



# Acute effect of photobiomodulation therapy on handgrip strength of chronic kidney disease patients during hemodialysis

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## Abstract

Pre-exercise photobiomodulation therapy (PBMT) reduces fatigue and enhances performance in different populations. However, PBMT benefits have never been tested on chronic kidney disease (CKD) patients, who present muscle weakness, fatigue, and reduced functional performance. The objective of this study was to evaluate the acute effect of three different doses of the PBMT on maximal handgrip strength of CKD patients. Fifteen volunteers ( $58 \pm 8$  years, 10 male/5 female) under chronic hemodialysis treatment ( $6 \pm 4$  years) participated in a randomized, crossover, double-blind, placebo-controlled trial. Each patient was assessed at four hemodialysis sessions with 1 week interval between evaluations. Placebo or PBMT (cluster probe with five 850 nm/200 mW laser diodes) were applied at three sites along the flexors of the finger (total doses of 60, 90, or 120 J per arm). The maximal handgrip strength was evaluated before and after PBMT/placebo treatment in each session. Repeated measures ANOVA and intraclass correlation coefficients (ICC) confirmed no learning effect on handgrip tests, and high scores for test-retest reliability (ICC scores = 0.89 to 0.95). Significant strength increases occurred after PBMT application with doses of 60 J/arm (4.85%,  $p = 0.005$ , ES = 0.32) and 90 J/arm (4.45%,  $p = 0.013$ , ES = 0.25), while no changes were detected with placebo or 120 J/arm. In conclusion, in consensus with a recent systematic review, a single bout of the 60 J/arm was the best dose/response for increased strength of the small muscles (handgrip strength). In view of the increasing implementation of exercise programs during hemodialysis, the current study opens a new field for PBMT for CKD patients.

**Keywords** Phototherapy · Low level laser therapy · Muscle · Strength · Chronic kidney disease (CDK) · Chronic disease

## Introduction

Chronic kidney disease (CKD) is a long-term metabolic condition that can need renal replacement therapy, such as hemodialysis (HD) or renal transplantation, to sustain life [1]. These patients have limited physical conditioning and many other health problems such as anemia, cardiac dysfunction, muscle

abnormalities, and depression [1–3]. Even an effective HD therapy is not able to avoid some accumulation of HD metabolites, which in turn lead to a persistent muscular atrophy (for more details, see Kouidi et al. [2]). CKD patients typically present low aerobic capacity with a significantly reduction in peak oxygen consumption, decreased strength, and reduced scores on functional tests (for review, see Koufaki et al. [3]).

The negative impact on CKD prognosis imposed by a low physical capacity can be significantly improved through specific exercise programs [4]. CKD patients engaged in resistance training programs shown improvements in muscle quantity, quality, and oxygen extraction capacity [5]. Nonetheless, the poor health conditions of some CKD patients and the heavy hospital/ambulatory routines, especially for patients under HD, are usually associated with a modest adherence to these kinds of adjunct therapies [2]. Therefore, clinicians should be aware for new strategies and/or resources to improve the exercise tolerance during the HD periods.

A single application of photobiomodulation therapy (PBMT) before exercise protocols has been shown to be

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effective in reducing muscle fatigue, improving exercise performance, and optimizing post-exercise recovery of healthy subjects (for review, see Vanin et al. [6]). In clinical settings, recent trials demonstrated that PBMT could increase muscular performance and reduce dyspnea and fatigue symptoms of patients with pulmonary [7, 8] and cardiovascular diseases [9]. These promising findings place this non-pharmacological therapy as a potential adjunct treatment in the physical rehabilitation. However, as far as we know, there is no study addressing the effects of PBMT on CKD patients. Therefore, we designed this randomized clinical trial to investigate the acute effects of different PBMT dosages on handgrip strength of CKD patients, an outcome considered as a predictor of survival time in this population [10].

## Methods

### Participants

In this randomized, crossover, double-blind, placebo-controlled trial, 21 CDK patients (ages ranging between 30 and 60 years old) undergoing hemodialysis (Hemodialysis Service at Irmandade da Santa Casa de Misericórdia de Porto Alegre – ISCMA) volunteered to participate (Fig. 1).

### Study design

During four HD sessions, PBMT (60, 90, and 120 J per arm) or placebo treatments were applied on the patients forearm flexor muscles. Handgrip strength test were performed immediately before and after PBMT/placebo applications. One week apart was respected between testing sessions. A single

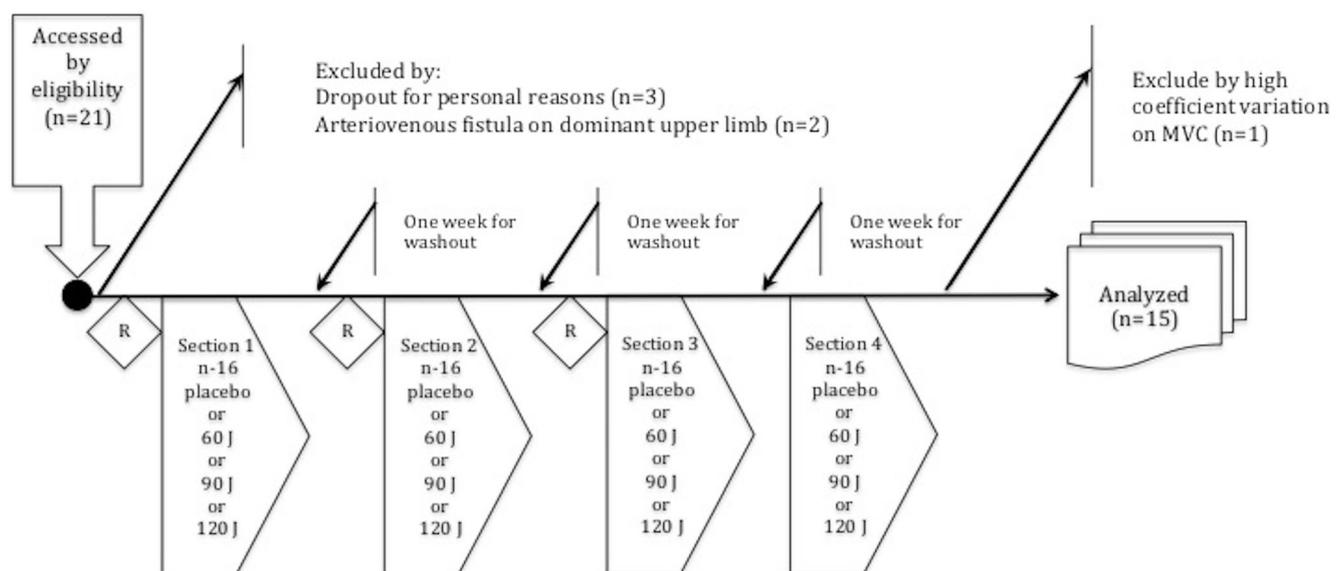
researcher was in charge of randomization and PBMT application. Volunteers and the other researchers were not aware of the order of treatments to assure double-blindness. A single researcher experienced in hand-gripping dynamometry conducts all strength tests. The participants were instructed to avoid vigorous exercise for upper limbs 24 h before the testing sessions and to take only routine medicines. A washout between PBMT/placebo was strictly assured.

### Handgrip strength test

The subject should be sitting (approximately 90° hip/knee/elbow flexion with a neutral shoulder position), while his dominant forearm is placed in a neutral position supported by the armchair [11]. The maximal handgrip strength was assessed by an isometric dynamometer (MIOTEC® model MD 100). A brief warm-up (submaximal handgrip contractions) and familiarization with the equipment was carried out before each testing session. The dynamometer was adjusted for each hand size. Three consecutive 5-s maximal voluntary contractions (MVC) were performed by each participant before and after PBMT/placebo application. A 2-min rest period was given between attempts to provide maximum strength recovery in each test. PBMT/placebo was applied 2 min after the last pre-treatment MVC, and post-treatment MVC was collected 2 min after PBMT/placebo. Only the highest value among these three attempts was taken for statistical analysis.

### PBMT/placebo application

Treatments were performed by the same researcher using an Intellect® Advantage 2766 (Chattanooga Corp.; Chattanooga, USA) with a cluster probe composed of five 850 nm/200 mW



**Fig. 1** Inclusion of patients and randomize procedures (flowchart). MVC maximal voluntary contraction, R randomize

**Fig. 2** Sites for cluster positioning (black circles on the forearm) and set parameters for the PBMT



PBMT parameters	
Number of diodes (cluster probe)	5
Wavelength	850 nm
Frequency	Continuous
Cluster size	44,16 cm <sup>2</sup>
Spot size (per diode)	0.029 cm <sup>2</sup>
Peak power (per diode)	200 mW
Power-density (per diode)	6.896 mW/cm <sup>2</sup>
Energy density (per diode)	206.9 J/cm <sup>2</sup>
Number of sites (per arm)	3
Treatment time (per site)	20s / 30s / 40s
Energy (per diode)	4 J / 6 J / 8 J
Energy (per site)	20 J / 30 J / 40 J
Energy (per arm)	60 J / 90 J / 120 J

LASER diodes (Chattanooga Corp.; Chattanooga, USA) placed at three sites of the forearm flexors (flexor carpi radialis, palmaris longus, flexor carpi ulnaris, flexor digitorum superficialis, and flexor pollicis longus), as illustrated in Fig. 2. The three doses used were 4 J/diode (20 J/site), 6 J/diode (30 J/site), and 8 J/diode (40 J/site), taking 20s, 30s, and 40s per site, respectively, correspond to 60, 90, and 120 J/arm. Placebo treatment was performed during 30 s and followed the same procedures as the experimental treatment, but with the device turned off. The subjects were kept blindfolded and opaque glasses were worn to prevent any light leakage that might reveal the type of treatment to the participant.

## Statistical analysis

Data normality and homogeneity were assessed by the Shapiro-Wilk and Mauchly tests, respectively. A repeated measures ANOVA, followed by LSD post hoc test, and intraclass correlation coefficients (ICC) were employed to account for a possible learning effect. A two-way repeated measures ANOVA, followed by LSD post hoc test, was used to compare the absolute strength results. Cohen's *d* was used to calculate the effect size (ES) promoted by each treatment. Relative changes (pre to post-treatment) were compared using a repeated measures ANOVA, followed by LSD post hoc test. Student's *t* test was used to compare predict values with measured handgrip strength. A significance level of 5% ( $p < 0.05$ ) and an observed power of 80% ( $OP > 0.80$ ) were assumed.

## Results

All participants were under HD for more than a year (Table 1), displaying good scores of urea rate reduction (URR) and urea deuration (Kt/V). "Unknown causes" were the most prevalent etiology (33%) of the CKD, followed by

glomerulonephritis (27%). When compared to the predict values [12] the handgrip strength was decreased by 41%: predict =  $45.12 \pm 14.64$  kg vs. evaluated =  $26.66 \pm 3.47$  ( $p < 0,001$ ). No learning effect was observed for handgrip tests throughout the study (Table 2; ICC scores = 0.89 to 0.95).

There was a significant treatment-time interaction for absolute values of handgrip strength ( $p = 0.039$ ;  $OP = 0.805$ ). Patients had a significant increase of strength after PBMT application with 60 and 90 J/arm (small effect sizes), but not with placebo or 120 J/arm (Fig. 3). Percentage change with

**Table 1** Clinical characteristics

<i>n</i> = 15		
Age (year)		57.60 ± 8.70
Male	10	66.66%
Female	5	33.33%
High (m)		1.69 ± 0.09
Weight (kg)		68.92 ± 10.72
Body mass index (kg/m <sup>2</sup> )		24.30 ± 3.74
Hemodialysis time (year)		5.34 (1.23 to 14.92)
URR (% of the reduction)		70.90 ± 6.97
Kt/V indices		1.26 ± 0.22
Etiology of CKD		
Glomerulonephritis	4	26.67%
Diabetes	1	6.67%
Hypertension	1	6.67%
Systemic lupus erythematosus	1	6.67%
Glomerulosclerosis focal	1	6.67%
Systemic vasculitis	1	6.67%
Kidney cancer	1	6.67%
Unknown causes	5	33.33%

Data are expressed as average ± standard deviation; median and range; and percentage prevalence; URR urea reduction rate [ $1 - \text{urea post} \div \text{urea pre} \div 100$ ]; Kt/V = urea deuration estimated by Lowrie method [ $\text{lg}(\text{urea post} \div \text{urea pre})$ ], CKD chronic kidney disease; \* =  $p < 0.001$  when compared to the predict grip strength by two sample (homoscedastic) Student's *t* test

**Table 2** Baseline handgrip strength (mean ± standard deviation)

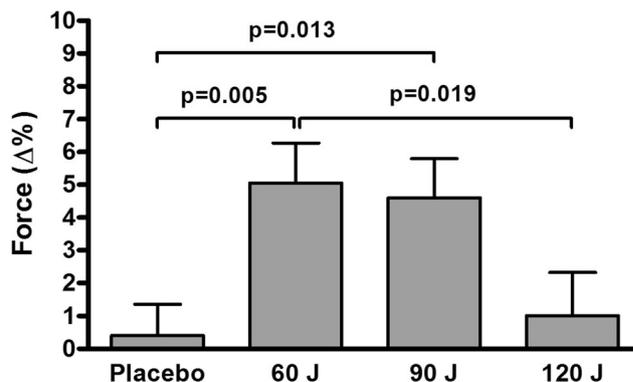
	1st session	2nd session	3rd session	4th session	<i>p</i> value
Handgrip strength (kg)	26.37 ± 5.19	26.81 ± 6.20	27.08 ± 5.24	26.49 ± 5.72	0.981

60 J was higher than those observed with placebo and 120 J, while percent change with 90 J was larger than placebo treatment (Fig. 4),

**Discussion**

This is the first study to investigate the effect of PBMT on muscle strength in CKD patients. Our main finding is that a single session with specific dosages of PBMT during hemodialysis can improve the patients’ handgrip strength.

Intracellular ATP synthesis improvement [13, 14] has been considered a central point to explain the beneficial effects of the PBMT on muscle performance in humans [6]. This energetic improvement seems to be mostly related to an enhanced oxidative metabolism. However, handgrip strength is highly dependent on anaerobic metabolism. But how to explain the increased muscle strength observed in our patients then? A plausible hypothesis is the integration between the aerobic and anaerobic ATP production (for a review, see Tonkonogi

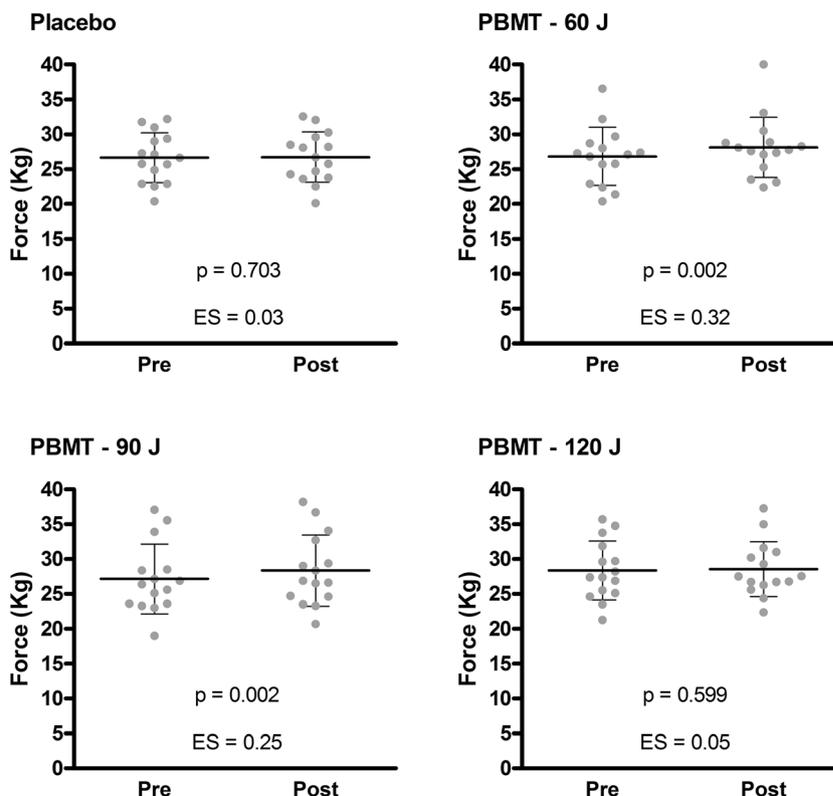


**Fig. 4** Percentage change (mean ± standard error) of handgrip strength of each experimental condition

M and Sahlin K [15]). Specific doses of PBMT led to higher peak force during electrical stimulation-induced contractions [16]. Regardless of the main type of metabolism involved, when ATP synthesis is reduced due to mitochondrial dysfunction the whole cell functioning might be compromised [17]. Therefore, by improving mitochondrial function (i.e., energy output and following redox state influences), PBMT treatment would improve muscle fiber proper functioning as a whole [18] and consequently enhance contractility (i.e., force).

Granata et al. [19] suggesting a clear deregulation of mitochondrial respiratory machinery in CKD patients closely associated with enhanced oxidative stress postulated that this increased production of reactivity oxygen species due to the effect of pro-inflammatory mediators

**Fig. 3** Mean values (bars) and individual behavior (connected dots) of handgrip strength (pre- and post-treatment)



may cause a profound inhibition of the oxidative phosphorylation system leading to a compensatory intracellular production of this oxidative stress agents [19]. Studies with animal models demonstrate that inflammatory cytokine (TNF) depressing specific force of muscle fibers, but this forces decreased can be prevent by selective depletion of muscle-derived reactive oxygen species [20]. Since PBMT decreases inflammation and oxidative stress in animal model [21], a potential acute interaction between light irradiation, reactive oxygen species, and inflammatory cytokine involved in muscle fibers contractile could also be hypothesized to explain our results. CKD patients are in such a severe state of electrochemical imbalance that a few stimuli promoted by a single application of PBMT might have elicited biochemical responses that were enough to improve contractile performance.

The ergogenic properties of the PBMT have been testing in health and young volunteers [6], where the dose-response effect seems to be a usual finding [22]. Vanin et al. [23] tested 10, 30, and 50 J/site before an eccentric exercise protocol and found greater strength recovery with 50 J. Antonialli et al. [22] also tested 10, 30, and 50 J/site before eccentric exercise, and their findings supported that 30 J/site was the optimal dosage. Lanfredini et al. [24] compared 15, 30, and 45 J/site before a cycling time-to-exhaustion test and observed the greatest effect with 15 J/site. These discrepancies on dose-response are a common finding since the biological and technological variances are decisive to the PBMT results, and must be properly considered on the treatment sets. A recent systematic review by Vanin et al. [6] recommended total doses of 20 to 60 J for small muscular groups in healthy subjects. Our findings support the recommendation of 60 J also for CKD, since that dosage was the best one in our study. The dose-response effects observed on muscle performance open another field to light irradiation on CKD patients. We speculate that functional increase observed in this small muscle group with a single PBMT session could be reproduced in a large muscle group (e.g., quadriceps), as well as optimize muscular responses to a resistance training program [25].

In conclusion, a single bout of PBMT (infrared low level therapy) applied during the HD increased the handgrip strength of CKD patients. The 60 J/arm was the best dose/response observed and this find corroborates with the systematic review recently published (Vanin et al. [6]). The current study opens a new field for PBMT in chronic diseases characterized by skeletal muscle impair such as CKD patients, as well as environments where PBMT remains unexplored by clinicians such as hemodialytic centers.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The Research Ethics Committees approved this study (CAAE: 34811314.4.0000.5335), and the recruitments start only after [ClinicalTrials.gov](http://ClinicalTrials.gov) endorsement (NCT02586376).

## References

1. Koufaki P, Greenwood S, Painter P, Mercer T (2015) The BASES expert statement on exercise therapy for people with chronic kidney disease. *J Sports Sci* 33(18):1902–1907
2. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guibataziampiri O et al (1998) The effects of exercise training on muscle atrophy in haemodialysis patients. *Nephrol Dial Transplant* 13(3): 685–699
3. Koufaki P, Kouidi E (2010) Current best evidence recommendations on measurement and interpretation of physical function in patients with chronic kidney disease. *Sports Med* 40(12):1055–1074
4. Painter P (2005) Physical functioning in end-stage renal disease patients: update 2005. *Hemodial Int* 9(3):218–235
5. Cheema BS, Abas H, Smith BC, O'Sullivan AJ, Chan M, Patwardhan A, Kelly J, Gillin A, Pang G, Lloyd B, Berger K, Baune BT, Fiatarone Singh MA (2011) Effect of resistance training during hemodialysis on circulating cytokines: a randomized controlled trial. *Eur J Appl Physiol* 111(7):1437–1445
6. Vanin AA, Verhagen E Barboza SD, Costa LOP, Leal-Junior ECP (2018) Photobiomodulation therapy for the improvement of muscular performance and reduction of muscular fatigue associated with exercise in healthy people: a systematic review and meta-analysis. *Lasers Med Sci* 33(1):181–214
7. Miranda EF, Leal-Junior EC, Marchetti PH, Dal Corso S (2014) Acute effects of light emitting diodes therapy (LEDT) in muscle function during isometric exercise in patients with chronic obstructive pulmonary disease: preliminary results of a randomized controlled trial. *Lasers Med Sci* 29:359–365
8. Miranda EF, de Oliveira LV, Antonialli FC, Vanin AA, de Carvalho Pde T, Leal-Junior EC (2015) Phototherapy with combination of super-pulsed laser and light-emitting diodes is beneficial in improvement of muscular performance (strength and muscular endurance), dyspnea, and fatigue sensation in patients with chronic obstructive pulmonary disease. *Lasers Med Sci* 30:437–443
9. Bublitz C, Renno AC, Ramos RS, Assis L, Sellera CA, Trimer R, Borghi-Silva A, Arena R, Guizilini S (2016) Acute effects of low-level laser therapy irradiation on blood lactate and muscle fatigue perception in hospitalized patients with heart failure—a pilot study. *Lasers Med Sci* 31(6):1203–1209
10. Bautmans I, Gorus E, Njemini R, Mets T (2007) Handgrip performance in relation to self-perceived fatigue, physical functioning and circulating IL-6 in elderly persons without Inflammation. *BMC Geriatr* 7:5
11. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA (2011) A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* 40(4):423–429
12. Günther CM, Bürger A, Rickert M, Crispin A, Schulz CU (2008) Grip strength in healthy Caucasian adults: reference values. *J Hand Surg Am* 33(4):558–565

13. 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
14. Ferraresi C, Kaippert B, Avci P, Huang YY, de Sousa MV, Bagnato VS, Parizotto NA, Hamblin MR (2015) Low-level laser (light) therapy increases mitochondrial membrane potential and ATP synthesis in C2C12 myotubes with a peak response at 3–6 h. *Photochem Photobiol* 91(2):411–416
15. Tonkonogi M, Sahlin K (2002) Physical exercise and mitochondrial function in human skeletal muscle. *Exerc Sport Sci Rev* 30(3):129–137
16. Santos LA, Marcos RL, Tomazoni SS, Vanin AA, Antonialli FC, Grandinetti Vdos S, Albuquerque-Pontes GM, de Paiva PR, Lopes-Martins RÁ, de Carvalho Pde T, 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
17. Allen DG, Lamb GD, Westerblad H (2008) Skeletal muscle fatigue: cellular mechanisms. *Physiol Rev* 88(1):287–332
18. Vladimirov YA, Osipov AN, Klebanov GI (2004) Photobiological principles of therapeutic applications of laser radiation. *Biochemistry (Mosc)* 69(1):81–90
19. Granata S, Zaza G, Simone S, Villani G, Latorre D, Pontrelli P, Carella M, Schena FP, Grandaliano G, Pertosa G (2009) Mitochondrial dysregulation and oxidative stress in patients with chronic kidney disease. *BMC Genomics* 10:388
20. Stasko SA, Hardin BJ, Smith JD, Moylan JS, Reid MB (2013) TNF signals via neuronal-type nitric oxide synthase and reactive oxygen species to depress specific force of skeletal muscle. *J Appl Physiol* 114(11):1629–1636
21. Assis L, Moretti AI, Abrahão TB, Cury V, Souza HP, Hamblin MR, Parizotto NA (2012) Low-level laser therapy (808 nm) reduces inflammatory response and oxidative stress in rat tibialis anterior muscle after cryolesion. *Lasers Surg Med* 44(9):726–735
22. 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* 29(6):1967–1976
23. Vanin AA, De Marchi T, Tomazoni SS, Tairova O, Leão Casalechi H, de Tarso Camillo de Carvalho P, Bjordal JM, Leal-Junior EC (2016) Pre-exercise infrared low-level laser therapy (810 nm) in skeletal muscle performance and postexercise recovery in humans, what is the optimal dose? A randomized, double-blind, placebo-controlled clinical trial. *Photomed Laser Surg* 34(10):473–482
24. Lanferdini FJ, Bini RR, Baroni BM, Klein KD, Carpes FP, Vaz MA (2017) Low-level laser therapy improves performance and reduces fatigue in competitive cyclists. *Int J Sports Physiol Perform* 19:1–27
25. Baroni BM, Rodrigues R, Freire BB, de Franke R A, Geremia JM, Vaz MA (2015) Effect of low-level laser therapy on muscle adaptation to knee extensor eccentric training. *Eur J Appl Physiol* 115(3):639–647