



# MIT Open Access Articles

## *Light-emitting diode therapy (LEDT) before matches prevents increase in creatine kinase with a light dose response in volleyball players*

The MIT Faculty has made this article openly available. **Please share** how this access benefits you. Your story matters.

<b>Citation</b>	Ferraresi, Cleber et al. "Light-Emitting Diode Therapy (LEDT) before Matches Prevents Increase in Creatine Kinase with a Light Dose Response in Volleyball Players." Lasers in Medical Science 30.4 (2015): 1281–1287.
<b>As Published</b>	<a href="http://dx.doi.org/10.1007/s10103-015-1728-3">http://dx.doi.org/10.1007/s10103-015-1728-3</a>
<b>Publisher</b>	Springer London
<b>Version</b>	Author's final manuscript
<b>Citable link</b>	<a href="http://hdl.handle.net/1721.1/106344">http://hdl.handle.net/1721.1/106344</a>
<b>Terms of Use</b>	Article is made available in accordance with the publisher's policy and may be subject to US copyright law. Please refer to the publisher's site for terms of use.

# Light-emitting diode therapy (LEDT) before matches prevents increase in creatine kinase with a light dose response in volleyball players

Cleber Ferraresi · Ricardo Vinicius dos Santos ·  
Guilherme Marques · Marcelo Zangrande · Roberley Leonaldo ·  
Michael R. Hamblin · Vanderlei Salvador Bagnato ·  
Nivaldo Antonio Parizotto

Received: 29 October 2014 / Accepted: 18 February 2015 / Published online: 27 February 2015  
© Springer-Verlag London 2015

**Abstract** Low-level laser (light) therapy (LLLT) has been applied over skeletal muscles before intense exercise (muscular pre-conditioning) in order to reduce fatigue and muscle damage (measured by creatine kinase, CK) in clinical trials. However, previous exercise protocols do not exactly simulate the real muscle demand required in sports. For this reason, the aim of this randomized and double-blind placebo-controlled trial was to investigate whether light-emitting diode therapy (LEDT) applied over the quadriceps femoris muscles, hamstrings, and triceps surae of volleyball players before

official matches could prevent muscle damage (CK) with a dose response, establishing a therapeutic window. A professional male volleyball team (12 athletes) was enrolled in this study, and LEDT was applied before 4 matches during a national championship. LEDT used an array of 200 light-emitting diodes (LEDs) arranged in 25 clusters of 4 infrared LEDs ( $850\pm 20$  nm; 130 mW) and 25 clusters of 4 red LEDs ( $630\pm 10$  nm; 80 mW). Athletes were randomized to receive one of four different total doses over each muscle group in a double-blind protocol: 105 J (20 s), 210 J (40 s), 315 J (60 s), and placebo (no light for 30 s). CK in blood was assessed 1 h before and 24 h after each match. LEDT at 210 J avoided significant increases in CK (+10 %;  $P=0.993$ ) as well as 315 J (+31 %,  $P=0.407$ ). Placebo (0 J) allowed a significant increase in CK (+53 %;  $P=0.012$ ) as well as LEDT at 105 J (+59 %;  $P=0.001$ ). LEDT prevented significant increases of CK in blood in athletes when applied before official matches with a light dose response of 210–315 J, suggesting athletes might consider applying LEDT before competition.

C. Ferraresi (✉) · N. A. Parizotto  
Laboratory of Electrothermophototherapy, Department of Physical Therapy, Federal University of Sao Carlos, Rodovia Washington Luís, km 235, 13565-905 Sao Carlos, SP, Brazil  
e-mail: cleber.ferraresi@gmail.com

C. Ferraresi · V. S. Bagnato · N. A. Parizotto  
Post-Graduation Program in Biotechnology, Federal University of Sao Carlos, Sao Carlos, SP, Brazil

C. Ferraresi · V. S. Bagnato  
Optics Group, Physics Institute of Sao Carlos, University of São Paulo, Sao Carlos, SP, Brazil

R. V. dos Santos · G. Marques · M. Zangrande · R. Leonaldo  
Sao Bernardo Volleyball Team, Sao Bernardo do Campo, SP, Brazil

M. R. Hamblin  
Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA

M. R. Hamblin  
Department of Dermatology, Harvard Medical School, Boston, MA, USA

M. R. Hamblin  
Harvard-MIT Division of Health Science and Technology, Cambridge, MA, USA

**Keywords** Photobiomodulation · LLLT · CK · Muscle damage · Exercise recovery · Muscle performance

## Introduction

The benefits of low-level laser (light) therapy (LLLT) to treat pain [1, 2], tendinopathies [3] and to promote tissue healing [2, 4] have been investigated for several years. The mechanism of the light-tissue interaction is thought to involve cytochrome c oxidase (Cox) as the main chromophore in the cells

able to absorb specific wavelengths of light [5–9]. Cox is a mitochondrial enzyme with a very important function in the electron transport chain and consequently promotes cell respiration and energy production in the form of adenosine triphosphate (ATP). For these reasons, LLLT has been widely used for several types of medical treatment, especially those indications that require stimulation of cells and improved healing.

Recently, LLLT has been used to increase muscle performance [10, 11]. When applied after exercise, LLLT promoted reduction of fatigue [12] and increased the workload in maximum effort tests [13] after training programs. When applied before the exercise (muscular pre-conditioning), LLLT increased the number of repetitions and was able to promote “muscle protection” against exercise-induced muscle damage [10, 11] measured by a lower increase of creatine kinase (CK) levels in the blood. In this context, it is valuable to highlight that CK is an important enzyme of the energy metabolism located inside muscle cells, but its increase in the bloodstream after a bout of exercise is an indicative of rupture of muscle cell membrane and consequently muscle damage [14].

In order to investigate the effects of LLLT on “muscle protection” against exercise-induced muscle damage, different protocols of exercise or neuromuscular electrical stimulation have been used to induce muscle fatigue and damage in experimental models [15–20] and in clinical trials [21–28]. These studies have evaluated different wavelengths and different light sources such as diode lasers and light-emitting diodes (LEDs) [29]. Three recent studies [10, 11, 30] reported fascinating results and point to the effectiveness of muscular pre-conditioning using diode lasers and LEDs to prevent muscle fatigue and muscle damage (CK) when applied before (5 min) a bout of exercise.

Having in mind all previous results for muscular pre-conditioning [10, 11, 30], the present study aimed to investigate the effectiveness of the LLLT by LED therapy (LEDT) in the prevention of muscle damage (CK) in professional volleyball players during a national championship. This randomized double-blind placebo-controlled study used an array of LEDs to irradiate equally all target muscle groups [13] with different doses of light in order to establish also a therapeutic window or dose response [31] for LEDT, thus translating these studies to clinical practice. Moreover, the LED array emitted red and infrared light at the same time based on studies that reported better absorption of the light by Cox using bandwidths in the red and near-infrared spectral regions [5–9]. The possible time response of 5 min widely reported in muscular pre-conditioning [10, 11, 30] was modified to 40–60 min, since previous studies already reported a range of 3–45 min for LLLT to increase ATP synthesis in cells [32, 33], and also made it possible to perform muscular pre-conditioning for all athletes before each official volleyball match.

## Materials and methods

### Study design and ethics statement

The present study was a randomized, double-blind, and placebo-controlled trial involving a professional team of volleyball players in the “Superliga” (national championship) in Brazil during four official matches. Each match was carried out in different stadiums, in accordance with the championship schedule. All researchers traveled with the coaching staff and volleyball players during the study. This study was conducted in compliance with the Declaration of Helsinki (1964) and its later amendments, and also approved by the Research Ethics Committee for Human Studies of the Federal University of Sao Carlos (number protocol approved 217/2012).

### Volunteers

Twelve professional volleyball players (the whole team) were enrolled in the study. They had an average age of  $25.5 \pm 5.3$  years old, body weight of  $90.6 \pm 7.3$  kg, and height of  $200 \pm 8.7$  cm. After their agreement, all players signed the informed consent statement.

### Inclusion criteria and exclusion criteria

Inclusion criterion used was healthy professional volleyball players. Exclusion criterion used was volleyball players having musculoskeletal injuries prior to the study or injured during the course of the study.

### Groups and randomization procedures

All athletes were randomly allocated into four different groups for muscular pre-conditioning in accordance with the assigned light dose (Joules, J) of the light-emitting diode therapy (LEDT):

- Dose 1—20 s of real LEDT (105 J total) over quadriceps femoris muscles, hamstrings, and triceps surae
- Dose 2—40 s of real LEDT (210 J total) over quadriceps femoris muscles, hamstrings, and triceps surae
- Dose 3—60 s of real LEDT (315 J total) over quadriceps femoris muscles, hamstrings, and triceps surae
- Dose 4—30 s of placebo LEDT (0 J total) over quadriceps femoris muscles, hamstrings, and triceps surae

Each athlete randomly received one of the light doses before each one of the four official matches of the championship. The randomization procedure was conducted at Randomization.com (<http://www.randomization.com>) using balanced permutations into one block with four different therapies: dose 1 to dose 4. The randomization procedure was carried out by evaluator #1 that operated

the LED device. This researcher was instructed not to inform athletes, researchers, and coaching staff which dose was applied to each athlete at each match.

During the course of the study, two athletes suffered musculoskeletal injuries and then were excluded. One athlete belonged to dose 4 (30 s of irradiation—placebo) and the second athlete belonged to dose 2 (20 s of irradiation). However, these exclusions did not affect the number of subjects per group once all statistical analyses were performed using data of all the six principal active players (not reserve players) in each match.

## Experimental protocol

### Light-emitting diode therapy

LEDT used a flexible array of  $34 \times 18$  cm ( $612 \text{ cm}^2$ ) similar to the one used in a previous study developed by our research group [34]. However, this prototype device has 200 LEDs arranged in 25 clusters of four infrared LEDs ( $850 \pm 20$  nm; 130 mW) and 25 clusters of four red LEDs ( $630 \pm 10$  nm; 80 mW) displayed at five lines of ten clusters. Each line has one infrared cluster interspersed by one red cluster, totaling five infrared clusters plus five red clusters per line. Irradiation lasted 20, 40, 60, or 30 s (placebo) over each muscle group (quadriceps femoris, hamstrings, triceps surae) of each athlete's leg with fixed parameters as described in Table 1. Real LEDT or

placebo was applied between 40 and 60 min before the start of each official match, in accordance with randomization procedures. LEDT placebo had no energy (0 J) and no power (0 mW) applied over these muscle groups. Optical power was measured with an optical energy meter PM100D Thorlabs® fitted with a sensor S130C (area of  $0.70 \text{ cm}^2$ ). All athletes were blinded for these therapies as well as the coaching staff and evaluator #2 until the end of the study. There was no perceptible sensation of heat to the skin from real LEDT.

### Blood samples for creatine kinase activity

Blood samples for creatine kinase activity measurement were collected by puncturing the athlete's ear lobe using sterile lancets 1 h before and 24 h after each official match. The puncture site was cleaned with alcohol and dried, and the first drop of blood was discarded. The blood collected ( $30 \mu\text{L}$ ) was immediately analyzed with Reflotron Plus® biochemical analyzer (Roche, Germany) [14] following the manufacturer's guidelines. This analysis was conducted by evaluator #2, and all results were blinded for evaluator #1, athletes, and coaching staff until the end of the study.

### Matches

The time of each match was monitored by evaluator #3 (coaching staff) as well as which were the six active players in each match (not reserve players).

**Table 1** Parameters of light-emitting diode therapy (LEDT)

Number of LEDs	200 (100 infrared-IR and 100 red-RED)
Wavelength	$850 \pm 20$ nm (IR) and $630 \pm 10$ nm (RED)
Number of clusters	25 (IR) and 25 (RED)
Frequency	Continuous output
Optical output (each cluster of 4 LEDs)	130 mW (IR) and 80 mW (RED)
Total optical output	5250 mW ( $25 \times 130$ mW plus $25 \times 80$ mW)
LED spot size ( $\text{cm}^2$ )	0.2
Power density (each cluster)	$185.74 \text{ mW/cm}^2$ (IR) e $114.28 \text{ mW/cm}^2$ (RED)
Treatment time over each muscle group (s)	20, 40, or 60
Energy per cluster at 20 s	2.6 J (IR) and 1.6 J (RED)
Energy per cluster at 40 s	5.2 J (IR) and 3.2 J (RED)
Energy per cluster at 60 s	7.8 J (IR) and 4.8 J (RED)
Energy density per cluster at 20 s	$3.71 \text{ J/cm}^2$ (IR) and $2.28 \text{ J/cm}^2$ (RED)
Energy density per cluster at 40 s	$7.42 \text{ J/cm}^2$ (IR) and $4.56 \text{ J/cm}^2$ (RED)
Energy density per cluster at 60 s	$11.13 \text{ J/cm}^2$ (IR) and $6.84 \text{ J/cm}^2$ (RED)
Total energy delivered per muscle group at 20 s	105 J [ $2.6 \text{ J} \times 25 = 65 \text{ J}$ (IR) plus $1.6 \times 25 = 40 \text{ J}$ (RED)]
Total energy delivered per muscle group at 40 s	210 J [ $5.2 \text{ J} \times 25 = 130 \text{ J}$ (IR) plus $3.2 \times 25 = 80 \text{ J}$ (RED)]
Total energy delivered per muscle group at 60 s	315 J [ $7.8 \text{ J} \times 25 = 195 \text{ J}$ (IR) plus $4.8 \times 25 = 120 \text{ J}$ (RED)]
Total energy delivered on body (J)	630
Total energy delivered on body (J)	1260
Total energy delivered on body (J)	1890
Application mode	Device held coupled in skin contact

## Statistical analysis

Although this study enrolled a whole team (12 athletes), and all athletes received one of the light doses before each match, the statistical analysis was applied to the six principal active players (not reserve players) in each match. Thus, each group (light dose) had 6 subjects, and the study had a total sample size of 24 subjects. Shapiro-Wilk's *W* test verified the normality of the data distribution. Creatine kinase activity among all groups was compared using two-way analysis of variance (ANOVA) with repeated measures and Tukey honest significant difference (HSD) post hoc test. Significance was set at  $P < 0.05$ .

## Results

### Matches

The average time of the matches was  $133.75 \pm 8.99$  min.

### Creatine kinase activity

All results of CK activity were presented as mean  $\pm$  standard deviation (SD). LEDT dose 1 (20 s, 105 J) allowed a significant mean increase in CK (from  $328.0 \pm 188.9$  to  $499.6 \pm 232.0$  U/L; +59 %;  $P = 0.001$ ). Dose 4 (30 s—placebo, 0 J) also allowed a significant increase in CK (from  $270.3 \pm 112.4$  to  $406.1 \pm 150.5$  U/L; +53 %;  $P = 0.012$ ). However, LEDT dose 2 (40 s, 210 J) avoided a significant increase in CK (from  $338.8 \pm 130.3$  to  $364.1 \pm 127.5$  U/L; +10 %;  $P = 0.993$ ). Dose 3 (60 s, 315 J) also prevented a significant increase in CK (from  $245.1 \pm 126.9$  to  $318.0 \pm 153.5$  U/L; +31 %;  $P = 0.407$ ). These results were measured in all six principal active players of each match and presented in Fig. 1.

## Discussion

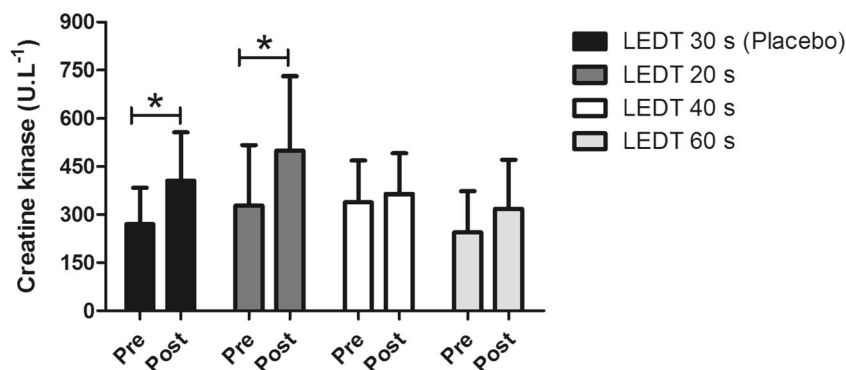
This study investigated the dose response of light-emitting diode therapy to prevent significant increases in creatine kinase

activity in volleyball players during official matches, establishing a “therapeutic window” (dose response of different doses of light). We applied LEDT on lower limb muscles aiming to cover the major muscle groups involved in jumping and landing movements that are required during volleyball matches. Moreover, the array of LEDs used in this study covered the entire target muscle groups as has been previously recommended by our research group [13]. To our knowledge, this is the first study that applied LEDT on muscles of professional athletes before official matches to prevent muscle damage.

The effects of low-level laser (light) therapy on muscle tissue when applied before or after intense exercise are mainly related to the prevention of exercise-induced damage, promotion of faster muscle recovery, and also producing increases in performance [10, 30, 11]. The use of LLLT to prevent muscle damage has been widely investigated in experimental models [15–20] and in clinical trials [21–28]. Experimental studies have used animal models to induce muscle damage, and clinical trials have used protocols of exercise in isokinetic dynamometers, fitness machines, or free weight lifting to induce muscle damage. However, all these studies could not exactly simulate the real muscular demand in athletes during official matches of any sport, motivating our research group to investigate the effectiveness of LEDT in volleyball players using a regimen of muscular pre-conditioning to prevent increases in CK.

Previous studies already reported benefits of the LLLT using diode lasers and LEDs to prevent increases in CK activity [10, 30, 11]. To our knowledge, the first study that used LLLT to prevent muscle damage was carried out by Lopes-Martins et al. [15] in an experimental animal model. These authors investigated the effects of different doses of light (0.5; 1.0 and 2.5 J/cm<sup>2</sup>) in muscular pre-conditioning to prevent muscle fatigue and muscle damage (CK) induced by neuromuscular electrical stimulation. These authors reported a LLLT dose response to decrease CK activity in muscle tissue. Another experimental study trained rats on an inclined treadmill and measured inhibition of inflammation, reduction of CK activity, and lowering of oxidative stress (malondialdehyde, MDA). They also found increases in

**Fig. 1** Mean and standard deviation (SD) for creatine kinase activity (CK) in blood pre and post each official match between groups. LEDT light-emitting diode therapy; asterisk represents statistical significance ( $P < 0.05$ ) in two-way analysis of variance (ANOVA) with repeated measures and Tukey HSD post hoc test



defense against oxidative stress (increased activity of superoxide dismutase, SOD) 24 and 48 h after exercise [16]. These studies were important to demonstrate the benefits of LLLT on exercise-induced muscle damage, inflammation, and oxidative stress.

More studies using experimental models were conducted to investigate the effects of LLLT on CK activity [18, 17, 19, 20]. Using a similar model of neuromuscular electrical stimulation previously reported [15], other studies also found LLLT dose responses of muscular pre-conditioning by decreased CK activity [18, 19], including assessment of different wavelengths [20]. Another study observed a reduction in CK activity when LLLT was applied after exercises in a model of swimming with workload [17]. Recently, LLLT using LEDs (LEDT) has demonstrated similar benefits to decrease CK activity when applied after exercise [35] or during rest intervals between bouts of physical activity [36]. All these studies assessed CK activity after 24 h or during a time range of 24–48 h after the exercise.

These aforementioned experimental studies created the scientific basis for the use of the LLLT, including LEDT, in prospective clinical trials that aimed to prevent exercise-induced muscle damage by assessing CK activity. Recently, this effect of “muscle protection” by LLLT has been observed in humans using different exercises protocols for the upper and lower limbs [10, 11, 30]. These studies reported lower increases in CK activity measured in blood when LLLT was applied before intense exercises. Light doses (Joules, J) used in previous studies were between 1 and 6 J delivered per diode laser, totaling 4 J [21] or 60 J [22] delivered to the biceps brachii; 30 and 40 J [23] or 180 J [24] delivered to the quadriceps femoris muscles. When the light source was LED, these studies used a cluster of 69 LEDs and applied 0.3 or 0.9 J per LED, totaling 41.7 J per site of irradiation and a total dose of 41.7 J delivered on biceps brachii [25]; 83.4 J [26] or 125.1 J [27] or 208.5 J [28] delivered to quadriceps femoris muscles.

Our results are in accordance with the total dose used in previous studies that used LEDs (LEDT) or combined LEDs and super-pulsed lasers to prevent increases in CK activity in the quadriceps femoris muscles with total doses from 60 to 300 J [29]. Our effective total doses of LEDT were 210 J [130 J (IR) plus 80 J (RED)—40 s of irradiation] and 315 J [195 J (IR) plus 120 J (RED)—60 s of irradiation] as reported similarly by a previous study [29]. LEDT placebo and the total dose of 105 J [(65 J (IR) plus 40 J (RED)—20 s of irradiation] allowed a significant increase of CK activity, indicating potential muscle damage and failure of the LEDT to promote “muscle protection.” In addition, we chose to use dual wavelengths (red and near-infrared at the same time) based on specific absorption bands of cytochrome c oxidase (Cox) [5–9] that is the main chromophore in the cells. Moreover, our results were observed using muscular pre-conditioning applied 40–60 min before the start of each official match. This

consideration is important because the waiting time can allow the muscles more time to respond to the light and could change the accepted paradigm that muscular pre-conditioning using LLLT for the prevention of exercise-induced muscle damage should be applied 5 min before the exercise.

The optimum doses of light delivered from each cluster of four LEDs were between 5.2 and 7.8 J for infrared and between 3.2 and 4.8 J for red. These energy doses are similar to doses emitted by diode lasers in a previous study [24], reinforcing the idea that light is light [37] and there is not a large difference between these light sources to prevent exercise-induced muscle damage (CK) if the total dose applied per muscle group is adequate. However, it is important to remark that it is possible that the light dose used to prevent muscle damage with LEDT in a pre-conditioning regimen may not be the same dose necessary if the light therapy is applied after the exercise [38]. It is accepted that cells under biochemical or mechanical stress have better responses to light [39] than cells in homeostasis.

The number of jumps and landings or of any other movement performed by each athlete during each match was not equal and could not be standardized among the six principal active players. This could be understood as a limitation, but the course of each match was unpredictable and could not be standardized.

Finally, the present study was not designed to elucidate the mechanisms of action of LEDT when used in muscular pre-conditioning to prevent exercise-induced muscle damage. However, previous studies reported better defenses against oxidative stress [16] if LLLT is applied over muscles after intense exercises as well as before exercise as reported in a previous clinical trial [40]. As mentioned above, the main chromophore, or red/NIR light-sensitive protein, present in biological tissues is Cox [5]. After absorbance of light, mitochondrial metabolism is modulated, promoting increases in ATP synthesis as one of the secondary responses [5]. We suggest that “muscle protection” against exercise-induced damage by LLLT is also a secondary response, but the connection between the light absorption and this effect is not fully understood. As a suggestion for future studies, we believe that LLLT could possibly modulate the proteins of membrane channels in muscle cells and/or in proteins involved in the transduction of the mechanical stress generated during muscle contraction involving the extracellular matrix and cytoskeleton. These modulations could improve the biochemical environment and the mechanical response of the muscle cells to exercise by stabilizing the muscle cell membrane.

It should be noted that there is no current position taken by the World Anti-Doping Agency (WADA) or the International Olympic Committee (IOC) regarding the use of LLLT for the enhancement of muscle performance. However, if the use of LLLT before athletic competition becomes widespread, we

expect discussions will have to take place in the appropriate circles on whether its use constitutes an unfair advantage.

## Conclusion

Use of red and near-infrared LEDT for muscular preconditioning was effective in the prevention of muscle damage (CK) in professional volleyball players during official matches. There was a therapeutic window (dose response) for this effect with a better dose of 210–315 J applied over the entire target muscles than with 0 J (placebo) or 105 J. Our results will stimulate more researchers and teams of high-performance sports to use LEDT for the prevention of muscle damage in professional athletes.

**Acknowledgments** Cleber Ferraresi would like to thank FAPESP for his PhD scholarships (numbers 2010/07194-7 and 2012/05919-0). MR Hamblin was supported by US NIH grant R01AI050875.

**Ethical statement** This study was conducted in compliance with the Declaration of Helsinki (1964) and its later amendments and also approved by the Research Ethics Committee for Human Studies of the Federal University of Sao Carlos (number protocol approved 217/2012).

**Conflict of interest** The authors declare no conflict of interest.

## References

- Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM (2009) Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet* 374(9705):1897–1908. doi:10.1016/S0140-6736(09)61522-1
- Enwemeka CS, Parker JC, Dowdy DS, Harkness EE, Sanford LE, Woodruff LD (2004) The efficacy of low-power lasers in tissue repair and pain control: a meta-analysis study. *Photomed Laser Surg* 22(4):323–329. doi:10.1089/1549541041797841
- Tumilty S, Munn J, McDonough S, Hurley DA, Basford JR, Baxter GD (2010) Low level laser treatment of tendinopathy: a systematic review with meta-analysis. *Photomed Laser Surg* 28(1):3–16. doi:10.1089/pho.2008.2470
- Gupta A, Avci P, Sadasivam M, Chandran R, Parizotto N, Vecchio D, de Melo WC, Dai T, Chiang LY, Hamblin MR (2012) Shining light on nanotechnology to help repair and regeneration. *Biotechnol Adv*. doi:10.1016/j.biotechadv.2012.08.003
- Karu T (1999) Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B* 49(1):1–17. doi:10.1016/S1044-98(98)00219-X
- Karu TI, Pyatibrat LV, Afanasyeva NI (2004) A novel mitochondrial signaling pathway activated by visible-to-near infrared radiation. *Photochem Photobiol* 80(2):366–372. doi:10.1562/2004-03-25-RA-123
- Karu TI, Kolyakov SF (2005) Exact action spectra for cellular responses relevant to phototherapy. *Photomed Laser Surg* 23(4):355–361. doi:10.1089/pho.2005.23.355
- Karu TI, Pyatibrat LV, Kolyakov SF, Afanasyeva NI (2008) Absorption measurements of cell monolayers relevant to mechanisms of laser phototherapy: reduction or oxidation of cytochrome c oxidase under laser radiation at 632.8 nm. *Photomed Laser Surg* 26(6):593–599. doi:10.1089/pho.2008.2246
- Karu TI (2010) Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. *IUBMB Life* 62(8):607–610. doi:10.1002/iub.359
- Ferraresi C, Hamblin MR, Parizotto NA (2012) Low-level laser (light) therapy (LLLT) on muscle tissue: performance, fatigue and repair benefited by the power of light. *Photonics Lasers Med* 1(4):267–286. doi:10.1515/plm-2012-0032
- Leal-Junior EC, Vanin AA, Miranda EF, de Carvalho PD, Dal Corso S, Bjordal JM (2013) Effect of phototherapy (low-level laser therapy and light-emitting diode therapy) on exercise performance and markers of exercise recovery: a systematic review with meta-analysis. *Lasers Med Sci*. doi:10.1007/s10103-013-1465-4
- Vieira WH, Ferraresi C, Perez SE, Baldissera V, Parizotto NA (2012) Effects of low-level laser therapy (808 nm) on isokinetic muscle performance of young women submitted to endurance training: a randomized controlled clinical trial. *Lasers Med Sci* 27(2):497–504. doi:10.1007/s10103-011-0984-0
- Ferraresi C, de Brito OT, de Oliveira ZL, de Menezes Reiff RB, Baldissera V, de Andrade Perez SE, Matheucci Junior E, Parizotto NA (2011) Effects of low level laser therapy (808 nm) on physical strength training in humans. *Lasers Med Sci* 26(3):349–358. doi:10.1007/s10103-010-0855-0
- Hornery DJ, Farrow D, Mujika I, Young W (2007) An integrated physiological and performance profile of professional tennis. *Br J Sports Med* 41(8):531–536. doi:10.1136/bjsm.2006.031351, discussion 536
- Lopes-Martins RA, Marcos RL, Leonardo PS, Prianti AC Jr, Muscara MN, Aimbire F, Frigo L, Iversen VV, Bjordal JM (2006) Effect of low-level laser (Ga-Al-As 655 nm) on skeletal muscle fatigue induced by electrical stimulation in rats. *J Appl Physiol* 101(1):283–288. doi:10.1152/japplphysiol.01318.2005
- Liu XG, Zhou YJ, Liu TC, Yuan JQ (2009) Effects of low-level laser irradiation on rat skeletal muscle injury after eccentric exercise. *Photomed Laser Surg* 27(6):863–869. doi:10.1089/pho.2008.2443
- Sussai DA, Carvalho Pde T, Dourado DM, Belchior AC, dos Reis FA, Pereira DM (2010) Low-level laser therapy attenuates creatine kinase levels and apoptosis during forced swimming in rats. *Lasers Med Sci* 25(1):115–120. doi:10.1007/s10103-009-0697-9
- Leal Junior EC, Lopes-Martins RA, de Almeida P, Ramos L, Iversen VV, Bjordal JM (2010) Effect of low-level laser therapy (GaAs 904 nm) in skeletal muscle fatigue and biochemical markers of muscle damage in rats. *Eur J Appl Physiol* 108(6):1083–1088. doi:10.1007/s00421-009-1321-1
- de Almeida P, Lopes-Martins RA, Tomazoni SS, Silva JA Jr, de Carvalho PT, Bjordal JM, Leal Junior EC (2011) Low-level laser therapy improves skeletal muscle performance, decreases skeletal muscle damage and modulates mRNA expression of COX-1 and COX-2 in a dose-dependent manner. *Photochem Photobiol* 87(5):1159–1163. doi:10.1111/j.1751-1097.2011.00968.x
- Santos LA, Marcos RL, Tomazoni SS, Vanin AA, Antonialli FC, Grandinetti Vdos S, Albuquerque-Pontes GM, de Paiva PR, Lopes-Martins RA, de Carvalho PT, Bjordal JM, Leal-Junior EC (2014) Effects of pre-irradiation of low-level laser therapy with different doses and wavelengths in skeletal muscle performance, fatigue, and skeletal muscle damage induced by tetanic contractions in rats. *Lasers Med Sci* 29(5):1617–1626. doi:10.1007/s10103-014-1560-1
- Felismino AS, Costa EC, Aoki MS, Ferraresi C, de Araujo Moura Lemos TM, de Brito Vieira WH (2014) Effect of low-level laser therapy (808 nm) on markers of muscle damage: a randomized double-blind placebo-controlled trial. *Lasers Med Sci* 29(3):933–938. doi:10.1007/s10103-013-1430-2
- Leal Junior EC, Lopes-Martins RA, Frigo L, De Marchi T, Rossi RP, de Godoi V, Tomazoni SS, Silva DP, Basso M, Filho PL, de Valls CF, Iversen VV, Bjordal JM (2010) Effects of low-level laser therapy

- (LLLT) in the development of exercise-induced skeletal muscle fatigue and changes in biochemical markers related to postexercise recovery. *J Orthop Sports Phys Ther* 40(8):524–532. doi:[10.2519/jospt.2010.3294](https://doi.org/10.2519/jospt.2010.3294)
23. Leal Junior EC, Lopes-Martins RA, Baroni BM, De Marchi T, Tauffer D, Manfro DS, Rech M, Danna V, Grosselli D, Generosi RA, Marcos RL, Ramos L, Bjordal JM (2009) Effect of 830 nm low-level laser therapy applied before high-intensity exercises on skeletal muscle recovery in athletes. *Lasers Med Sci* 24(6):857–863. doi:[10.1007/s10103-008-0633-4](https://doi.org/10.1007/s10103-008-0633-4)
  24. Baroni BM, Leal Junior EC, De Marchi T, Lopes AL, Salvador M, Vaz MA (2010) Low level laser therapy before eccentric exercise reduces muscle damage markers in humans. *Eur J Appl Physiol* 110(4):789–796. doi:[10.1007/s00421-010-1562-z](https://doi.org/10.1007/s00421-010-1562-z)
  25. Leal Junior EC, Lopes-Martins RA, Rossi RP, De Marchi T, Baroni BM, de Godoi V, Marcos RL, Ramos L, Bjordal JM (2009) Effect of cluster multi-diode light emitting diode therapy (LEDT) on exercise-induced skeletal muscle fatigue and skeletal muscle recovery in humans. *Lasers Surg Med* 41(8):572–577. doi:[10.1002/lsm.20810](https://doi.org/10.1002/lsm.20810)
  26. Leal Junior EC, Lopes-Martins RA, Baroni BM, De Marchi T, Rossi RP, Grosselli D, Generosi RA, de Godoi V, Basso M, Mancalossi JL, Bjordal JM (2009) Comparison between single-diode low-level laser therapy (LLLT) and LED multi-diode (cluster) therapy (LEDT) applications before high-intensity exercise. *Photomed Laser Surg* 27(4):617–623. doi:[10.1089/pho.2008.2350](https://doi.org/10.1089/pho.2008.2350)
  27. Baroni BM, Leal Junior EC, Geremia JM, Diefenthaler F, Vaz MA (2010) Effect of light-emitting diodes therapy (LEDT) on knee extensor muscle fatigue. *Photomed Laser Surg* 28(5):653–658. doi:[10.1089/pho.2009.2688](https://doi.org/10.1089/pho.2009.2688)
  28. Leal Junior EC, de Godoi V, Mancalossi JL, Rossi RP, De Marchi T, Parente M, Grosselli D, Generosi RA, Basso M, Frigo L, Tomazoni SS, Bjordal JM, Lopes-Martins RA (2011) Comparison between cold water immersion therapy (CWIT) and light emitting diode therapy (LEDT) in short-term skeletal muscle recovery after high-intensity exercise in athletes—preliminary results. *Lasers Med Sci* 26(4):493–501. doi:[10.1007/s10103-010-0866-x](https://doi.org/10.1007/s10103-010-0866-x)
  29. Antonialli FC, De Marchi T, Tomazoni SS, Vanin AA, Dos Santos Grandinetti V, de Paiva PR, Pinto HD, Miranda EF, de Tarso Camillo de Carvalho P, Leal-Junior EC (2014) Phototherapy in skeletal muscle performance and recovery after exercise: effect of combination of super-pulsed laser and light-emitting diodes. *Lasers Med Sci*. doi:[10.1007/s10103-014-1611-7](https://doi.org/10.1007/s10103-014-1611-7)
  30. Borsa PA, Larkin KA, True JM (2013) Does phototherapy enhance skeletal muscle contractile function and postexercise recovery? A systematic review. *J Athl Train* 48(1):57–67. doi:[10.4085/1062-6050-48.1.12](https://doi.org/10.4085/1062-6050-48.1.12)
  31. Huang YY, Chen AC, Carroll JD, Hamblin MR (2009) Biphasic dose response in low level light therapy. *Dose-Response* 7(4):358–383. doi:[10.2203/dose-response.09-027.Hamblin](https://doi.org/10.2203/dose-response.09-027.Hamblin)
  32. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliarriello E, Catalano IM, Cingolani A (1984) Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 175(1):95–99
  33. Karu T, Pyatibrat L, Kalendo G (1995) Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. *J Photochem Photobiol B* 27(3):219–223
  34. Ferraresi C, Beltrame T, Fabrizzi F, Nascimento ES, Karsten M, Francisco CO, Borghi-Silva A, Catai AM, Cardoso DR, Ferreira AG, Hamblin MR, Bagnato VS, Parizotto NA (2015) Muscular pre-conditioning using light-emitting diode therapy (LEDT) for high-intensity exercise: a randomized double-blind placebo-controlled trial with a single elite runner. *Physiother Theory Pract*:1–8. doi: [10.3109/09593985.2014.1003118](https://doi.org/10.3109/09593985.2014.1003118)
  35. Camargo MZ, Siqueira CP, Preti MC, Nakamura FY, de Lima FM, Dias IF, Togninho Filho Dde O, Ramos Sde P (2012) Effects of light emitting diode (LED) therapy and cold water immersion therapy on exercise-induced muscle damage in rats. *Lasers Med Sci* 27(5):1051–1058. doi:[10.1007/s10103-011-1039-2](https://doi.org/10.1007/s10103-011-1039-2)
  36. da Costa Santos VB, de Paula RS, Milanez VF, Correa JC, de Andrade Alves RI, Dias IF, Nakamura FY (2014) LED therapy or cryotherapy between exercise intervals in Wistar rats: anti-inflammatory and ergogenic effects. *Lasers Med Sci* 29(2):599–605. doi:[10.1007/s10103-013-1371-9](https://doi.org/10.1007/s10103-013-1371-9)
  37. Enwemeka CS (2005) Light is light. *Photomed Laser Surg* 23(2):159–160. doi:[10.1089/pho.2005.23.159](https://doi.org/10.1089/pho.2005.23.159)
  38. Dos Reis FA, da Silva BA, Laraia EM, de Melo RM, Silva PH, Leal-Junior EC, de Carvalho PT (2014) Effects of pre- or post-exercise low-level laser therapy (830 nm) on skeletal muscle fatigue and biochemical markers of recovery in humans: double-blind placebo-controlled trial. *Photomed Laser Surg* 32(2):106–112. doi:[10.1089/pho.2013.3617](https://doi.org/10.1089/pho.2013.3617)
  39. Karu T (2013) Is it time to consider photobiomodulation as a drug equivalent? *Photomed Laser Surg* 31(5):189–191. doi:[10.1089/pho.2013.3510](https://doi.org/10.1089/pho.2013.3510)
  40. De Marchi T, Leal Junior EC, Bortoli C, Tomazoni SS, Lopes-Martins RA, Salvador M (2012) Low-level laser therapy (LLLT) in human progressive-intensity running: effects on exercise performance, skeletal muscle status, and oxidative stress. *Lasers Med Sci* 27(1):231–236. doi:[10.1007/s10103-011-0955-5](https://doi.org/10.1007/s10103-011-0955-5)