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ORIGINAL ARTICLE

Photobiomodulation therapy increases functional capacity of patients with chronic kidney failure: randomized controlled trial

Jociane Schardong[1] · Mariana Falster[1] · Isadora Rebolho Sisto[1] · Ana Paula Oliveira Barbosa[1] · Tatiana Coser Normann[1] · Kellen Sábio de Souza[1] · Gabriela Jaroceski[2] · Camila Bassani Bozzetto[1] · Bruno Manfredini Baroni[1] · Rodrigo Della Méa Plentz[1]

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Abstract

Photobiomodulation (PBM) has been used in different populations as a strategy to attenuate muscle fatigue and improve exercise performance. Recent findings demonstrated that a single session with specific PBM doses during hemodialysis (HD) increased the upper limb muscle strength of chronic kidney failure (CKF) patients. Now, the primary objective of this study was to evaluate the chronic effect of PBM on the functional capacity of this population. Secondarily, we aimed at investigating the effects of PBM on the patients' strength, muscle thickness and echogenicity, perception of pain, fatigue, and quality of life. A randomized controlled trial was conducted in which the intervention group (IG, $n = 14$) received 24 sessions of PBM (810 nm, 5 diodes × 200 mW, 30 J/application site) on lower limb during HD. The control group (CG, $n = 14$) did not receive any physical therapy intervention, it only underwent HD sessions. As a result, there was an increase in the functional capacity (assessed through the six-minute walk test) for the IG compared with the CG [50.7 m (CI95% 15.63; 85.72), $p = 0.01$, large effect size, d = 1.12], as well as an improvement on lower limb muscle strength (assessed through the sit-and-stand test) [− 7.4 s (CI95% − 4.54; − 10.37), $p = 0.00$, large effect size, $d = 1.99$]. For other outcomes evaluated, no significant difference between-group was observed. Finally, PBM applied as monotherapy for 8 weeks in the lower limb improves functional capacity and muscle strength of CKF patients.

Keywords Renal insufficiency, chronic · Renal dialysis · Low-level light therapy · Randomized controlled trial

Introduction

Chronic kidney failure (CKF) causes systemic manifestations that also affect muscular homeostasis [1]. The muscle fibers of patients with CKF present morphological and functional alterations possibly due to chronic uremia and to the state of metabolic acidosis. These changes include a reduced number of capillaries and contractile proteins, increased cellular oxidation, and enzymatic modifications [2].

Muscle atrophy, particularly of type II fibers [2], is highly prevalent in CKF patients undergoing hemodialysis (HD) [3] and associated with other comorbidities such as cardiovascular diseases [4], bone mineral disease [5], anemia [6], and peripheral neuropathy [7] is responsible for the reduction of physical capacity [8] and functional independence [9], as well as for the increase in mortality rates in this population [10]. Moreover, muscle atrophy specifically implies a reduction of peripheral muscle strength, increased fatigue, and reduced functional capacity, leading to a sedentary lifestyle and worse quality of life [11].

Photobiomodulation (PBM) therapy, through low-level laser (LLL) and light-emitting diodes (LEDs), has demonstrated largely positive effects on the improvement of muscle performance and on the delay in fatigue time in healthy individuals and athletes [12]. Mechanisms are not fully understood but are presumed to be related to increased cytochrome c oxidase (CCO) enzyme activity and local blood flow [13], minimizing oxidative stress [14] and accelerated lactate removal [15].

✉ Jociane Schardong
joci_fisioufsm@yahoo.com.br

[1] Physiotherapy Department, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite, 245, Porto Alegre, Rio Grande do Sul, Brazil

[2] Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil

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Wang et al., [16] in an experiment on healthy subjects, demonstrated that the positive regulation of the CCO induced by laser leads to a linear increase in the oxygenated hemoglobin (HbO) concentration according to an energy dose accumulated over time. As the CCO enzyme is the main photoreceptor of LLL, positive regulation of CCO will increase electron transport and enzyme activity and result in a significant increase in the rate of oxygen consumption in tissue mitochondria, production of adenosine triphosphate (ATP), and photodissociation of nitric oxide [16–18]. Consequently, there will be an increase in the hemodynamic oxygen supply and in the total blood volume around the irradiated area due to the need for more oxygen and electrons [16].

Regarding patients with CKF, a randomized crossover trial recently published [19] demonstrated for the first time the acute effect of PBM during HD. The findings of this study suggested that a single session with specific dosages of infrared PBM increased the palmar grip strength of such patients. Those promising results have led us to believe that long-term intervention with PBM on the key locomotor muscles could be beneficial for patients.

Thus, the primary objective of this study was to evaluate the effect of PBM on the functional capacity of CKF patients undergoing HD. Secondarily, we aimed at investigating the effects of PBM on the patients' strength muscle thickness and echogenicity, perception of pain, fatigue, and quality of life.

Methods

Design and ethical issues

This study is characterized as a randomized controlled trial (RCT), and it was performed with CKF patients during HD session. Functional capacity was considered the primary outcome, and lower limb strength, quadriceps muscle thickness and echogenicity, perception of pain, fatigue, and quality of life were considered secondary outcomes. The project was approved by the Human Research Ethics Committees of the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) hospital and of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFSCPA) (CAAE: 65845317.1.0000.5335; report number: 2.030.610) and thus implemented in accordance with the ethical standards of the Declaration of *Helsinki* (1964), revised in 2013 in Brazil. Informed consent was obtained from all patients prior to any procedure, and the project was registered in the ClinicalTrials.gov system (NCT03250715 identifier) before data collection began.

Participants

Patients with CKF on HD for a period equal to or greater than 3 months, of both sexes, aged between 18 and 80 years old, adequate urea clearance (URR $\geq 65\%$) and weekly dialysis frequency of three times/week were included in the study. Exclusion criteria were cognitive dysfunction that prevented performing the evaluations, as well as inability to understand the informed consent form; epidermal lesions at the site of PBM application; patients with active carcinoma, stroke sequelae; recent acute myocardial infarction (2 months); uncontrolled hypertension (SBP > 230 mmHg and DBP > 120 mmHg); IV grade heart failure according to the *New York Heart Association* or decompensated; unstable angina; deep venous thrombosis in the lower limb; incapacitating osteoarticular or musculoskeletal disease; uncontrolled diabetes (glycemia > 300 mg/dL); febrile state and/or infectious disease; and smokers.

Procedures

All the patients from the HD outpatient of Santa Clara hospital at ISCMPA were invited verbally to participate in the study, and electronic records were consulted to check the eligibility criteria for the interested volunteers. When a patient was included, an interview was conducted prior to assessments to collect identification and demographic data, risk factors for chronic kidney disease (CKD), and anthropometric characteristics. Hospital records were used to assess biochemical profile, primary disease, and medications used.

After randomization (see details next), the patients were evaluated before and after the 8-week treatment with PBM for the IG or the same period for CG and prior to the second weekly dialysis session, always by the same evaluator.

All the procedures were performed between October 2017 and September 2018 at the ISCMPA dialysis unit.

Randomization

Eligible patients were randomized (1:1 allocation ratio) into two groups: intervention group (IG) or control group (CG). Randomization occurred through the www.random.org website. The sequence of numbers was generated by a researcher "blinded" to the study, and it was kept confidential until the beginning of the intervention to guarantee the concealment of the allocation. Patients allocated to the IG were engaged in an 8-week treatment with PBM concurrently with the HD sessions, while CG patients performed only the regular HD.

Functional capacity evaluation

The six-minute walking test (6MWT) was used to evaluate functional capacity following the recommendations of the *American Thoracic* Society [20]. The patient was instructed to walk as far as possible, for 6 min, in a 30-m corridor, and the distance covered was recorded in meters. Every minute, the patient was verbally encouraged by standard phrases. Vital signs were checked at the beginning and end of the test as a safety measure.

Muscle strength evaluation

The muscle strength of the lower limb was evaluated by the sit-and-stand test (SST10). The SST10 is an indirect and functional measure to quantify the muscle strength [21], and it was performed in a chair without arms, 44.5 cm high and 38 cm deep [22]. The patient began the test seated, arms crossed in front of the chest, and back resting on the chair. The patient was instructed to stand up and return to the seated position as soon as possible in order to perform 10 complete and consecutive repetitions, being verbally encouraged [23]. The time to perform the 10 repetitions was recorded by the evaluator.

Muscle structure evaluation

Ultrasound images of the vastus lateralis (VL), rectus femoris (RF), and vastus medial (VM) muscles were acquired through a high-resolution ultrasound device (Vivid-i, GE, Stamford, CT, USA) by a single experienced examiner.

The midpoint between the greater trochanter and the lateral condyle of the femur was used as a reference point to evaluate the VL and RF, while measurements of the VM were performed at 25–30% of this distance, according to the characteristics of the patients [24]. Three images were obtained with the ultrasound transducer longitudinally positioned on the muscle fibers of each of the knee extensor muscles to evaluate the muscle thickness [25], and three images were obtained with the transducer positioned transversally on the RF to evaluate echogenicity [26]. A bubble level was attached to the ultrasound probe to ensure a minimum inclination during data collection of the echogenicity [26].

To standardize the measurement sites, the anatomical points were marked on plastic sheets and the measurements. All images were subsequently analyzed using the ImageJ software (National Institutes of Health, Bethesda, MD, USA). The mean value of each outcome obtained from the three recorded ultrasound images was considered for subsequent statistical analysis [24].

Perception of pain and fatigue evaluation

The visual analogue scale (VAS) was used to evaluate the perception of muscle pain in the lower limb. The patient was asked about the intensity of their pain within a range of 0 to 10, where 0 indicates no pain and 10 maximum pain [27]. The modified Borg effort perception scale was used to evaluate the lower limb fatigue. On this scale, 0 indicates no effort and 10 indicates maximum effort [28]. Both scales were applied before and immediately after the 6MWT.

Quality of life evaluation

Two questionnaires were used to evaluate the quality of life.

The *EuroQol-5D health questionnaire* (EQ-5D) is a generic instrument for measuring quality of life. It evaluates mobility, personal care, habitual activities, pain/discomfort, and anxiety/depression, and it allows to generate a general index of the value of an individual's health status. Number 1 indicates the best state of health (perfect health) and 0 the worst state of health (death) [29].

The *Kidney Disease and Quality-of-Life Short-Form questionnaire* (KDQOL-SF™) includes specific items about CKD and the SF-36 questionnaire. The specific part about kidney disease includes 43 items divided into 11 dimensions, and the SF-36 consists of 36 items, divided into eight dimensions. A score between 0 and 100 is generated for each category and higher scores corresponding to a better quality of life status [30].

The patients completed the questionnaires during the HD session, and the physiotherapist only helped when there were doubts.

Intervention

PBM was applied as monotherapy between the 2nd and 3rd hour of the HD session, three times/week, for 8 weeks (i.e., 24 sessions). The patients were positioned in dorsal decubitus, with the knees on a foam wedge on the dialysis armchair. The PBM was applied with a properly calibrated probe cluster, containing five LLL diodes (Thor® Photomedicine, DD2, London/UK). PBM was applied at six points demarcated in the quadriceps (two points in the distal region of the VL muscle, two points in the center of the RF muscle, and two points in the distal region of the VM muscle) and two points in the gastrocnemius muscle, bilaterally [31, 32]. The PBM application sites were copied on plastic sheets after the first session in order to ensure that the other applications were performed at same sites. The patella was considered as a reference for making the map. The treatment was performed with the probe fixed in contact with the skin, at an angle of 90° and the parameters described in Chart 1 [12]. The patients and the physiotherapist used antiradiation goggles during the PBM applications, and vital signs were monitored as a safety measure.

Statistical analysis

The sample calculation was based on an RCT conducted with patients with CKF on HD [33]. To calculate the difference of the means and standard deviations between the groups, the distance walked in the 6MWT was used and an alpha error

Chart 1 Parameters for PBM application on the lower limb

Parameter	
Wavelength	810 nm
Output power (cluster)	1000 mW
Output power (per diode)	200 mW
Total area of the cluster	8.5 cm^2
Beam area	0.029 cm^2
Power density (cluster)	34.5 W/cm^2
Power density (per diode)	6.9 W/cm^2
Dose (cluster)	30 J/application site
Dose (per diode)	6 J
Density (cluster)	1034.5 J/cm^2
Density (per diode)	206.9 J/cm^2
Time of application	30 s
Emission mode (frequency)	Continuous
Total dose (per leg)	240 J
Total dose (quadriceps)	180 J
Total dose (gastrocnemius)	60 J

of 5% and power of 80% were adopted, resulting in 14 patients per group.

Statistical analysis was performed using SPSS software version 23. Distribution normality was checked using the *Shapiro-Wilk* test. The baseline characteristics of the patients were compared by Student's *t* test for independent samples or by the Mann-Whitney test according to the distribution normality. Categorical variables were compared by the chi-square test. To evaluate the within-group effect, we used the paired Student's *t* test or Wilcoxon's test. To verify the between-group effect, we used the Student's *t* test for independent samples or the Mann-Whitney test to compare the difference between the pre and post intervention assessments. The estimate of the intervention effect on the outcomes was analyzed using Cohen's d, where < 0.2 represents a trivial effect, > 0.2 a small effect, > 0.5 a moderate effect, and 0.8 a large magnitude of effect [34]. The significance level adopted was 5% ($p < 0.05$), and the analysis was performed by protocol.

All analyses were conducted by a researcher blind to the study procedures (randomization, evaluations, and intervention).

Results

Thirty-six patients with CKF on HD were evaluated for eligibility and possible admission into the study. Twenty-eight met the inclusion criteria and finalized the protocol. Admission of the patients and group composition are detailed in Fig. 1.

Table 1 shows that demographic, anthropometric, clinical, and biochemical data, as well as primary disease and risk factors for CKD, were similar for IG and CG. No difference was found in baseline values for the functional capacity, strength, muscle thickness, echogenicity, perception of pain, and fatigue (Table 2). Quality of life, with the exception of the dialysis team stimulation domain ($p = 0.02$) of the KDQOL-SF™ questionnaire, also did not differ between groups at baseline (Table 3).

Functional capacity increased for the treated group after 8 weeks of PBM therapy ($p = 0.00$), but the same was not observed for GC ($p = 0.67$). When comparing the two groups, there was a significant difference of 50.7 m (CI95% 15.63; 85.72; $p = 0.01$) in the distance covered in the 6MWT favorable to the IG (Table 2; Fig. 2).

In relation to lower limb muscle strength, IG showed a significant reduction in the time to perform the 10 repetitions of the SST after therapy ($p = 0.00$). CG did not show any change in this outcome over 8 weeks ($p = 0.61$). Still, there was a significant difference that was favorable to the IG [−7.4 s (CI95% -4.54; − 10.37), $p = 0.00$] when the two groups were compared (Table 2; Fig. 3).

Regarding the muscle architecture of the femoral quadriceps, the CG presented a reduction in the thickness of the VM muscle ($p = 0.03$) over 8 weeks. There were no significant changes for the other muscles in relation to thickness (CG—Right VL: $p = 0.06$; Left VL: $p = 0.97$; Right RF: $p = 0.05$; Left RF: $p = 0.93$; Left VM: $p = 0.64$; IG—Right VL: $p = 0.98$; Left VL: $p = 0.49$; Right RF: $p = 0.36$; Left RF: $p = 0.67$; Right VM: $p = 0.26$; Left VM: $p = 0.29$) and neither for the echogenicity of the RF muscle (CG—Right RF: p = 0.29; Left RF: $p = 0.40$; IG—Right RF: $p = 0.65$; Left RF: $p = 0.62$) in any of the groups over time. There was also no difference when CG and IG were compared for the thickness measurements of the right VL ($p = 0.17$), left VL ($p = 0.68$), right RF ($p = 0.35$), left RF ($p = 0.77$), right VM (p = 0.68), left VM ($p = 0.89$), and echogenicity of the right RF (p = 0.65) and left RF ($p = 0.83$) after treatment (Table 2).

Regarding the perception of pain in the lower limb after the 6MWT, there was a tendency to reduce the pain numerical score for the treated group, but this was not significant ($p = 0.22$). On the other hand, CG presented a significant increase in pain levels ($p = 0.03$) over time. When compared, the groups did not present a different behavior for this outcome ($p = 0.09$) (Table 2).

The perception of fatigue in the lower limb after the 6MWT did not change over time for the CG ($p = 0.15$) and for the IG ($p = 0.10$) even when one group is compared with the other ($p = 0.05$) (Table 2).

There was improvement in quality of life when evaluated by the EQ-5D questionnaire for the group that received PBM therapy after 8 weeks of treatment ($p = 0.01$). The same did not occur with CG ($p = 0.49$). There were also no significant differences between IG and CG ($p = 0.08$) at the end of the protocol (Table 3).

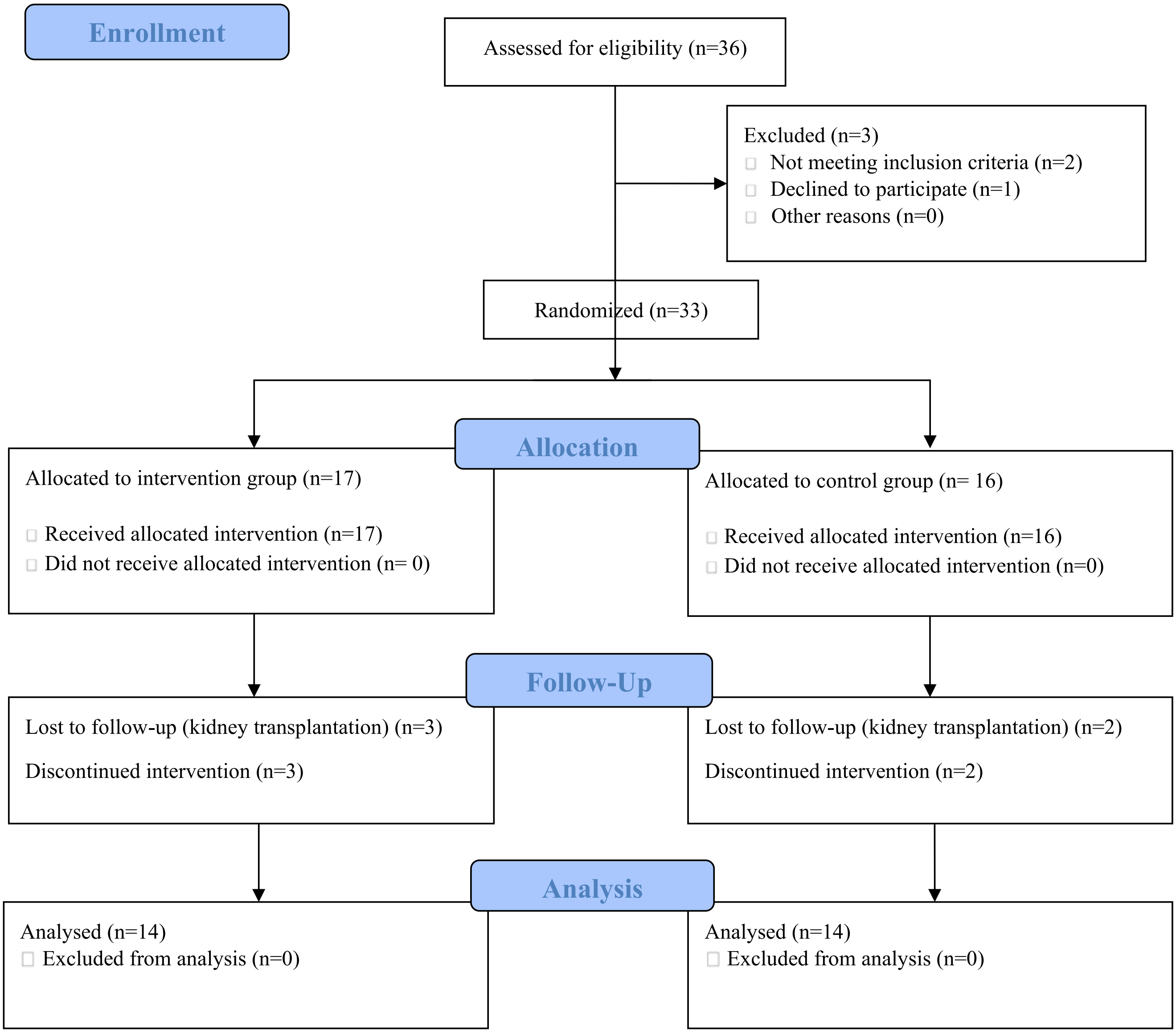

Fig. 1 Flowchart of patients' admission and group composition

When the quality of life was evaluated by the KDQOL-SF™ questionnaire, an increase was observed for emotional wellness (IG: $p = 0.03$; CG: $p = 0.09$), social functioning (IG: $p = 0.01$; CG: $p = 0.24$), and vitality (energy/fatigue) (IG: $p = 0.00$; CG: $p = 0.45$) domains only for the IG over time. For the pain domain, both groups improved after 8 weeks of follow-up (IG: $p = 0.00$; CG: $p = 0.01$). There were no significant differences between groups for any of the dimensions of the KDQOL-SF™ (Table 3).

Regarding the safety of this therapy, no changes were observed in patients' vital signs and adverse effects during laser applications, as well as in the interval between them. The adherence of the patients to the protocol was considered satisfactory since there were no losses due to intolerance to PBM.

Discussion

This study demonstrated for the first time that PBM therapy when applied as monotherapy for 8 weeks in the quadriceps and gastrocnemius muscles increases functional capacity and lower limb muscle strength. Furthermore, PBM seems to modulate the perception of pain and to improve specific aspects of the quality of life of patients with CKF on HD without a relevant effect on fatigue and muscle structure.

Our findings showed that PBM with LLL increased the distance covered by the 6MWT by 50.7 m when compared with the CG, ensuring a large effect size ($d = 1.12$) and an improvement in functional capacity. On the other hand, Stein et al. [35] applied LLL on the quadriceps muscle of patients with heart disease, with wavelength (850 nm),

Table 1 Characteristics of patients admitted to the study

	Control group ($n = 14$)	Intervention group ($n = 14$)
Sex (F/M)	7/7	5/9
Age (years)	58.1 ± 16.9	53.0 ± 17
Dry weight (kg)	67.6 ± 12.9	67.1 ± 15
Wet weight (kg)	70.5 ± 13.7	69.3 ± 15.5
BMI (kg/m^2)	25.5 ± 5.1	24.6 ± 4.4
HD time (months)	32 (11.8–70.3)	48 (8.8–105)
URR (%)	72.5 (69.2–76.6)	74.6 (65–77.1)
Primary disease		
Glomerulonephritis	2	0
Hypertension	4	2
Diabetes mellitus	1	2
FSG	0	2
Polycystic kidney disease	0	1
Nephrolithiasis	2	2
Other	4	1
Unknown	1	4
Risk factors		
Ex-smoker	1	1
Hypertension	13	13
Sedentary lifestyle	12	12
Diabetes mellitus	4	2
Heart disease	1	6
FH heart disease	0	3
Peripheral vascular disease	1	1
Serum biochemistry		
Predialysis urea (mg/dL)	144.3 ± 34.5	171.1 ± 45.6
Postdialysis urea (mg/dL)	40.5 ± 13.4	45.4 ± 23.1
Creatinine (mg/dL)	9.3 ± 2.6	10.4 ± 3.3
Albumin (mg/dL)	4.0 ± 0.3	3.9 ± 0.3
Hemoglobin (g/dL)	11.2 ± 1.7	10.7 ± 1.4
Hematocrit (%)	34.3 ± 5.8	33.5 ± 4.9

Data are expressed as mean ± standard deviation; median and interquartile range (P25–P75) or frequency

F female, *M* male, *BMI* body mass index, *HD* hemodialysis, *URR* urea reduction rate, *FSG* focal segmental glomerulosclerosis, *FH* family history

number of application sites (8 sites), and dose (30 J/site) very similar to those defined in our study, and the authors did not find significant results for this outcome. Although populations (chronic kidney and cardiac disease patients) have similar physical and functional limitations, the absence of positive effects in this study may be related to the volume of application (a single application vs 24 applications). Also, unlike the present study, we chose to radiate the gastrocnemius muscle beyond the quadriceps since it also plays an important role in gait [12], which may have contributed to the increase in distance covered in the 6MWT.

Corroborating our findings, Melo et al. [36] used LLL (810 nm, 200 mW, 4–6 J/site, 6 application sites) in elderly women with osteoarthritis of the knee and, even using a lower dose, they also obtained an increase in the distance covered in the 6MWT after 8 weeks of intervention (2 times/week, 16 applications).

Functional capacity was considered the primary outcome of this study since it is an independent predictor of mortality. In chronic kidney patients, a distance equivalent to 100 m in the 6MWT implies a 5.3% increase in the survival rate [37]. In this sense, it can be said that our finding, besides being significant, also has clinical relevance.

The SST10, which consists of an indirect and functional measure of muscle strength and is widely used in clinical practice [21, 38], demonstrated that the PBM has positive effects on this outcome since the IG presented a reduction of 7.4 s to perform the test when compared with the CG, with a large effect size ($d = 1.99$). This result is relevant since the impairment of the physical performance of the lower limb in functional tests is strongly associated with increased mortality in CKD patients [39].

There are studies that demonstrate the increase of muscle strength after a session of PBM in patients with CKF [19] and also when this therapy was used for a long period (chronic effect) but associated with exercise in other populations [40]. This agrees with our results; however, this was the first study to demonstrate the positive effect of PBM on lower limb muscle strength when radiation is applied for a long time and as monotherapy in CKF patients.

As expected, muscle structure did not show changes after PBM, except for the reduction of right VM thickness to CG over time; however, this can be attributed to chance or to the sensitivity of the ultrasound technique. According to the literature and to the best of our knowledge, PBM induces changes in the enzymatic metabolism of cellular mitochondria (oxidase c cytochrome way) but no structural alterations [13]. Thus, a possible effect on muscle structure could occur indirectly since by improving the functional capacity of this patient, he could become more active. Still, neuromuscular electric stimulation [41] or physical exercise may be more specific strategies to avoid muscle atrophy, which is a process inherent of CKD. In addition, the absence of findings regarding echogenicity is probably related to the volumetric variation that this patient suffers weekly as result of the HD sessions.

Regarding the perception of pain outcome, there was a tendency to reduce it in the group that received to PBM therapy, but not significantly. On the other hand, an increase in the pain threshold in the lower limb during the follow-up was presented for CG with a large effect size ($d = 1.59$). The findings suggest a likely protective effect of LLL for pain of the lower limb, although there was no significant difference between the groups after 8 weeks of treatment.

Table 2 Values for functional capacity, strength, pain perception, fatigue, muscle thickness and echogenicity before and after PBM

	Control group (n = 14)			Intervention group (*n* = 14)			
	Pre	Post	d1	Pre	Post	d1	d2
Functional capacity							
6MWT (m)	440.3 ± 76.2	446.1 ± 79.3	0.12	428.5 ± 104.9	485 ± 106.9**	1.41	1.12
Muscle strength							
SST10 (s)	24.8 ± 6.2	24.3 ± 7.2	0.14	27 ± 7.7	19.1 ± 5.0**	1.88	1.99
Muscle thickness							
Right VL (cm)	1.38 ± 0.25	1.28 ± 0.30	0.54	1.45 ± 0.35	1.45 ± 0.25	0.01	0.54
Left VL (cm)	1.28 ± 0.35	1.27 ± 0.29	0.01	1.47 ± 0.34	1.49 ± 0.34	0.19	0.01
Right RF (cm)	0.86 ± 0.18	0.76 ± 0.25	0.56	0.92 ± 0.33	0.88 ± 0.29	0.26	0.36
Left RF (cm)	0.78 ± 0.22	0.77 ± 0.27	0.02	0.80 ± 0.28	0.78 ± 0.27	0.12	0.11
Right VM (cm)	1.04 ± 0.33	0.94 ± 0.28 *	0.63	1.12 ± 0.45	1.05 ± 0.31	0.32	0.16
Left VM (cm)	1.09 ± 0.27	1.07 ± 0.33	0.13	1.04 ± 0.31	1.00 ± 0.32	0.29	0.05
Echogenicity							
Right RF (a.u)	63.71 ± 22.11	59.70 ± 17.81	0.29	65.92 ± 19	64.29 ± 22.44	0.12	0.18
Left RF (a.u)	65.72 ± 21.56	62.09 ± 22.11	0.23	66.04 ± 24.67	63.77 ± 23.97	0.14	0.08
Pain	0 (0–2.5)	3 (0.75–4.25) *	1.59	3 (0–5)	0 (0–5.25)	0.80	0.47
Fatigue	2.5 (0–3.25)	3 (1–4)	0.19	3 (2–5)	1.5 (0–4.25)	0.58	0.95

Data are expressed as mean ± standard deviation or median and interquartile range (P25–P75). *: within group difference; **: within and between difference; Significance level $p < 0.05$

6MWT six-minute walking test, SST10 sit-and-stand test of 10 repetitions, VL vastus lateralis, RF rectus femoris, VM vastus medialis, d1 effect size for within group difference, d2 effect size for difference between groups

* Within group difference; ** within and between difference

Melo et al. [36] performed 16 applications of LLL (810 nm; 4–6 J/point) to the knees of elderly women with osteoarthritis and observed a reduction in the VAS score after the 6MWT. On the other hand, Vanin et al. [42] in a study with athletes performed only one laser application on the quadriceps muscle, prior to a resistance exercise protocol, and they did not obtain a reduction of pain levels. It is reiterated that the wavelength (810 nm) and the dose (30 J/site) used by Vanin et al. [42] are the same as those adopted in our study; however, the authors did not use only the VAS but also the algometer to measure this outcome. Based on this evidence, it is believed that for the perception of pain, the parameters adopted were not the only determinants. Besides the population evaluated, the measurement instrument (subjective scale) and application volume may influence the results.

The perception of fatigue was also evaluated in our study using numerical scale, and significant alterations were not identified after PBM treatment for this outcome. However, the effect size was considered large when the two groups were compared ($d = 0.95$), indicating a tendency to reduce the perception of fatigue in the IG and increase in the CG.

Corroborating our findings, Miranda et al. [43], in a study evaluating the effect of LEDs (660 and 850 nm; 41.7 J/application site) on the quadriceps muscle function of COPD patients, did not observe any change in the perception of fatigue after isometric exercise when it was evaluated using the modified Borg's scale of effort perception. On the other hand, the endurance time assessed through a loading cell increased after PBM compared with the sham group. Therefore, once again, the subjectivity of the evaluation instrument adopted in our study can influence the results.

Although the modified Borg's scale of effort perception is not a direct measure of fatigue, we cannot refute that the findings regarding this outcome may also be related to the parameters adopted. In a later study, Miranda et al. [32] used the same scale to measure fatigue in patients with COPD and obtained significant results for this outcome. However, two light sources (LLL and LEDs) with different wavelengths (LLL: 905 nm, LEDs: 875 and 640 nm) were used simultaneously, which could be a hypothesis for the improvement of fatigue.

When the patients were evaluated by EQ-5D questionnaire, IG showed a significant improvement of quality of life after 8 weeks of PBM with a large effect size ($d = 0.84$). There was no difference between groups for this outcome at the end of the follow-up; however, the effect size was considered moderate ($d = 0.69$), indicating a tendency for improvement favorable to the treated group.

Table 3 Values for quality of life before and after intervention with PBM

	Control group (n = 14)			Intervention group (n = 14)			
	Pre	Post	d1	Pre	Post	d1	d2
EQ-5D index	0.636 ± 0.15	0.658 ± 0.12	0.19	0.604 ± 0.17	0.713 ± 0.16*	0.84	0.69
KDQOL-SF™							
- Symptoms /Problems	71.9 (62–81.3)	71.9 (64.6–79.7)	0.11	75.9 (59.9–89.1)	81 (72.4–90.1)	0.33	0.21
- Effects of CKD on daily life	75 (81.3–79.7)	70.3 (61.7–82)	0.04	67 (53.1–85.2)	71 (58.6–82)	0.19	0.14
- Burden imposed by the CKD	37.5 (18.8–45-3)	50 (29.7–64.1)	0.52	46.4 (25–70.3)	50.4 (29.7–71.9)	0.15	0.29
- Work status	0 (0–50)	0 (0–50)	0.10	32.1 (0–50)	35.7 (0–62.5)	0.27	0.00
- Cognitive function	86.7 (71.7–100)	90 (80–100)	0.08	73.8 (58.3–100)	81.4 (71.7–88.3)	0.54	0.30
- Quality of social interactions	80 (63.3–88.3)	80 (70–95)	0.21	71.4 (53.3–88.3)	79 (56.7–95)	0.43	0.17
- Sexual function	100 (50–100)	100 (0–100)	0.46	73.2 (75–100)	55.4 (0–100)	0.26	0.17
- Sleep	62.5 (46.9–86.3)	62.5 (46.9–75.6)	0.14	73.9 (56.3–90.6)	80.4 (66.9–98.1)	0.49	0.53
- Social support	66.7 (12.5–100)	66.7 (58.3–100)	0.15	71.4 (62.5–100)	82.1 (62.5–100)	0.32	0.09
- Dialysis staff encouragement	68.8 (40.6–87.5)#	87.5 (43.8–100)	0.20	87.5 (84.4–100)#	75 (75–100)	0.32	0.50
- Patient satisfaction	58.3 (50–87.5)	66.7 (50–100)	0.16	77.4 (66.7–83.3)	81 (66.7–87.5)	0.20	0.00
+ Physical functioning	60 (42.5–77.5)	55 (38.8–77.5)	0.12	56.4 (40–76.3)	57.5 (33.8–80)	0.07	0.20
+ Physical function	50 (0–56.3)	50 (18.8–100)	0.29	42.9 (0–81.3)	60.7 (25–100)	0.50	0.08
+ Emotional wellness	68 (47–86)	84 (65–89)	0.41	67.1 (49–92)	77.4 (65–89)*	0.56	0.07
+ Social functioning	75 (62.5–100)	93.8 (71.9–100)	0.36	60.7 (37.5–81.3)	80.4 (62.5–100)*	0.79	0.49
+ Mental health	66.7 (25–100)	100 (33–100)	0.37	59.5 (33.3–100)	71.4 (58.3–100)	0.28	0.06
+ Pain	45 (39.4–60)	67.5 (52.5–82.5)*	0.93	54.3 (35–67.5)	76.1 (55–100)*	1.03	0.13
+ Vitality (energy/fatigue)	52.5 (42.5–61.3)	55 (40–70)	0.21	44.3 (23.8–55)	61.8 (48.8–77.5)*	1.18	0.53
+ General health perception	47.5 (38.8–61.3)	47.5 (35–67.5)	0.03	49.6 (28.8–65)	55 (32.5–76.3)	0.32	0.23

Data are expressed as mean ± standard deviation or median and interquartile range (P25–P75). Significance level $p < 0.05$

EQ-5D EuroQol-5D health questionnaire, *KDQOL-SF*™ Kidney Disease and Quality-of-Life Short-Form, *CKD* chronic kidney disease. - specific items on CKD, + general items

* Within group difference; # between group difference

In addition, improvement of some aspects of quality of life was observed over time when patients were evaluated by KDQOL-SF™. There was a significant increase with a moderate effect size for emotional wellness ($d = 0.56$) and social functioning ($d = 0.79$) dimensions for IG, and this can be attributed to the fact that the patient is engaged in a

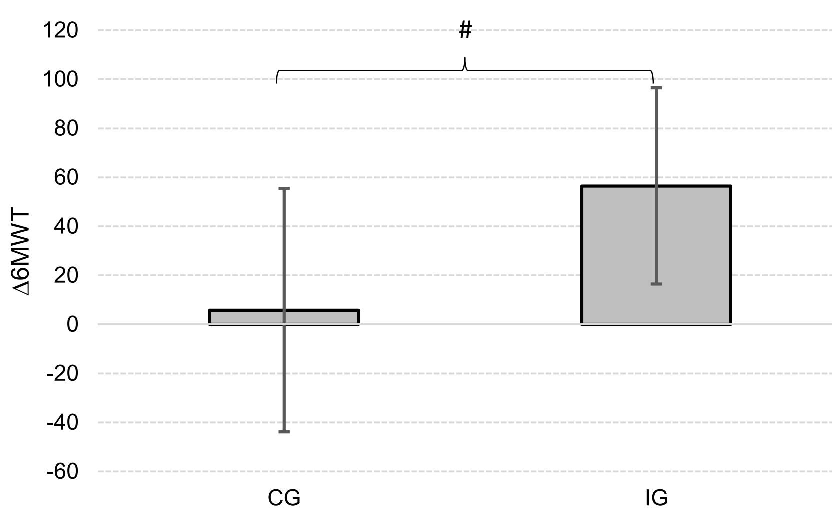

Fig. 2 Mean difference and CI95% for distance covered (meters) in six-minute walk test (6MWT) between control (CG) and intervention (IG) groups after photobiomodulation. Number sign (#): significance level $p = 0.01$

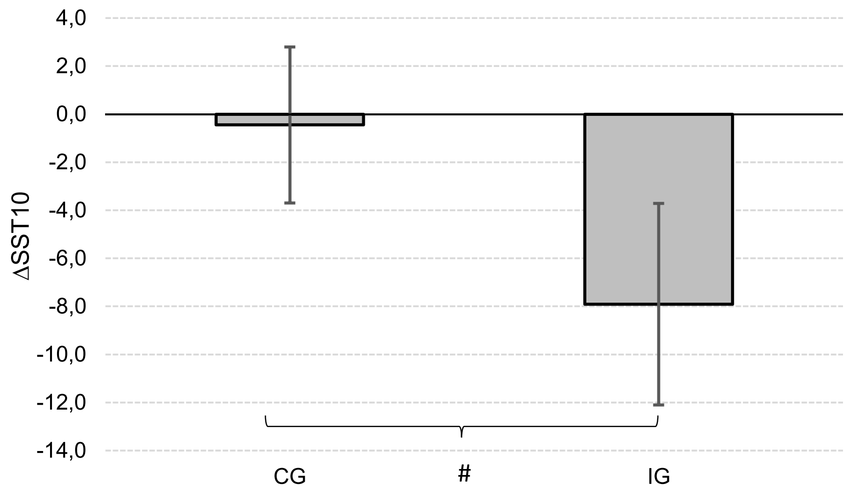

Fig. 3 Mean difference and CI95% for time (seconds) in sit-to-stand test of 10 repetitions (SST10) between control (GC) and intervention (GI) groups after photobiomodulation. Number sign (#): significance level $p = 0.00$

rehabilitation program and feels assisted by the health staff. Furthermore, there was an increase with a large effect size for the pain ($d = 1.03$) and vitality (energy/fatigue) ($d = 1.18$) dimensions. These variables are directly related to the therapeutic effects of PBM (analgesic and anti-inflammatory effect) [44], and therefore the findings are justified. Overall, the absence of significant differences between groups for quality of life can also be related to the intervention time (only 8 weeks) and to the sample size, which was calculated for the primary outcome of this RCT. Finally, another study [45] used different technique for the rehabilitation of this population, and it found results similar to ours for quality of life. This is a complex outcome, and it probably involves more than one approach for relevant changes to occur.

Anyway, the findings in our study are positive and promising, but further studies are needed since the best therapeutic window (dose-response) for the treatment of the lower limb of CKF patients is not yet known. However, the dose used in our study is in accordance with the recommendations proposed by Leal-Junior et al. [46] for large muscle groups when the goal is to improve performance during physical exercise.

Finally, to date, it is believed that the effects of PBM on improving physical performance are due to the increase in the enzymatic activity of oxidase c cytochrome [13], vasodilatation [47], improvement of collateral circulation, increase of the level of oxygen in the tissue, and therefore of ATP in peripheral muscle mitochondria [13]. However, it cannot be ruled out that the therapeutic effects achieved in this study are related to a thermal effect of laser radiation on oxidase c cytochrome, even if minimal, since, it is a low-level laser [48]. In this sense, further investigation is necessary about on thermal effects of this therapy on muscle tissue.

Among the limitations of this RCT are the non-assessment of skin temperature, absence of a placebo comparator, and follow-up to verify the duration of the treatment effect. However, it should be mentioned that biochemical outcomes as mediators of inflammation, oxidative stress, and DNA damage are being analyzed by our group as proposed in the registration protocol (NCT03250715) and will be published in future. These, in turn, can elucidate the findings found in this study, minimizing these fragilities.

Conclusion

PBM therapy when performed for 8 weeks as monotherapy improves the functional capacity and lower limb muscle strength of CKF patients on HD. In addition, it seems to influence the perception of pain and specific aspects of quality of life.

No adverse effects were observed for the use of PBM during the protocol; therefore, it can be considered a safe and prophylactic strategy for the impairment of physical capacity, as well as an adjuvant therapy for a conventional rehabilitation program.

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Authors' contributions Idealization and design: JS, RDMP, BMB. Data analysis/interpretation: JS; RDMP. Writing of article: JS, RDMP. Critical review: RDMP, BMB. Statistical analysis: JS, RDMP. Data collection: JS, MF, IRS, APOB; TCN; KSS; GJ; CBB.

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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: 65845317.1.0000.5335), and the recruitments start only after ClinicalTrials.gov endorsement (NCT03250715).

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