

The effect of photobiomodulation versus placebo on functional capacity and fatigability in post COVID-19 elderly

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Abstract

Introduction: Post-pandemic syndrome has lasting functional and psychological consequences, especially for the elderly. This timeline requires a quick search for procedures that will enable us to implement safe and non-invasive therapeutic instruments as prophylactic or adjuvant therapies for post-COVID-19 consequences. Photobiomodulation (PBM) may decrease inflammation and improve leg circulation. So, this study aims to assess the impact of PBM on post-COVID-19 functional capacity and fatigability.

Material and methods: Two groups of 100 elders with a positive COVID-19 history were established. The PBM group got photobiomodulation on both lower calf muscles for four weeks (diode laser, Continuous output, stationary in skin contact mode, 100mW, 808 nm, beam spot area of 0.0314 cm², 127.39 J/cm²/point, 40 s). The control group got placebo PBM for four weeks. Both groups' exhaustion was measured using the FSS. Functional ability was evaluated using the KATZ score before and after the trial.

Results: After four weeks of PBM, there was a substantial suppression in the FSS level from 4.57 ± 0.26 to 3.97 ± 0.23 and the KATZ score was significantly elevated from 2.98 ± 0.79 to 3.94 ± 0.77 , P value for both was <0.05 . In addition, the placebo intervention improved the FSS level and KATZ score to an acceptable level.

Conclusions: PBM enhanced functional capacities as evaluated by the KATZ score and fatigability perception as measured by the FSS scale in post-COVID-19 older people. Also, placebo intervention had a considerable effect on the elderly, with an 8.1 percent improvement in fatigue perception and a 19.1 percent improvement in functional ability evaluation.

Keywords: coronavirus, geriatrics, low-level light therapy, physical performance

Introduction

COVID-19 is a new infectious disease whose course ranges from asymptomatic to one characterized by severe pneumonia in combination with severe acute respiratory syndrome (SARS), which can lead to death [1].

Although post-COVID-19 syndrome affects the majority of those who have apparently recovered from COVID-19 regardless of disease severity, age, or hospitalization status, it remains not fully understood. The most common symptom reported in most studies is exhaustion and difficulty breathing, which can last for months



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after acute COVID-19 [2]. In addition, COVID-19 survivors may still experience COVID-19-like symptoms. They may develop respiratory problems, unexplained fatigue, and a reduction in their ability to complete functional tasks for up to six months post-COVID-19, which in turn leads to a decreased quality of life [3,4].

Because of their difficulty coping with physical and emotional stressors, older people are regarded as a high-risk subset of the overall population. Getting old is physiologically allied with cognitive debility and a compromised stress response [5]. Rehabilitation of patients displaying post-COVID-19 is needed to reduce disabilities, regain functional objectivity, and enhance the capability to accomplish Activities of Daily Living (ADL). The key aims when treating post-COVID-19 include increasing functional capability, improving the quality of life, smoothing the societal restoration post-hospitalization, and reducing exhaustion, dyspnea, anosmia and anxiety. Consequently, initial rehabilitation accomplishments should be attainable by patients following discharge from hospitals, with the aim of minimizing any negative consequences of COVID-19 [6].

Recent progress in understanding COVID-19 indicates that it manifests as a general infection that considerably disturbs the hematopoietic system and haemostasis, both of which are influenced by the light environment, particularly in the visible and infrared radiation spectrum [7]. Photobiomodulation (PBM), which is also known as low-level laser therapy (LLLT), can encourage cell proliferation. It is a non-invasive therapy that relieves pain and reduces inflammation while also speeding up tissue healing. PBM has been used in the treatment of numerous diseases and conditions, such as diabetes, brain injury, spinal cord impairment, skin problems and oral conditions [8].

Light induces photochemical responses in biological structures. After being absorbed by photoreceptors, light beams are converted into electrical signals and transmitted to the visual processing areas of the brain. One form of phototherapy that has been found to beneficial is PBM [9]. PBM therapy has been proposed as a harmless, non-invasive, side-effect-free intervention, particularly suited to at-risk groups. However, studies are needed to determine its effectiveness in preventing COVID-19 infection and disease; the procedure may not only benefit the elderly and chronically ill, but could represent a low-risk, low-cost intervention for the prevention and management of a variety of disorders [10].

The current wave of post-pandemic syndrome experienced by those who have survived COVID-19 is characterised by ongoing unfavourable functional and psychological consequences, particularly for the elderly.

As such, there is a need for new approaches for implementing harmless and non-invasive therapeutic instruments for preventative or even adjuvant treatments in the management of post-COVID-19 syndrome. Some research suggests that photobiomodulation treatment (PBMT) can reduce inflammation and enhance lower leg circulation. As a result, the current investigation aimed to determine the effect of PBMT (infrared low-level laser therapy) on functional capacity and fatigability in seniors with post-COVID-19 syndrome.

Material and methods

Participants

A randomized, double-blind, placebo-controlled study was organised. The study took place between November 2020 and March 2021, and it was listed on clinicaltrials.gov with the number NCT04676074. The goal and potential dangers of the study were explained to all patients. All participants signed a consent form, indicating their willingness to take part in the study. The Ethical Committee of Cairo University's Faculty of Physical Therapy has given their approval (No: P.T.REC/012/003314).

A hundred elderly people, both sexes, were recruited from Kasr Al-Ainy Hospital, Cairo University. Their age ranged from 60 to 70 years old, and their BMI was 30 to 35 kg/m². All had a past history of positive COVID-19, confirmed by positive PCR, and reported suffering from general fatigability and a decrease in functional capacity while performing their routine activities of daily living. The exclusion criteria comprised uncontrolled diabetes, uncontrolled hypertension, class 2, 3, and morbid obesity, fibromyalgia, mental illness, a previous injury to the plantar flexor muscle, and any skin problem or photo-hypersensitivity. A flow chart of the selection procedure is given in Figure 1.

Procedure

The participants were assigned to receive active or placebo PBMT in the first session based on drawing lots (A or B). A random table of numbers (1–100) indicating group A or B was created using Microsoft Excel 2010. Researcher (1) received the allocation number and prepared the probe and PBMT. Another blind researcher (2) gave researcher (1) the prepared laser. The randomization researcher (1) was told not to tell the subjects or the laser researcher (2) what treatment they received. Researcher (2) left the lab while researcher (1) adjusted the laser treatment, thus blinding the researcher who administered the laser. A blind solder was also present on the laser probe. All participants, the laser researcher, and the data analyst were blind to the treatments.

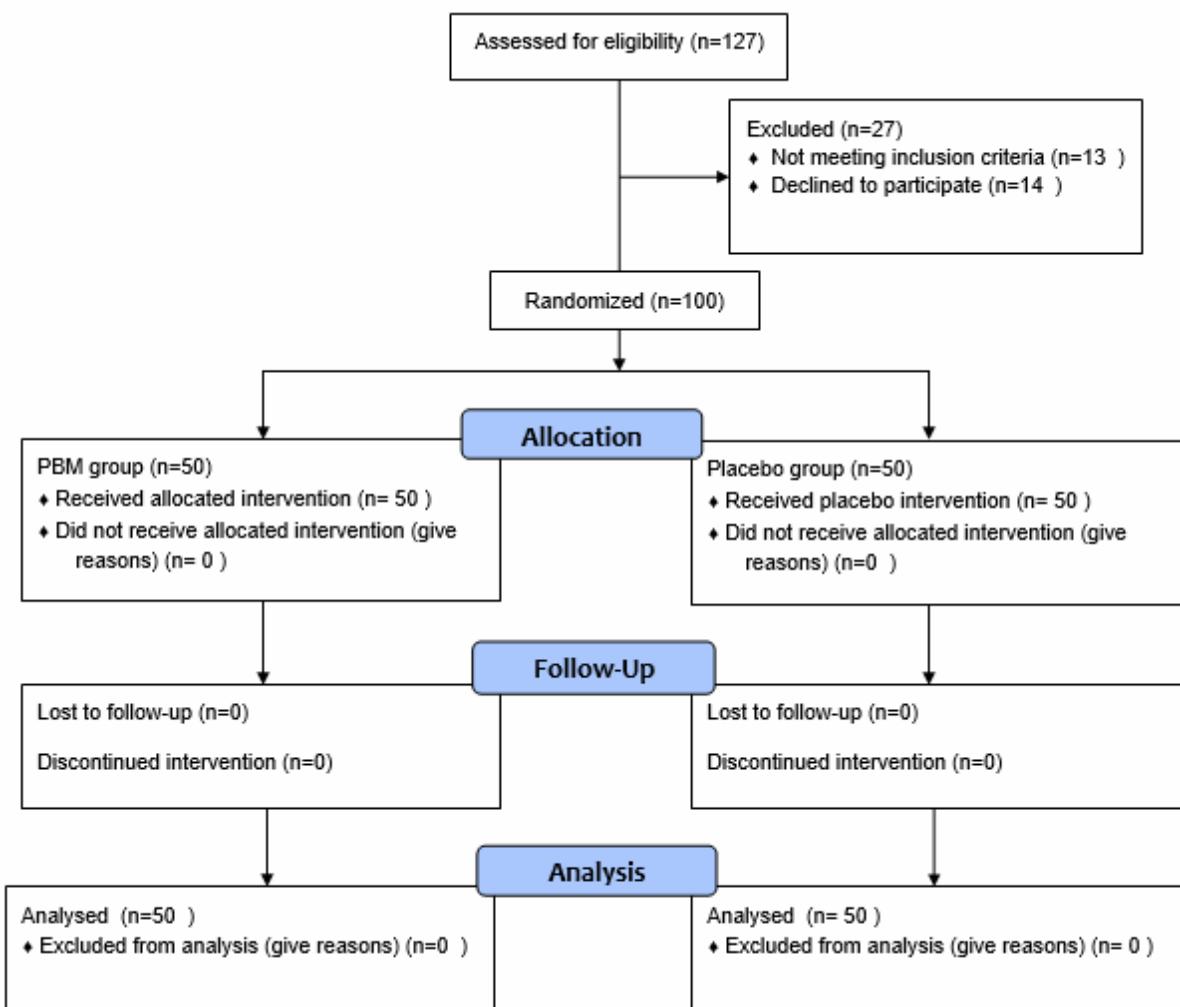


Fig. 1. Study flow chart

Outcome measures

Fatigability

In this study, fatigue and exhaustion were evaluated using the Fatigue Severity Scale (FSS). The FSS measures exhaustion in a single dimension using nine questions in a single scale. Each FSS question comprises a statement that is scored on a seven-point scale from 1 (strongly disagree) to 7 (strongly agree) [11].

Function

The Katz Index of Independence in Tasks of Everyday Living, often known as the Katz ADL (KATZ), is used to assess functional status, reflected in the ability to performed daily activities independently. Bathing, dressing, toileting, transferring, continence, and feeding are all rated as adequate by the Index. Individuality in each of the six functions is assessed as yes or no. A score of 6 means that all functions are normal, a score of 4 indicates moderate impairment, and a score of 2 or less indicates significant impairment [12].

Intervention

A PBM laser was used at one medial and one lateral sites of the calf muscles of both lower limbs [13] (diode laser, continuous output, stationary in skin contact mode, 100 mW, 808 nm, beam spot area of 0.0314 cm^2 , $127.39 \text{ J/cm}^2/\text{point}$, 40 s) [14] three times per week for four weeks. During application, the patients remained prone, their feet out of the plinth, performing a circulatory exercise consisting of dorsiflexion and plantar flexion: two minute intervals of working out were interspersed with one minute rests for 10-minutes for each foot separately.

The control group received the placebo PBM at the same medial and lateral sites of the calf muscles of both lower limbs, (diode laser, continuous output, stationary in skin contact mode, 0 mW, 808 nm, beam spot area of 0.0314 cm^2 , $0 \text{ J/cm}^2/\text{point}$, 40 s), three sessions per week for four weeks. Like the other group, the patients remained prone during treatment, their feet removed from the plinth, performing circulatory exercise consisting of dorsiflexion and plantar flexion: two minute

intervals were interspersed with one minute rests, for 10 minutes for each foot.

In all cases, the laser was delivered using a punctual, contact approach at the two locations on the muscular belly of the calf muscle. During application, at each spot, the laser probe was kept still at a 90-degree angle to the skin surface with light pressure. All safety measures regarding the participants and the researchers were taken into consideration.

Statistical analysis

Statistical analyses were performed using SPSS version 22. Age and BMI (mean and standard deviation) were compared using an unpaired T-test. Significant within-group changes in FSS and KATZ scores, i.e. before and after intervention, were analyzed with the Wilcoxon Signed Ranks Test, while inter-group differences, i.e. before and after treatment, were analyzed using the Independent Samples Mann-Whitney U test. P < 0.05 was considered statistically significant.

Results

In total, 100 seniors were enrolled and divided into two equal groups at random. No significant difference in age or BMI was noted between the two groups ($p < 0.05$), as shown in Table 1.

Regarding fatigability assessment, significant differences were detected between pre- and post-intervention FSS and KATZ scores in the PBM group, with P-values of (<0.05), with respective percentage changes of 13.13% and 32.2% (Tab. 2).

In the placebo group, significant differences were also found between the pre and post-treatment scores for FSS and KATZ ($p < 0.05$), with their respective percentage changes being 8.1% and 19.1% (Tab. 3).

No significant inter-group differences (i.e. between the PBM and placebo groups) were found for the pre-intervention FSS and KATZ scores (respective P-values being 0.298 and 0.712). However, a significant difference in FSS was noted between the two groups after

Tab. 1. Demographic data and physical characteristics of patients in both groups

Items	PBM group	Placebo group	Comparison	
	Mean ± SD	Mean ± SD	t-value	P-value
Age (years)	63.48 ± 2.82	63.62 ± 2.87	0.246	0.807
BMI (kg/m ²)	27.27 ± 1.25	27.44 ± 1.33	0.668	0.506

P – probability, SD – standard deviation.

Tab. 2. A comparison of the mean FSS and KATZ scores before and after treatment in the study group

	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	p	% of change
FSS	4.57 ± 0.26	3.97 ± 0.23	p < 0.05*	13.13%
KATZ score	2.98 ± 0.79	3.94 ± 0.77	p < 0.05*	32.2 %

FSS – Fatigue Severity Scale, KATZ – Katz Index of Independence in Tasks of Everyday Living, *p < 0.05 is statistically significant, SD – standard deviation.

Tab. 3. A comparison of the pre – and post-treatment FSS and KATZ scores for the placebo group

	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	p	% of change
FSS	4.62 ± 0.25	4.25 ± 0.26	p < 0.05*	8.1%
KATZ score	3.04 ± 0.86	3.62 ± 0.86	p < 0.05*	19.1 %

FSS – Fatigue Severity Scale, KATZ – Katz Index of Independence in Tasks of Everyday Living, *p < 0.05 is statistically significant, SD – standard deviation.

Tab. 4. Comparison between groups regarding in pre – and post-treatment mean FSS and KATZ scores

	PBM group		Placebo group		Between groups	
	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Pre-treatment	Post-treatment
FSS	4.57 ± 0.26	3.97 ± 0.23	4.62 ± 0.25	4.25 ± 0.26	p = 0.298	p < 0.05*
KATZ score	2.98 ± 0.79	3.94 ± 0.77	3.04 ± 0.86	3.62 ± 0.86	p = 0.712	p = 0.071

FSS – Fatigue Severity Scale, KATZ – Katz Index of Independence in Tasks of Everyday Living, *p < 0.05 is statistically significant, SD – standard deviation.

treatment (p < 0.05; Tab. 4), with the percentage changes being 13.13% in the study group and 8.1% in the control group (Tab. 2, Tab. 3).

Discussion

The main aim of this investigation was to compare the effect of PBM treatment versus placebo on fatigability and functional status in elderly patients who had recently recovered from COVID-19, and to identify potential gaps and novel trends in research. Our findings suggest that PBM can help seniors with post-COVID-19 syndrome because it is linked to immune system regulation, inflammation reduction, better circulation, and other health-restoring activities.

The impact of laser treatment is determined by the quantity of laser energy per cm² determines. The minimal therapeutic dose for a bio-stimulant impact is 0.01 J/cm² for red and infrared lasers and 0.001 J/cm² for blue, ultraviolet, and green lasers. When employed in settings that need suppression, such as lowering the inflammatory response to avoid or minimize the flood of pro-inflammatory cytokines, dosages greater than 10 J/cm² have been found to elicit inhibitory effects [15].

Phototherapy has been used to treat illnesses since Ancient Greece, when the sick were exposed to the sun to treat their maladies, a treatment known as heliotherapy. During the 1918 Spanish flu crisis, phototherapy was verified to be a valuable ally in the treatment of the epidemic, and was cited as one of the most important contributors to lowering mortality. Several studies have been carried out since then to better understand the positive benefits of light, particularly blue, violet, red, and infrared light [16].

Although most attention given to COVID-19 concerns the acute signs and symptoms of the disease and patient recovery, many survivors continue to experience physical, mental and emotional effects after the typical symptoms have passed. The most persistent and devastating symptoms are fatigue and a decreased

ability to perform functional activities [11]. Our findings demonstrate that while both PBM and placebo sessions produce a significant improvement in the functional capacity and fatigability level in post-COVID-19 elderly people, a greater improvement was observed for PBM.

A previous study on the special effects of PBM on fatigue level and performance in thirty older women found that applying PBM to the rectus femoris muscle revealed an improvement in peripheral muscle fatigue, determined by surface electromyography (EMG) and blood lactate analysis. PBM was found to reduce muscular fatigue by dramatically increasing the electromyographic fatigue index and significantly lowering lactate concentrations. Despite this, there was no indication that PBM might aggregate muscle function, as revealed by an isokinetic dynamometer. hence, it was possible to determine that PBM was helpful in reducing fatigue points. However, no evidence indicated that PBM may have an effect on muscle performance [12].

A recent study found that two weeks of light-emitting diode PBM therapy is effective in reducing non-specific low back pain and fatigue in working nurses [13], and phototherapy has been shown to improve pain, quality of life, and sleep disorders in people with fibromyalgia [14]. A review of 27 articles published between 2008 and 2017 showed that low-level laser therapy could be used to improve performance and make people feel less tired after hard exercise [15]. Applying PBM six hours before and immediately before an isokinetic exercise procedure on eighteen physically active men resulted in the same total effort being produced but with lower fatigue, which may enable the performance of further exercise sets [16].

When applied to the lower limb muscles as a single therapy for eight weeks, PBM was found to improve functional ability and lower limb muscular strength. It also appears to alter pain awareness and improve several aspects of quality of life in chronic kidney failure patients without having a substantial effect on fatigue perception [17].

Another study found that PBM has no clear effect on resistance training among postmenopausal women. Its findings suggest that while resistance training can enhance muscle power and functional performance in post-menopausal women, it notes that PBM does not appear to support further changes to the outcomes measured [18].

A recent study, performed in 2021, found that low-level laser therapy may increase the range of muscle signal and fiber enrollment, as well as the strength of signal transmission on spastic muscle fibers; the authors propose that more research is needed to understand how exhausted fibers behave in spastic individuals. PBM was also found to potentially diminish pain and fatigue, which may signify a novel therapeutic procedure for neurological patients [19].

In a group of 40 cancer survivors, mean age of 47.3 years, placebo intervention resulted in changes in cancer-related fatigue (CRF), exercise regularity, temper, and quality of life. Hence, it appears that even using placebos will improve dopaminergic systems, as also found in the present study. These findings have important implications for the use of placebo interventions in managing cancer symptoms [20].

A combination of ceramic biomaterials and PBM increased bone repair and regeneration in experimental models of bone lesions in 16 investigations employing animal models [21]. In addition, PBM therapy at a dose of 4 J/cm² improved the overall healing dynamics of diabetes-induced neuropathic wounds in Wistar rats [22]. Furthermore, when used between two rounds of different types of exercise and sports, PBMT can reduce skeletal muscle exhaustion, as measured by the fatigue index, speed up recovery after exercise, and improve physical performance [23].

The results of ongoing clinical trials on may provide an insight into the effectiveness of PBMT in improving breathing, inflammation, blood clotting and various morbidity-mortality parameters in patients.

Conclusions

The use of low-level laser PBM therapy in the elderly following COVID-19 appears to increase functional performance, ADL activities and fatigue perception, thus influencing the various physical, psychological, and mental components. To independently verify this method, clinical trials and research with larger and more varied sample groups are required, both in terms of prevention and therapy support. Previous research has shown that PBM is helpful in lowering inflammation, boosting immunity, and increasing peripheral and

central blood flow, making it a prospective treatment for unfavorable post-COVID-19 health outcomes.

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Conflicts of Interest

The authors have no conflict of interest to declare.

References

1. River-Lillo G, Torres-Castro R, Puppo H, Vilaro J. Comment on: Early rehabilitation in post-acute coVid-19 patients: Data from an italian coVid-19 rehabilitation unit and proposal of a treatment protocol. *Eur J Phys Rehabil Med.* 2021; 57(1): 171 – 2.
2. SJ Y. Long COVID or post-COVID19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond).* 2021; 53(10): 737-54.
3. Osikomaiya B, Erinoso O, Wright KO, Odusola AO, Thomas B, Adeyemi O, et al. 'Long COVID': persistent COVID-19 symptoms in survivors managed in Lagos State, Nigeria. *BMC Infect Dis.* 2021; 21(1): 304.
4. Sanchez-Ramirez DC, Normand K, Zhaoyun Y, Torres-Castro R. Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. *Biomedicines.* 2021; 9(8): 900.
5. Vahia IV, Jeste DV, Reynolds CF. Older Adults and the Mental Health Effects of COVID-19. *JAMA.* 2020; 324(22): 2253-4.
6. Curci C, Pisano F, Negrini F, DE Sire A. Authors' reply to: Rivera-lillo et al. Comment on: Early rehabilitation in post-acute coVid-19 patients: Data from an italian COVID-19 rehabilitation unit and proposal of a treatment protocol. *Eur J Phys Rehabil Med.* 2021; 57(1): 172-3.
7. Fernandes AB, De Lima CJ, Villaverde AGJB, Pereira PC, Carvalho HC, Zângaro RA. PBM: Shining Light on COVID-19. *Photobiomodul Photomed Laser Surg.* 2020; 39(2): 395-7.
8. Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A, et al. PBM-Underlying Mechanism and Clinical Applications. *J Clin Med.* 2020; 9(6): 1724.
9. Juanita j. Anders. Photobiomodulation [Internet]. United States: American Society for Laser Medicine and Surgery; 2016 [cited 2021 Aug 25]. Available from: <https://www.aslms.org/for-the-public/treatments-using-lasers-and-energy-based-devices/PBM>
10. Liebert A, Bicknell B, Markman W, Kiat H. A Potential Role for PBM Therapy in Disease Treatment and

- Prevention in the Era of COVID-19. *Aging Dis.* 2020; 11(6): 1352-62.
11. Feng C, He Q, Wu Y, Hu X, Wu J, He X, et al. Psychometric properties of fatigue severity scale in Chinese systemic lupus erythematosus patients. *Health Qual Life Outcomes.* 2019; 17(1): 1-6.
 12. Reijneveld SA, Spijker J, Dijkshoorn H. Katz' ADL index assessed functional performance of Turkish, Moroccan, and Dutch elderly. *J Clin Epidemiol.* 2007; 60(4): 382-8.
 13. Tomazoni SS, Machado CDSM, De Marchi T, Casalechi HL, Bjordal JM, De Carvalho PDTC, et al. Infrared Low-Level Laser Therapy (PBM Therapy) before Intense Progressive Running Test of High-Level Soccer Players: Effects on Functional, Muscle Damage, Inflammatory, and Oxidative Stress Markers – A Randomized Controlled Trial. *Oxid Med Cell Longev.* 2019; 2019: 6239058.
 14. das Neves MF, dos Reis MCR, de Andrade EAF, Lima FPS, Nicolau RA, Arisawa EÂL, et al. Effects of low-level laser therapy (LLLT 808 nm) on lower limb spastic muscle activity in chronic stroke patients. *Lasers Med Sci.* 2016; 31(7): 1293-1300.
 15. Mokmeli S, Vetrici M. Low level laser therapy as a modality to attenuate cytokine storm at multiple levels, enhance recovery, and reduce the use of ventilators in COVID-19. *Can J Respir Ther.* 2020; 56: 25-31.
 16. Enwemeka CS, Bumah VV, Masson-Meyers DS. Light as a potential treatment for pandemic coronavirus infections: A perspective. *J Photochem Photobiol B.* 2020; 207: 111891.
 17. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 Fatigue: Potential Contributing Factors. *Brain Sci.* 2020; 10(12): 1-7.
 18. Toma RL, Oliveira MX, Renno ACM, Laakso EL. Effects of PBM on the fatigue level in elderly women: an isokinetic dynamometry evaluation. *Lasers Med Sci.* 2016; 31(2): 275-82.
 19. Lin YP, Su YH, Chin SF, Chou YC, Chia WT. Light-emitting diode PBM therapy for non-specific low back pain in working nurses: A single-center, double-blind, prospective, randomized controlled trial. *Medicine (Baltimore).* 2020; 99(32): e21611.
 20. da Silva MM, Albertini R, de Tarso Camillo de Carvalho P, Leal-Junior ECP, Bussadori SK, Vieira SS, et al. Randomized, blinded, controlled trial on effectiveness of PBM therapy and exercise training in the fibromyalgia treatment. *Lasers Med Sci.* 2017; 33(2): 343-51.
 21. Alves VMN, Furlan RMM, Motta AR. Immediate effects of PBM with low-level laser therapy on muscle performance: an integrative literature review. *Rev. CEFAC.* 2019; 21(4): 1-9.
 22. Rossato M, Dellagrana RA, Sakugawa RL, Baroni BM, Diefenthäler F. Dose-Response Effect of PBM Therapy on Muscle Performance and Fatigue During a Multiple-Set Knee Extension Exercise: A Randomized, Crossover, Double-Blind Placebo-Controlled Trial. *Photobiomodul Photomed Laser Surg.* 2020; 38(12): 758-65.
 23. Schardong J, Falster M, Sisto IR, Barbosa APO, Normann TC, de Souza KS, et al. PBM therapy increases functional capacity of patients with chronic kidney failure: randomized controlled trial. *Lasers Med Sci.* 2020; 36(1): 119-29.
 24. Almeida JN, Prado WL, Terra CM, Oliveira MG, Garcia RA, Pinfieldi CE, et al. Effects of PBM on muscle strength in post-menopausal women submitted to a resistance training program. *Lasers Med Sci.* 2019; 35(2): 355-63.
 25. Stamborowski SF, Lima FPS, Leonardo PS, Lima MO. A Comprehensive Review on the Effects of Laser PBM on Skeletal Muscle Fatigue in Spastic Patients. *Int J Photoenergy.* 2021; 2021: 1-13.
 26. Zhou ES, Hall KT, Michaud AL, Blackmon JE, Partridge AH, Recklitis CJ. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. *Support Care Cancer.* 2018; 27(6): 2179-87.
 27. Magri AMP, Parisi JR, de Andrade ALM, Rennó ACM. Bone substitutes and PBM in bone regeneration: A systematic review in animal experimental studies. *J Biomed Mater Res Part A.* 2021; 109(9): 1765-75.
 28. Karkada G, Maiya GA, Arany P, Rao M, Adiga S, Kamath SU. Effect of PBM Therapy on Oxidative Stress Markers in Healing Dynamics of Diabetic Neuropathic Wounds in Wistar Rats. *Cell Biochem Biophys.* 2022; 80(1): 151-60.
 29. Aleixo-Junior I de O, Leal-Junior ECP, Leal-Junior ECP, Leal-Junior ECP, Casalechi HL, Vanin AA, et al. Immediate effects of PBM therapy combined with a static magnetic field on the subsequent performance: a preliminary randomized crossover triple-blinded placebo-controlled trial. *Biomed Opt Express.* 2021; 12(11): 6940-53.