]. This strategy appears to be especially effective when used in combination with regular exercise training programs that can last for days or even weeks [58,14]. In addition, the use of PBM after each session training of exercise training programs also seems to increase the potential gains of performance, including defense against oxidative stress, muscle cell proliferation, energy muscle content (glycogen and ATP) and mitochondrial metabolism [58], in addition to several other effects reported previously (see review [1]). However, this issue is not completely clear in the literature, since a recent study reported better results in favor of muscular pre-conditioning in training programs [59]. We believe that further investigations to answer this question in are necessary.

The parameters of PBM reported in the literature show a large degree of variation. The total power of the device, time of irradiation, total energy of the light delivered to muscles, the energy density or fluence (J/cm^2), and the power density or irradiance (mW/cm^2) have not been standardized, and wide variations are apparent between the parameters used in different studies. One of the main factors that contributes to this variability is the wide diversity of different devices available, that can either be custom-made or commercially available, and exactly how they are used by the researchers. However, based on the present review, it is possible to establish a range for the aforementioned PBM parameters, mainly light dose (J), that produced positive effects in muscular pre-conditioning, or irradiations after a bout of exercise or training program.

We could identify a therapeutic window, or PBM window, suggesting a biphasic dose-response [73,74] for total energy applied on the *biceps brachii* (20–80 J), regardless whether PBM was applied as a muscular pre-conditioning protocol or after exercise. Parameters within the therapeutic window increased the number of repetitions, time of contractions, and decreased delayed onset muscle soreness (DOMS) in elbow flexion exercises. However, some studies presented ambiguous results (either positive or no effects) regarding these outcomes [21,27]. It is important to highlight that 41.7 J was the maximum energy per site of irradiation using cluster of LEDs, while 5 J was the maximum energy per point of irradiation using laser probes. Studies that applied total energy inside the identified range (20–80 J), but applied more than 41.7 J per site of irradiation, or more than 5 J per point of irradiation did not achieve positive effects [9,28] [Figure 6]. Finally, the light power and total time of irradiation ranged from 50 mW to 1500 mW and 30 seconds to 720 seconds, respectively.

For *quadriceps femoris* muscles, PBM used acutely also produced a biphasic dose-response [73,74]. to increase fatigue resistance or increase number of repetitions, increase muscle force or work, and decrease CK or related markers of muscle damage [12,30–40,42,43,46–49]. The range in total energy (J) identified to produce the most positive effects was 56–315 J, regardless if PBM was applied as muscular pre-conditioning or after exercise. It is important to note that only energy applied on the *quadriceps femoris* muscles of the references [33,48,49] were considered in the years 2011, 2015 and 2016, respectively [Figure 7]. The light power and total time of irradiation ranged from 60 mW to 2500 mW and 60 seconds to 3876 seconds, respectively.

A possible explanation for the negative or ambiguous effects of PBM parameters that were within the range of light dose (J) identified, could be attributed to: a) the type of test used to assess muscle performance and/or induce muscle damage (Wingate tests) [31–33], b) differences between cluster of lasers/LEDs as well as single laser probes, c) differences between the populations treated or enrolled in each study [38,35]. We suggest further investigations are needed to clarify these results.

Regarding exercise performed on a treadmill, the PBM effects on oxygen uptake or ventilatory responses, time of running, and muscle damage (CK) were more pronounced with light doses (J) ranging from 360–510 J applied on the body (mainly the lower limbs [50,52], plus trunk and upper limbs [51]) [Figure 8]. The light power and total time of irradiation ranged from 131.25 mW to 2500 mW and 360 seconds to 3876 seconds, respectively. Regarding the study conducted by Malta et al. [53], the authors applied 60 J per site of irradiation. As discussed for the *biceps brachii*, possibly 60 J per site of irradiation may be excessive.

PBM in conjunction with exercise training programs have demonstrated positive effects on *quadriceps femoris* muscles regarding 1-RM, torque, fatigue resistance [14,15,54,55,57,59], and ambiguous effects on hypertrophy and muscle work [14,15,57,59]. We could identify a large range in light dose (J) applied on *quadriceps femoris* muscles in chronic response (18–240 J) [Figure 9]. The light power and total time of irradiation ranged from 100 mW to 5000 mW and 15 seconds to 1368 seconds, respectively. These results require further

investigation, mainly regarding the best time to apply PBM (muscular pre-conditioning *versus* after exercise).

Regarding the number of points or the arrangement of sites of irradiation on the muscles, the reports show a larger number on the lower limbs, where the muscles are naturally larger than the muscles of the arms. It appears logical to irradiate as much of the muscle area as possible [14,1], but avoiding excessive light doses (energy - J) per muscle group.

We believe that it will be necessary to arrive at a standardization of the parameters of light irradiation [power of the light (mW), energy (J), fluence (J/cm^2), irradiance (mW/cm^2), number of irradiation points or irradiated area] as well as devices for PBM in sports/exercise settings. Although there are several important positive results already achieved in laboratory settings, some results of PBM are contradictory between studies both within and between research groups. This issue is evident after a thorough analysis of all parameters of PBM and results summarized in each of the tables in this review. While some studies report effects in favor of PBM (positive effects), other studies report no effects using the same or similar light parameters. Some examples: references [13] and [21] disagree about the total time of contractions (table 2); references [23] and [28] disagree about the total number of repetitions (table 2); references [35] and [38] disagree about the light dose of 30 J per site of irradiation (table 3); references [50] and [53] disagree regarding time to exhaustion (table 4). However, there are more positive effects in favor of PBM than there are conflicting results or negative results. In addition if all the positive results achieved in laboratory settings go on to demonstrate comparable improvements in sports performance in the real world, PBM will become very popular mainly amongst high level athletes.

It must be noted if the use of PBM becomes widespread in high level sports competitions, especially before major National or International competitions, or during athletic training, it is possible that the World Anti-Doping Agency (WADA) or the International Olympic Committee (IOC) will need to discuss the position they will take on whether PBM will be allowed or not. If they decide it should not be allowed, they will be faced with the tricky problem of how to forensically detect if muscles have been exposed to light? We cannot envisage a biochemical test that could be conducted on blood or urine that would conclusively detect whether muscles had been exposed to the “banned light” used in PBM. However we believe that discussions about this issue will happen soon.

CONCLUSION

After an extensive search of the literature, with considerable selection and analysis, all the studies included in this review matched our primary objective: to determine the effects of photobiomodulation (PBM) in clinical trials that enrolled both untrained and trained healthy subjects, or athletes. Moreover, all parameters have been assessed and summarized in tables in the present review and these allowed us to identify ranges in PBM parameters that promoted positive effects (“worked”), gave no effects (did not “work”) and some studies had ambiguous effects (both positive and no effects). However, the identified ranges in light dose (J) are not designed to be recommendations, or prescriptions of the best light dose to be used in future studies or clinical practice at present. We are aware of several factors that affect

light penetration and absorption by human tissues, and the existence of the biphasic dose-response that is typical of PBM. All these considerations may preclude a final prescription of the exact doses of light for general use. Finally, we suggest caution be exercised in generalization of the findings.

LIMITATIONS

This review was conducted searching only one database (MEDLINE via Pubmed) and did not assess the risk of bias and quality of evidence by the GRADE or PEDRo approach. In addition, this review did not perform a comparative analysis (meta-analysis). However, to our best knowledge, such analysis could not be easily accomplished due to the lack of consistency in PBM parameters, and the lack of uniformity in PBM devices found in current literature.

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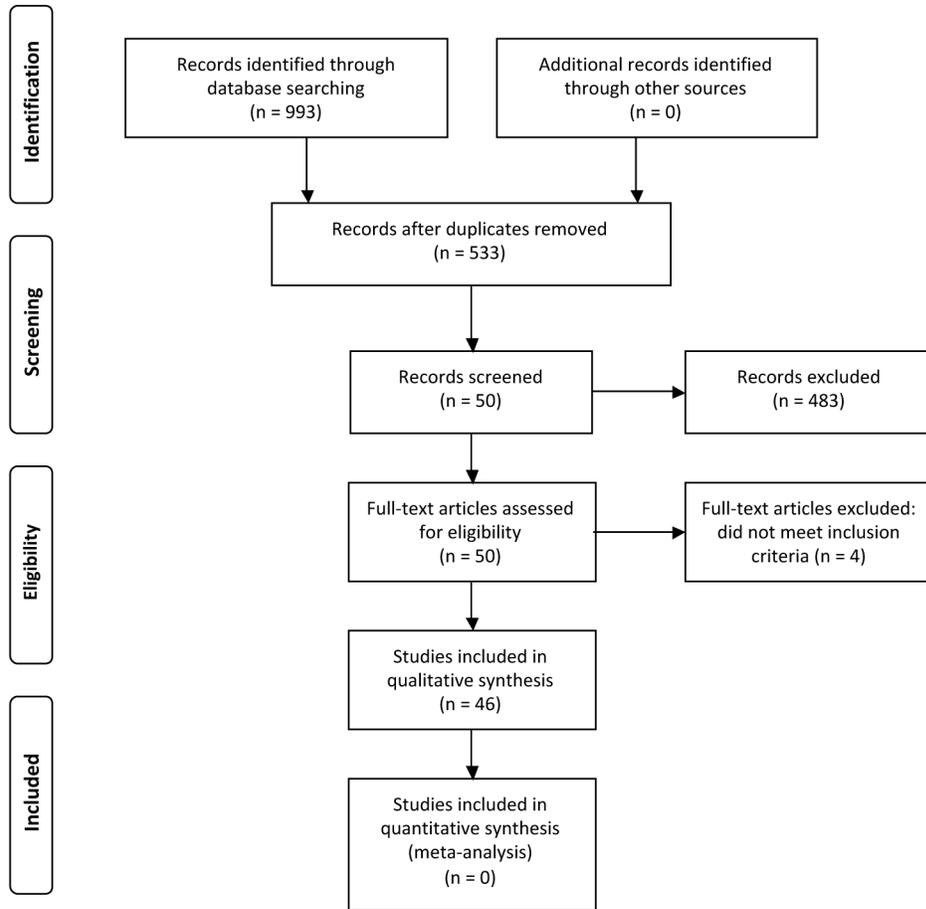


Figure 1. Flow diagram of the systematic review recommended by PRISMA [15]



Figure 2.

A) Example of muscular pre-conditioning irradiating multiple sites or points on the *biceps brachii*. B) Exercise test on a Scott bench.

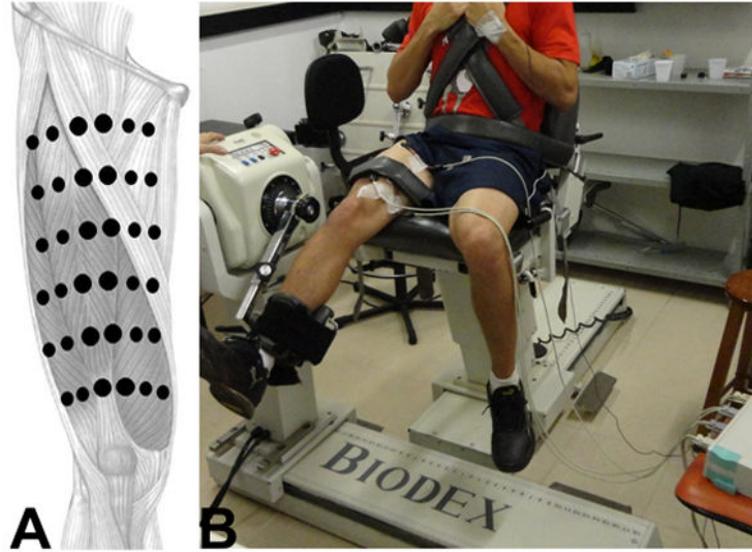


Figure 3.
A) Muscular pre-conditioning irradiating multiple sites or points of the *quadriceps femoris* muscles in order to cover the whole muscle group. B) Exercise testing in an isokinetic dynamometer in conjunction with surface electromyography analysis.

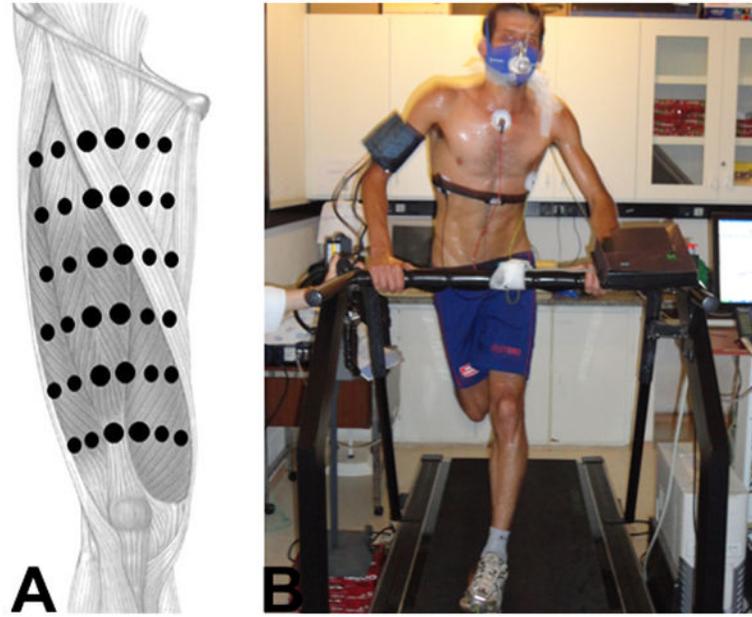


Figure 4.
A) Muscular pre-conditioning irradiating multiple sites or points of the *quadriceps femoris* muscles in order to cover all muscle group. B) Cardiopulmonary exercise testing on a treadmill.

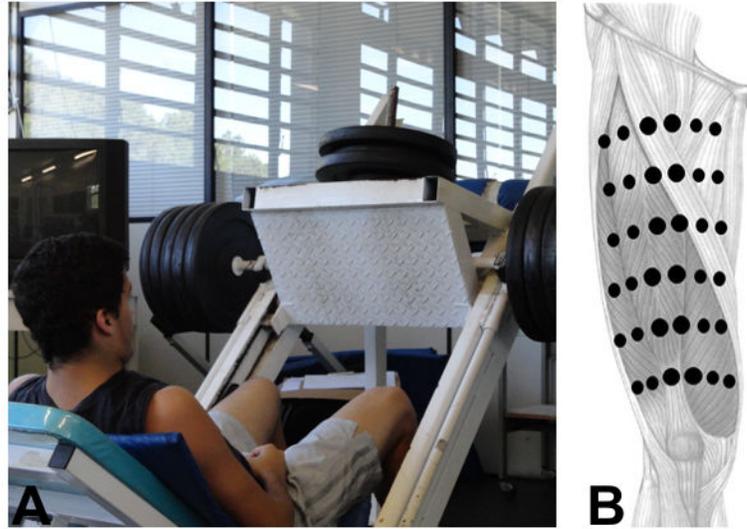


Figure 5. A) Exercise training program in a leg press. B) Photobiomodulation irradiating multiple sites or points of the *quadriceps femoris* muscles in order to cover all the muscle group applied after each training session.

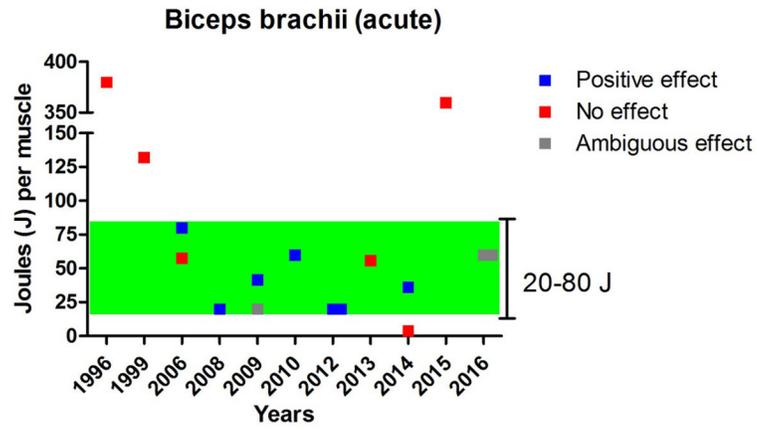


Figure 6. Total energy (Joules - J) applied on *biceps brachii* that produced positive effects, no effects, and ambiguous effects (positive and no effects) on the following outcomes: fatigue resistance or number of repetitions, time of contraction and delayed onset muscle soreness (DOMS) in studies included in this review.

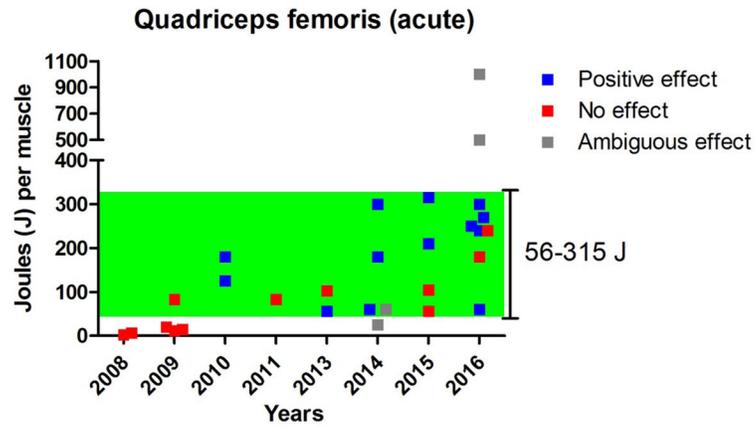


Figure 7. Total energy (Joules - J) applied on *quadriceps femoris* muscles that produced positive effects, no effects, and ambiguous effects (positive and no effects) on the following outcomes: fatigue resistance or number of repetitions, muscle force or work, and creatine kinase (CK) or a related marker of muscle damage in studies included in this review.



Figure 8. Total energy (Joules - J) applied on body muscles that produced positive effects or no effects on the following outcomes: oxygen uptake or ventilatory responses, time of running, and muscle damage (CK) in studies included in this review.

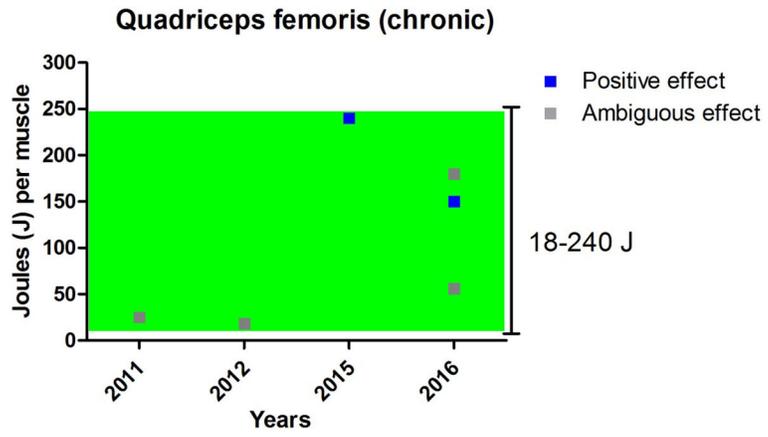


Figure 9. Total energy (Joules - J) applied on *quadriceps femoris* muscles during training programs that produced positive effects or ambiguous effects on the following outcomes: 1-RM, torque, fatigue resistance, hypertrophy and muscle work in studies included in this review.

Table 1

Search strategy via Pubmed and number of identified studies

Term	# studies retrieved
#1 LLLT AND muscle damage	43
#2 LEDT AND muscle damage	6
#3 Phototherapy AND muscle damage	119
#4 LLLT AND CK	28
#5 LEDT AND CK	5
#6 Phototherapy AND CK	41
#7 LLLT AND fatigue	60
#8 LEDT AND fatigue	13
#9 Phototherapy AND fatigue	152
#10 LLLT AND time to exhaustion	9
#11 LEDT AND time to exhaustion	4
#12 Phototherapy AND time to exhaustion	11
#13 LLLT AND lactate	46
#14 LEDT AND lactate	7
#15 Phototherapy AND lactate	186
#16 LLLT AND DOMS	3
#17 LEDT AND DOMS	0
#18 Phototherapy AND DOMS	7
#19 LLLT an AND d torque	17
#20 LEDT AND torque	1
#21 Phototherapy AND torque	20
#22 LLLT AND 1RM	2
#23 LEDT AND 1RM	0
#24 Phototherapy AND 1RM	2
#25 LLLT AND repetition	44
#26 LEDT AND repetition	1
#27 Phototherapy AND repetition	63
#28 LLLT AND MVC	10
#29 LEDT AND MVC	2
#30 Phototherapy AND MVC	63
#31 LLLT AND MVIC	0
#32 LEDT AND MVIC	1
#33 Phototherapy AND MVIC	1
#34 LLLT AND treadmill	12
#35 LEDT AND treadmill	1
#36 Phototherapy AND treadmill	13

Table 2
Clinical trials of photobiomodulation (PBM) in acute responses in exercises with upper limb muscles

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[10]	Cluster with 31 laser diodes; 660 nm; 950 nm; Cluster area 12 cm ² ; 527.77 mW (calculated) 31.7 J/cm ² (720 s) Pulsed frequencies (Hz): 2.5; 5; 20; 1 site of irradiation per limb Total delivered: 380 J (calculated)	Contact After exercise	1 site of irradiation on <i>biceps brachii</i> Elbow flexion (free weights)	RCT with 60 subjects (12 control; 12 placebo; 36 LLLT) No effect of PBM in DOMS No effect of PBM in mechanical pain threshold No effect of PBM in MPT, VAS and McGill questionnaire
[11]	Cluster with 31 laser diodes; 660 nm; 950 nm; Cluster area 12 cm ² ; 534 mW 11 J/cm ² (240 s) Pulsed frequency (Hz): 73 1 site of irradiation per limb Total delivered: 132 J (calculated)	Contact After exercise	1 site of irradiation on <i>biceps brachii</i> Elbow flexion (free weights)	RCT with 36 subjects (12 control, 12 placebo, 12 LLLT) No effect of PBM in DOMS No effect of PBM in mechanical pain threshold No effect of PBM in MPT, VAS and McGill questionnaire
[9]	Cluster with 32 LEDs; 950 nm; Cluster area 18 cm ² ; 160 mW; 8.8 mW/cm ² (calculated) 3.2 J/cm ² (360 s); 1 site of irradiation per limb Total delivered: 57.6 J (calculated)	Contact After exercise	1 site of irradiation on <i>biceps brachii</i> Elbow flexion (isokinetic dynamometer)	RCT with 32 subjects (16 placebo; 16 LEDT) No effect of PBM in DOMS No effect of PBM in mechanical pain threshold No effect of PBM in isokinetic peak torque
[8]	Cluster with 36 LEDs; 32 LEDs 880 nm; 4 LEDs 660 nm; Cluster area 5 cm ² ; 500 mW (calculated); 100 mW/cm ² ; 40 J per site of irradiation (80 s); 8 J/cm ² ; 2 sites of irradiation per limb Total delivered: 80 J	Contact After exercise	2 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench)	RCT with 27 subjects (9 Control; 9 Placebo; 9 LEDT) PBM decreased DOMS after 48 h No effect of PBM in girth No effect of PBM in resting extension angle
[13]	Laser diode 655 nm; Diode area 0.1 cm ² ; 50 mW; 500 J/cm ² ; 5 W/cm ² ; 5 J per diode (100 s); 4 sites of irradiation per limb Total delivered: 20 J	Contact Muscular pre-conditioning	4 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) Maximum voluntary contraction until exhaustion	RCT with 12 volleyball players (6 Placebo; 6 LLLT) PBM increased number of repetitions PBM increased total time of contractions No effect of PBM in blood lactate
[21]	Laser diode 830 nm; Diode area 0.0028 cm ² ; 100 mW; 35.7 W/cm ² ; 5 J (50 s), 1.785 J/cm ² ; 4 sites of irradiation per limb Total delivered: 20 J	Contact Muscular pre-conditioning	4 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) Maximum voluntary contraction until exhaustion	RCT with 10 volleyball players (crossover study) PBM increased number of repetitions No effect of PBM in blood lactate No effect of PBM in total time of contractions
[22]	Laser diode 660 nm; Diode area 0.0028 cm ² ; 50 mW; 17.85 W/cm ² ; 5 J (100 s); 1.785 J/cm ² ; 4 sites of irradiation per limb Total delivered: 20 J <i>versus</i> Laser diode 830 nm; Diode area 0.0028 cm ² ; 50 mW; 17.85W/cm ² ; 5 J (100 s), 1.785 J/cm ² ; 4 sites of irradiation per limb	Contact Muscular pre-conditioning	4 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) Maximum voluntary contraction (60 s)	RCT with 10 subjects (crossover study) PBM 630 nm increased mean force PBM 630 nm increased peak force PBM 830 nm increased mean force PBM 830 nm increased peak force

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[23]	Total delivered: 20 J Cluster with 5 laser diodes 810 nm; Diode area 0.0364 cm ² ; 200 mW; 5.495 W/cm ² ; 6 J per diode (30 s); 164.85 J/cm ² ; 30 J per site of irradiation: 5 × 6 J Total delivered: 60 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) Maximum voluntary contraction until exhaustion	RCT with 9 volleyball players (crossover study) PBM increased number of repetitions PBM increased total time of contractions PBM decreased blood lactate 5 min post-exercise PBM decreased CK in blood post-exercise PBM decreased C-reactive protein post-exercise
[24]	Cluster with 69 LEDs; LED area 0.2 cm ² ; 34 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 35 LEDs 850 nm; 30 mW; 150 mW/cm ² ; 0.3 J LED 660 nm (30 s), 1.5 J/cm ² ; 0.9 J LED 850 nm (30 s), 4.5 J/cm ² ; 41.7 J per site of irradiation; 1 site of irradiation per limb Total delivered: 41.7 J	Contact Muscular pre-conditioning	1 site of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) Maximum voluntary contraction until exhaustion	RCT with 10 volleyball players (crossover study) PBM increased number of repetitions PBM decreased blood lactate post-exercise PBM decreased CK in blood post-exercise PBM decreased C-reactive protein post-exercise
[25]	LED 630 nm; LED area 1.77 cm ² ; 300 mW; 169.49 mW/cm ² ; 9 J (30 s); 5.1 J/cm ² ; 4 sites of irradiation per limb Total delivered: 36 J	Contact Muscular pre-conditioning	4 sites of irradiation on <i>biceps brachii</i> Elbow flexion (Scott bench) 30 eccentric contraction	RCT with 17 subjects (9 placebo; 8 LEDT) PBM decreased DOMS from 48 h to 96 h post-exercise PBM decreased isometric force loss from 24 h to 96 h PBM improved range of motion from 24 h to 96 h
[26]	Laser diode 808 nm; Diode area 0.0028 cm ² ; 100 mW; 35.71 W/cm ² ; 1 J (10 s), 357.14 J/cm ² 4 sites of irradiation per limb Total delivered: 4 J	Contact Between sets of exercise	4 sites of irradiation on <i>biceps brachii</i> Elbow flexion (biceps curl) 10 sets of 10 repetitions	RCT with 22 subjects (11 placebo; 11 LLLT) No effect of PBM in 1-repetition maximum (1-RM) PBM decreased CK in blood after 72 h post-exercise
[27]	Large cluster with 33 diodes: 5 laser diodes; 850 nm; 100 mW; 0.06 cm ² ; 1,666.6 mW/cm ² ; 3.2 J (32 s); 53.3 J/cm ² each; 12 LEDs; 670 nm; 10 mW; 1.92 cm ² ; 5.20 mW/cm ² ; 0.3 J (32 s); 0.15 J/cm ² each; 8 LEDs; 980 nm; 25 mW; 1.28 cm ² ; 19.53 mW/cm ² ; 0.8 J (32 s); 0.62 J/cm ² each 8 LEDs; 950 nm; 15 mW; 1.28 cm ² ; 11.71 mW/cm ² ; 0.5 J (32 s); 0.39 J/cm ² each 2 sites of irradiation per limb Total delivered: 60 J <i>versus</i> Small cluster with 9 diodes: 5 laser diodes; 850 nm; 100 mW; 0.06 cm ² ; 1,666.6 mW/cm ² ; 5.6 J (56 s); 93.3 J/cm ² each; 4 LEDs; 670 nm; 10 mW; 0.64 cm ² ; 15.62 mW/cm ² ; 0.56 J (56 s); 0.87 J/cm ² each 2 sites of irradiation per limb Total delivered: 60 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>biceps brachii</i> Maximum isometric voluntary contraction until exhaustion (isokinetic dynamometer)	RCT with 10 subjects (crossover study) PBM increased time to exhaustion No effect of PBM on peak torque No effect of PBM on electromyography analyses
[28]	Laser diode 808 nm; Diode area 0.0028 cm ² ; 100 mW; 35.7 W/cm ² ; 7 J (70 s), 2,500 J/cm ² ;	Contact Muscular pre-conditioning	8 sites of irradiation on <i>biceps brachii</i> Elbow flexion	RCT with 20 subjects (crossover study) No effect of PBM in number of repetitions No effect of PBM in blood lactate post-exercise

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[29]	8 sites of irradiation per limb Total delivered: 56 J Cluster with 2 laser diodes 800 nm and 970 nm; Diode area not provided; 3 W (50% duty cycle); average power output 1.5 W; 24 J point of irradiation (16 s -calculated); 15 sites of irradiation per limb Total delivered: 360 J	Contact Muscular pre-conditioning	15 sites of irradiation on <i>biceps brachii</i> Elbow flexion (isokinetic dynamometer)	No effect of PBM on fatigue by surface electromyography RCT with 39 subjects (crossover study) PBM decreased discreetly maximum voluntary isometric contraction No effect of PBM on muscle tenderness No effect of PBM on muscle strength

Table 3
Clinical trials of photobiomodulation (PBM) in acute responses in exercises using lower limb muscles

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[12]	Cluster with 4 laser diodes 808 nm; 500 mW; 8.3 mW/cm ² ; Groups: 7 J (10 min); 3 J (5 min); 1 site of irradiation per limb Total delivered: 7 J/3 J	Scanning Muscular pre-conditioning	1 site of radiation on <i>quadriceps femoris</i> Maximum voluntary contraction	RCT with 5 subjects (crossover study) No effect of PBM on muscle fatigue
[30]	Laser diode 830 nm; Diode area 0.0028 cm ² ; 100 mW; 35.714 W/cm ² ; Volleyball athletes: 4 J (40 s); 1,428.57 J/cm ² Soccer Athletes: 3 J (30 s); 1,071.43 J/cm ² 5 sites of irradiation per limb Total delivered: 20 J (volleyball athletes)/15 J (soccer athletes)	Contact Muscular pre-conditioning	5 sites of irradiation on <i>rectus femoris</i> Wingate test	RCT with 20 athletes (crossover study) PBM decreased blood lactate 15 min post-exercise PBM decreased CK in blood 3 min post-exercise No effect of PBM on muscle work
[31]	Laser diode 810 nm; Diode area 0.036 cm ² ; 200 mW; 5.5 W/cm ² ; 6 J (30 s); 164.84 J/cm ² ; 2 sites of irradiation per limb Total delivered: 12 J <i>Versus</i> Cluster with 69 LEDs; LED area 0.2 cm ² ; 34 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 35 LEDs 850 nm; 30 mW; 150 mW/cm ² ; 0.3 J LED 660 nm (30 s), 1.5 J/cm ² ; 0.9 J LED 850 nm (30 s), 4.5 J/cm ² ; 41.7 J per site of irradiation; 2 sites of irradiation per limb Total delivered: 83.4 J	Contact Muscular pre-conditioning	2 sites of radiation on <i>rectus femoris</i> Wingate test	RCT with 8 athletes (crossover study) PBM (LEDT) decreased CK in blood 3 min post-exercise No effect of PBM (LLLT) on muscle peak and mean power No effect of PBM (LEDT) on muscle peak and mean power No effect of PBM (LLLT) in CK 3 min post-exercise No effect of PBM (LLLT) in blood lactate post-exercise No effect of (LEDT) in blood lactate post-exercise
[32]	Cluster with 69 LEDs; LED area 0.2 cm ² ; 34 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 35 LEDs 950 nm; 15 mW; 75 mW/cm ² ; 0.3 J LED 660 nm (30 s), 1.5 J/cm ² ; 0.4 J LED 950 nm (30 s), 2.2 J/cm ² ; 25.9 J per site of irradiation; 4 sites of irradiation per limb Total delivered: 103 J	Contact Between 2° and 3° Wingate	2 sites of radiation on <i>rectus femoris</i> 1 site on <i>vastus lateralis</i> 1 site on <i>vastus medialis</i> Wingate test	RCT with 18 athletes (crossover study) No effect of PBM on muscle peak power No effect of PBM on fatigue index No effect of PBM in blood lactate levels
[33]	Cluster with 69 LEDs; LED area 0.2 cm ² ; 34 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 35 LEDs 850 nm; 30 mW; 150 mW/cm ² ; 0.3 J LED 660 nm (30 s), 1.5 J/cm ² ; 0.9 J LED 850 nm (30 s), 4.5 J/cm ² ; 41.7 J per site of irradiation 5 sites of irradiation per limb	Contact After exercise	2 sites of irradiation on <i>quadriceps femoris</i> 2 sites on hamstrings 1 site on gastrocnemius 3 Wingate tests	RCT with 6 athletes (crossover study) PBM decreased CK in blood post-exercise PBM decreased blood lactate post-exercise No effect of PBM on muscle peak power No effect of PBM on mean muscle power No effect of PBM in C-reactive protein

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[34]	Total delivered: 208.5 J <i>Versus</i> Cryotherapy (water immersion for 5 minutes at 5 °C) Cluster with: 1 laser diode 905 nm; Diode area 0.44 cm ² ; 1.25 mW; 2.84 mW/cm ² ; 4 LEDs 875 nm; Diode area 0.9 cm ² ; 17.5 mW; 19.44 mW/cm ² ; 4 LEDs 640 nm; Diode area 0.9 cm ² ; 15 mW; 16.67 mW/cm ² ; 39.37 J per site of irradiation: 300 s 6 sites of irradiation per limb Total delivered: 240 J	Contact After exercise	2 sites of irradiation on <i>vastus medialis</i> 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i> Maximum voluntary isometric contraction (isokinetic dynamometer)	RCT with 50 subjects (10 placebo; 10 cryotherapy, 10 PBM; 10 PBM + cryotherapy; 10 cryotherapy + PBM) PBM decreased CK post-exercise from 24 h to 96 h PBM decreased DOMS from 24 h to 96 h PBM improved MIVC PBM+cryotherapy reduced efficacy of PBM Cryotherapy+PBM and cryotherapy were similar to placebo
[35]	Cluster with 5 laser diodes 810 nm; Diode area 0.029 cm ² ; 200 mW; 6.89 W/cm ² ; 6 J per diode (30 s); 206.89 J/cm ² ; 30 J per site of irradiation: 5 × 6 J 6 sites of irradiation per limb Total delivered: 180 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>vastus medialis</i> 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i> Maximum voluntary isometric contraction (isokinetic dynamometer)	RCT with 36 subjects (18 placebo; 18 LLLT) PBM increased maximum voluntary contraction PBM increased LDH activity 48 h post-exercise PBM decreased blood lactate 24 h and 48 h post-exercise PBM decreased CK in blood 24 h and 48 h post-exercise No PBM effect in DOMS
[36]	Cluster with 69 LEDs; LED area 0.2 cm ² ; 34 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 35 LEDs 850 nm; 30 mW; 150 mW/cm ² ; 0.3 J LED 660 nm (30 s), 1.5 J/cm ² ; 0.9 J LED 850 nm (30 s), 4.5 J/cm ² ; 41.7 J per site of irradiation (30 s) 3 sites of irradiation per limb Total delivered: 125.1 J	Contact Muscular pre-conditioning	1 site of radiation on <i>rectus femoris</i> 1 site on <i>vastus medialis</i> 1 site on <i>vastus lateralis</i> Maximum voluntary isometric contraction (isokinetic dynamometer)	RCT with 17 subjects (crossover study) PBM decreased the decay of the knee extensor peak torque after a fatigue exercise protocol
[37]	Cluster with: 4 laser diodes 905 nm; Diode area 0.44 cm ² ; 0.3125 mW; 0.71 mW/cm ² ; 4 LEDs 875 nm; Diode area 0.9 cm ² ; 17.5 mW; 19.44 mW/cm ² ; 4 LEDs 640 nm; Diode area 0.9 cm ² ; 15 mW; 16.66 mW/cm ² ; Groups: 10 J per site of irradiation: 76 s 30 J per site of irradiation: 228 s 50 J per site of irradiation: 381 s 6 sites of irradiation per limb Total delivered: 60 J/180 J/300 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>vastus medialis</i> ; 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i> Eccentric contractions and maximum voluntary isometric contraction (isokinetic dynamometer)	RCT with 40 subjects (10 placebo; 30 PBM) PBM 10 J, 30 J and 50 J increased the percentage of the knee extensor peak torque immediately after and until 96 h after eccentric exercise protocol PBM 30 J and 50 J decreased DOMS PBM 10 J, 30 J and 50 J decreased CK in blood from 1 h to 96 h
[38]	Cluster with 5 laser diodes 810 nm; Diode area 0.036 cm ² ; 200 mW; 5.495 W/cm ² ; 2 J per diode (10 s); 54.95 J/cm ² ; 6 J per diode (30 s); 164.84 J/cm ² ; 10 J per diode (50 s); 274.73 J/cm ² ;	Contact Muscular pre-conditioning	2 sites of irradiation on <i>vastus medialis</i> 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i>	RCT with 28 athletes (7 placebo; 21 LLLT) PBM 50 J increased knee extensor peak torque immediately after and until 96 h after eccentric exercise protocol

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[39]	<p>Groups:</p> <p>10 J per site of irradiation: 5×2 J</p> <p>30 J per site of irradiation: 5×6 J</p> <p>50 J per site of irradiation: 5×10 J</p> <p>6 sites of irradiation per limb:</p> <p>Total delivered: 60 J/180 J/300 J</p> <p>Cluster with 69 LEDs;</p> <p>LED area 0.2 cm²;</p> <p>34 LEDs 660 nm; 10 mW; 50 mW/cm²;</p> <p>35 LEDs 850 nm; 30 mW; 150 mW/cm²;</p> <p>Groups:</p> <p>0.3 J LED 660 nm (30 s), 1.5 J/cm²;</p> <p>0.9 J LED 850 nm (30 s), 4.5 J/cm²;</p> <p>41.7 J per site of irradiation (30 s)</p> <p>0.6 J LED 660 nm (60 s), 3.0 J/cm²;</p> <p>1.8 J LED 850 nm (60 s), 9.0 J/cm²;</p> <p>83.4 J per site of irradiation (60 s);</p> <p>1.2 J LED 660 nm (120 s), 6.0 J/cm²;</p> <p>3.6 J LED 850 nm (120 s), 18 J/cm²;</p> <p>166.8 J per site of irradiation (120 s);</p> <p>6 sites of irradiation per limb</p> <p>Total delivered: 250.2 J/500.4 J/1,000.8 J</p>	Contact Muscular pre-conditioning	<p>2 site of irradiation on <i>rectus femoris</i></p> <p>2 sites of irradiation on <i>vastus medialis</i></p> <p>2 sites of irradiation on <i>vastus lateralis</i></p> <p>Maximum voluntary isometric contraction and number of repetitions (isokinetic dynamometer)</p>	<p>PBM 10 J increased knee extensor peak torque after 24 h until 96 h after eccentric exercise protocol</p> <p>PBM 10 J and 50 J decreased CK and IL-6 from 24 h to 96 h</p> <p>PBM (10 J, 30 J and 50 J) had no effect on DOMS</p> <p>PBM 30 J had any effect in all assessments</p> <p>RCT with 34 subjects (crossover study)</p> <p>PBM (83.4 J) increased number of repetition (knee extension)</p> <p>PBM (166.8 J) increased number of repetition (knee extension)</p> <p>No effects of PBM (41.7 J) in number of repetition (knee extension), torque or blood lactate levels.</p> <p>No effects of PBM (all doses) on blood lactate levels and torque.</p>
[40]	<p>Laser diode 808 nm;</p> <p>Diode area 0.00785 cm²; 100 mW; 12.7 W/cm²;</p> <p>7 J (70 s), 892 J/cm²;</p> <p>8 sites of irradiation per limb</p> <p>Total delivered: 56 J</p>	Contact Muscular pre-conditioning	<p>8 sites of irradiation on <i>rectus femoris</i></p> <p>Knee extension (extensor chair)</p>	<p>RCT with 24 subjects (crossover study)</p> <p>PBM increased number of repetitions</p> <p>No effect of PBM on surface electromyography</p>
[41]	<p>Laser diode 780 nm</p> <p>Diode area 0.2 cm²; 30 mW; 0.15 W/cm²;</p> <p>0.81 J (27 s), 4 J/cm²;</p> <p>29 sites of irradiation per limb</p> <p>Total delivered: 23.49 J</p>	Contact Muscular pre-conditioning	<p>29 sites of irradiation on <i>tibialis anterior</i></p> <p>Ankle dorsiflexion (isokinetic dynamometer)</p>	<p>Controlled trial with 12 subjects (crossover study)</p> <p>PBM increased ankle dorsiflexion peak torque in strength test</p> <p>No effect of PBM on surface electromyography</p> <p>No effect of PBM in blood lactate</p>
[42]	<p>Laser diode 808 nm;</p> <p>Diode area 0.0028 cm²; 100 mW; 35.71 W/cm²;</p> <p>4 J (40 s); 1,428.57 J/cm²;</p> <p>5 sites of irradiation per limb</p> <p>Total delivered: 20 J \times 3 times = 60 J</p>	Contact Between sets of exercise	<p>3 sites of irradiation on <i>rectus femoris</i></p> <p>1 site on <i>vastus lateralis</i></p> <p>1 site on <i>vastus medialis</i></p> <p>Knee extension (isokinetic dynamometer)</p>	<p>RCT with 7 subjects (crossover study)</p> <p>PBM increased number of repetitions</p> <p>PBM decreased fatigue index in surface electromyography</p>
[43]	<p>Laser diode 808 nm;</p> <p>Diode area 0.028 cm²; 100 mW; 3.57 W/cm²;</p> <p>7 J (70 s), 250 J/cm²;</p> <p>8 sites of irradiation per limb</p> <p>Total delivered: 56 J</p>	Contact Muscular pre-conditioning	<p>8 sites of irradiation on <i>rectus femoris</i></p> <p>Knee extension (isokinetic dynamometer)</p>	<p>RCT with 30 subjects (crossover study)</p> <p>PBM decreased blood lactate 6 min post fatigue exercise protocol</p> <p>PBM decreased muscle fatigue by surface electromyography</p> <p>No effect of PBM on muscle peak torque</p> <p>No effect of PBM on muscle average power</p> <p>No effect of PBM on muscle total work</p>

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[44]	Cluster with 7 laser diodes 850 nm; Diode area 0.05 cm ² ; 100 mW; 2 W/cm ² ; 2 J per diode (20 s), 40 J/cm ² ; 14 J per site of irradiation: 7 × 2 J 4 sites of irradiation per limb; Total delivered: 56 J	Contact Muscular pre-conditioning	1 site of irradiation on <i>vastus medialis</i> , 1 site on <i>vastus lateralis</i> 1 site on <i>rectus femoris</i> 1 site on gastrocnemius Running on treadmill until exhaustion	No effect of PBM on muscle fatigue index RCT with 18 subjects (crossover study) PBM increased the peak oxygen uptake PBM increased cardiovascular efficiency No effect of PBM on muscle fatigue in surface electromyography
[45]	Laser diode 810 nm; Diode area 0.028 cm ² ; 100 mW; 3.57 W/cm ² ; 3 J (30 s), 107.14 J/cm ² ; Total delivered: 24 J	Contact After exercise	8 sites of irradiation on adductor muscles 200 m maximal free style swim, 30-s crossbar jump	RCT with 20 subjects (10 placebo; 10 PBM) PBM improved moderately 30-s crossbar jump test No effect of PBM on 200 m maximal swim No effect of PBM on CK and LDH No effect of PBM on IL-1β, IL-10, TNF-α
[46]	Cluster with 6 laser diodes 830 nm; Diode area 0.0028cm ² ; 60 mW; 21.42W/cm ² 0.6 J per diode (10 s), 214.28 J/cm ² 3.6 J per site of irradiation: 6 × 0.6 J 7 sites of irradiation per limb Total delivered: 25.2 J	Contact Muscular pre-conditioning/after exercise	7 sites of irradiation on <i>quadriceps femoris</i> Knee extension	RCT with 27 subjects (9 placebo; 9 PBM pre-conditioning; 9 PBM after exercise) PBM applied after exercise decreased blood lactate PBM applied after exercise decreased CK in blood No effects of PBM (pre-conditioning) in number of maximum repetitions No effects of PBM (pre-conditioning) on time to fatigue
[47]	Cluster with 5 laser diodes 810 nm; Diode area 0.029cm ² ; 200 mW; 6.9 W/cm ² 6 J per diode (30 s), 206.9 J/cm ² 30 J per site of irradiation: 5 × 6 J 8 sites of irradiation per limb Total delivered: 240 J	Contact Muscular pre-conditioning/after exercise	3 sites on <i>quadriceps femoris</i> 2 sites on <i>vastus medialis</i> 3 sites on <i>vastus lateralis</i> Knee extension/flexion (plyometric exercise)	RCT with 24 subjects (12 PBM pre-conditioning; 12 PBM after exercise) - placebo therapy applied on contralateral limb PBM (pre-conditioning or after exercise) promoted smaller muscle damage No effects of PBM (pre-conditioning or after exercise) in MVC No effects of PBM (pre-conditioning or after exercise) on VAS
[48]	Cluster with: 4 laser diodes 905 nm; Diode area 0.44 cm ² ; 0.3125 mW; 0.71 mW/cm ² ; 4 LEDs 875 nm; Diode area 0.9 cm ² ; 17.5 mW; 19.44 mW/cm ² ; 4 LEDs 640 nm; Diode area 0.9 cm ² ; 15 mW; 16.66 mW/cm ² ; 30 J per site of irradiation: 228 s 17 sites of irradiation per limb Total delivered: 510 J	Contact Muscular pre-conditioning	3 sites of irradiation on <i>vastus medialis</i> , 3 sites of irradiation on <i>vastus lateralis</i> 3 sites of irradiation on <i>rectus femoris</i> 3 sites of irradiation on <i>biceps femoris</i> 3 sites of irradiation on <i>semitendinosus</i> and <i>semimembranosus</i> Bangsbo Sprint Test	RCT with 12 athletes (crossover study) PBM improved average time in the sprints PBM decreased fatigue index PBM promoted lower percentage of increment in blood lactate No effects of PBM in the best time of sprint
[49]	Array with 200 LEDs; 100 LEDs 850 nm arranged in 25 clusters of 4 LEDs, 130 mW, 185.74 mW/cm ² ; 100 LEDs 630 nm arranged in 25 clusters of 4 LEDs, 80 mW, 114.28 mW/cm ² ;	Contact Muscular pre-conditioning	Whole <i>quadriceps femoris</i> , Whole hamstrings Whole <i>triceps surae</i> Before official volleyball matches	RCT with 6 athletes (crossover study) PBM 210 J and 315 J could prevent significant increases in CK in blood 24 h after professional volleyball matches

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
	Groups: 105 J (20 s), total delivered 315 J 210 J (40 s), total delivered 630 J 315 J (60 s), total delivered 945 J Placebo - 0 J (30 s) Sites of irradiation per limb: Whole <i>quadriceps femoris</i> , hamstrings and <i>triceps surae</i> Total delivered: 315 J/630 J/945 J			

Table 4 Clinical trials of photobiomodulation (PBM) in acute responses (5 sessions) in exercises on treadmill

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[50]	Cluster with 5 laser diodes 810 nm; Diode area 0.0364 cm ² ; 200 mW; 5.495 W/cm ² ; 6 J per diode (30 s), 164.85 J/cm ² ; 30 J per site of irradiation: 5 × 6 J 12 sites of irradiation Total delivered: 360 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>vastus medialis</i> 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i> 4 sites on hamstrings 2 sites on gastrocnemius Running on treadmill until exhaustion	RCT with 22 subjects (crossover study) PBM increased oxygen uptake PBM increased time of running PBM could prevent increases in LDH PBM could prevent increases in CK in blood PBM could prevent increases in lipid peroxidation
[51]	Array with 50 LEDs 850 nm; Diode area 0.2 cm ² ; 50 mW; 250 mW/cm ² ; 0.75 J per diode (15 s); 3.75 J/cm ² ; 37.5 J applied per muscle group; 50 × 0.75 J Sites of irradiation per limb <i>Biceps brachii</i> + <i>triceps brachii</i> External oblique + <i>latissimus dorsi</i> <i>Quadriceps femoris</i> , Hamstrings <i>Tibialis anterior</i> + <i>peroneus longus</i> Gastrocnemius + soleus Total delivered: 450 J	Contact Muscular pre-conditioning	Irradiation on whole <i>biceps brachii</i> and <i>triceps brachii</i> Whole external oblique and <i>latissimus dorsi</i> Whole <i>quadriceps femoris</i> Whole hamstrings Whole <i>tibialis anterior</i> Whole <i>peroneus longus</i> , gastrocnemius and soleus Running on treadmill until exhaustion	Case-control with 1 athlete (crossover study) PBM improved speed of muscular VO ₂ adaptation PBM decreased O ₂ deficit PBM increased the VO ₂ PBM increased the time of running PBM decreased CK in blood PBM decreased lactate in urine PBM decreased alanine in urine
[52]	Cluster with: 4 laser diodes 905 nm; Diode area 0.44 cm ² ; 0.3125 mW; 0.71 mW/cm ² ; 4 LEDs 875 nm; Diode area 0.9 cm ² ; 17.5 mW; 19.44 mW/cm ² ; 4 LEDs 640 nm; Diode area 0.9 cm ² ; 15 mW; 16.66 mW/cm ² ; 30 J per site of irradiation: 228 s 17 sites of irradiation per limb Total delivered: 510 J	Contact Muscular pre-conditioning	3 sites of irradiation on <i>vastus medialis</i> 3 sites of irradiation on <i>rectus femoris</i> 3 sites of irradiation on <i>vastus lateralis</i> 3 sites of irradiation on <i>biceps femoris</i> 3 sites of irradiation on <i>semitendinosus</i> and <i>semimembranosus</i> 2 sites of irradiation on <i>gastrocnemius</i> Running on treadmill until exhaustion	20 subjects (crossover study) PBM increased distance covered PBM increased time to exhaustion PBM increased ventilatory rate PBM decreased dyspnea
[53]	Cluster with 104 LEDs 56 LEDs 660 nm; 10 mW; 50 mW/cm ² ; 1.5 J/cm ² ; 0.2 cm ² 48 LEDs 850 nm; 30 mW; 150 mW/cm ² ; 4.5 J/cm ² ; 0.2 cm ² 60 J per site of irradiation: 30 s 5 sites of irradiation per limb Total delivered: 300 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>quadriceps femoris</i> 2 sites of irradiation on <i>biceps femoris</i> 1 site of irradiation between <i>gastrocnemius</i> and <i>soleus</i> Running on treadmill until exhaustion	15 subjects (crossover study) No effect of PBM on maximal accumulated oxygen deficit No effect of PBM on aerobic metabolism No effect of PBM on glycolysis metabolism No effect of PBM on phosphagen metabolism No effect of PBM on time to exhaustion No effect of PBM on lactate levels No effect of PBM on perceived exertion No effect of PBM on heart rate

Table 5
Clinical trials of photobiomodulation (PBM) in chronic responses in exercises with lower limb muscles

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[14]	Cluster with 6 laser diodes 808 nm; Diode area 0.0028cm ² ; 60 mW; 21.42W/cm ² 0.6 J per diode (10 s), 214.28 J/cm ² 3.6 J per site of irradiation: 6 × 0.6 J 7 sites of irradiation per limb Total delivered: 25.2 J	Contact After exercise	7 sites of irradiation on <i>quadriceps femoris</i> Leg press training and isokinetic dynamometer	RCT with 36 subjects (12 control; 12 training; 12 training+PBM) PBM increased load in maximum repetition (1-RM) PBM increased knee extensor peak torque No effect of PBM on thigh perimetry
[15]	Cluster with 6 laser diodes 808 nm Diode area 0.0028cm ² ; 60 mW; 21.42W/cm ² 0.6 J per diode (10 s), 214.28 J/cm ² 3.6 J per site of irradiation: 6 × 0.6 J 5 sites of irradiation per limb Total delivered: 18 J	Contact After exercise	5 sites of irradiation on <i>quadriceps femoris</i> Cycle ergometer training and isokinetic dynamometer	RCT with 45 subjects (15 control; 15 training; 15 training+PBM) PBM decreased fatigue index of knee extensor muscles No effect of PBM in total knee extensor work
[54]	Array with 50 LEDs 850 nm; Diode area 0.2 cm ² ; 100 mW; 500 mW/cm ² ; 1.5 J per diode (15 s); 7.5 J/cm ² ; 75 J applied per muscle group: 50 × 1.5 J Sites of irradiation per limb <i>Quadriceps femoris</i> Total delivered: 150 J	Contact After exercise	Irradiation on whole <i>quadriceps femoris</i> Leg press training Leg extension training	Case-control with 2 subjects monozygotic twins (1 placebo; 1 PBM) PBM increased maximal load PBM increased muscle hypertrophy PBM decreased CK in blood PBM decreased fatigue PBM increased gene expression of muscle hypertrophy and defense against oxidative stress PBM decreased gene expression of inflammation and muscle atrophy
[55]	Cluster with 5 laser diodes 810 nm Diode area 0.029 cm ² ; 200 mW; 6.89 W/cm ² 6 J per diode (30 s); 206.89 J/cm ² 30 J per site of irradiation: 5 × 6 J 8 sites of irradiation per limb Total delivered: 240 J	Contact Muscular pre-conditioning	2 sites of irradiation on <i>vastus medialis</i> 3 sites on <i>vastus lateralis</i> 3 sites on <i>rectus femoris</i> Eccentric training in isokinetic dynamometer	RCT with 30 subjects (10 control; 10 training; 10 training+PBM) PBM increased muscle thickness PBM increased isometric knee extensor peak torque PBM increased eccentric knee extensor peak torque
[56]	Laser diode 660 nm; Diode area 0.06 cm ² ; 30 mW; 0.5 W/cm ² ; 0.24 J (8 s), 4 J/cm ² ; 8 sites of irradiation per limb Total delivered: 1.92 J	Contact Muscular pre-conditioning and after exercise	8 sites on <i>triceps surae</i> Vertical jumps	RCT with 22 subjects (8 control; 7 LLLT-6 days; 7 LLLT-10 days) No effect of PBM on vertical jump performance (power and fatigue) No effect of PBM on delayed onset muscle soreness
[57]	Laser diode 808 nm; Diode area 0.028 cm ² ; 100 mW; 35.71 W/cm ² ; 7 J (70 s), 250 J/cm ² ; 8 sites of irradiation per limb Total delivered: 56 J	Contact After exercise	8 sites of irradiation on <i>quadriceps femoris</i> Leg extension training	RCT with 48 subjects (15 control; 17 training+LLLT; 16 training) PBM increased work compared to control PBM increased peak torque compared to control PBM increased power compared to control No effect of PBM on fatigue index No effect of PBM on lactate levels No effect of PBM on 6-min walk test No effect of PBM on surface electromyography No effect of PBM in 1 maximum repetition (1-RM)

Reference	PBM parameters	Mode of irradiation	Muscle/exercise	Main findings
[59]	Cluster with: 4 laser diodes 905 nm; Diode area 0.44 cm ² ; 0.3125 mW/cm ² ; 4 LEDs 875 nm; Diode area 0.9 cm ² ; 17.5 mW; 19.44 mW/cm ² ; 4 LEDs 640 nm; Diode area 0.9 cm ² ; 15 mW; 16.66 mW/cm ² ; 30 J per site of irradiation; 228 s 6 sites of irradiation per limb Total delivered: 180 J	Contact Muscular pre-conditioning/ after exercise/pre-conditioning and after exercise	2 sites of irradiation on <i>vastus medialis</i> , 2 sites on <i>vastus lateralis</i> 2 sites on <i>rectus femoris</i> Leg press training Leg extension training	RCT with 48 subjects (12 placebo; 36 PBM) PBM (pre-conditioning only-12 subjects) increased 1-RM in leg press PBM (pre-conditioning only-12 subjects) increased 1-RM in leg extension PBM (pre-conditioning only-12 subjects) increased peak torque in MVC PBM (pre-conditioning and after-12 subjects) added no effect PBM (after only-12 subjects) added no effect PBM (all modalities-36 subjects) did not increase thigh perimeter