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Effects of light-emitting diode therapy (LEDT) on cardiopulmonary and hemodynamic adjustments during aerobic exercise and glucose levels in patients with diabetes mellitus: A randomized, crossover, double-blind and placebo-controlled clinical trial

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ABSTRACT

The aim of this study was to evaluate the acute effects of light-emitting diode therapy (LEDT) on cardiopulmonary adjustments and muscle oxygenation dynamics during transition to moderate exercise, as well as in glucose and lactate levels in patients with type 2 diabetes mellitus (T2DM). Sixteen individuals with T2DM (age 55.1 ± 5.4 years) performed four separate tests receiving LEDT or placebo in random order, at intervals of at least 14 days. A light-emitting diode array (50GaAIAs LEDs, 850nm, 75mW per diode) was used to perform LEDT bilaterally on the *quadriceps femoris* and *triceps surae* muscles for 40s at each site. After, a moderate cycling exercise was performed and oxygen uptake, muscular deoxyhemoglobin, heart rate and cardiac output were measured. Lactate and glucose levels were measured before LEDT/placebo and after the exercise. The LEDT decreased the glucose levels after the exercise compared with values before LEDT (173.7 ± 61.0 to 143.5 ± 53.5 mg/dl, P = 0.02) and it did not affect the cardiopulmonary and hemodynamic adjustments in exercise, as well as lactate levels in both groups. In conclusion, the LEDT in combination with moderate exercise acutely decreased the glucose levels in men with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia resulting from defects in insulin action, is the most common form of diabetes, accounting for 90–95% of all cases.[1,2] T2DM is associated with many complications including long-term damage, dysfunction and failure of nerves, heart, and blood vessels. Consequently, T2DM is associated with higher incidence of hypertension, atherosclerotic cardiovascular and peripheral vascular disease cases.[1,2]

The glycemic control in T2DM through diet, medication and exercise are key factors in the prevention of long-term disease complications.[3–5] The beneficial effects of regular physical exercise in preventing or delaying the complications associated with T2DM are well documented.[4,6] However, the T2DM patient adherence to exercise programs remains poor. [7,8] Exercise intolerance[9–11] and premature muscular fatigue[11,12] are pointed out as one of the main reasons for this

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low adherence.[8]

By stimulating or inhibiting some chemical functions at cellular level, studies have shown that photobiomodulation (PBM) by low-level laser therapy (LLLT) or light-emitting diode therapy (LEDT) could improve exercise tolerance,[13–15] muscular function, fatigue and resistance [16] in healthy individuals.

PBM applied before exercise may preserve the muscle tissue against exercise-induced damage and accelerate recovery,[16] improve the aerobic power assessed by oxygen consumption ($\dot{V}O_2$) peak[14,17] and local blood flow.[18] Therefore, PBM could be useful for subjects with T2DM to improve muscle function and exercise capacity,[19] increasing their functional capacity and quality of life.[20]

In order to verify whether LEDT can be used as an ergogenic aid in subjects with T2DM, the primary aim of this study was to evaluate the acute effects of LEDT on cardiopulmonary and hemodynamic adjustments during the transition from rest to moderate aerobic exercise. Additionally, the effects of LEDT on glucose and lactate levels were evaluated. We hypothesized that PBM may accelerate the adjustments of oxygen uptake, muscle oxygenation, heart rate and cardiac output, which could lead to better exercise tolerance. In addition, we hypothesized that PBM may reduce glucose and lactate levels, which could be helpful for glycemic control and muscle fatigue.

2. Materials and methods

2.1. Design

This crossover, double-blind, randomized, placebo-controlled clinical trial was approved by the local ethics committee (number 13573013.1.0000.5504) and registered at ClinicalTrials.gov (number NCT01889784). All subjects were informed about the experimental procedures and signed a written term of informed consent.

2.2. Subjects

Sixteen men with T2DM aged between 45 and 64 years participated in the study. All participants were diagnosed with T2DM following American Diabetes Association (ADA) recommendations.[1]

Exclusion criteria were: body mass index (BMI) higher than 35 kg/m^2; smoking; anemia; alcoholism; use of anti-inflammatory or inhalable drugs; known coronary, respiratory or inflammatory diseases; congestive heart failure and disability conditions that precluded the practice of physical exercise.

2.3. Sample characterization

After 4 h of fasting, body composition was evaluated by tetrapolar bioelectrical impedance analysis (model BC-558, Tanita Corporation of America Inc., Arlington Heights, IL, USA). Glycohemoglobin (HbA_{1C}), fasting plasma insulin level, fasting plasma glucose and lipid profile were measured after 10 to–12 hours of fasting using the analyzer ADVIA 1800 Chemistry System (Siemens, Tarrytown, NY, USA). The degree of insulin resistance was determined at baseline by the homeostasis model assessment of insulin resistance (HOMA-IR).[21]

2.4. Protocol

After the screening session, the subjects returned to the laboratory on five different days to perform the experimental protocol detailed in Fig. 1. All exercise tests were executed on a cycle ergometer (Quinton Corival 400, USA). During the first visit, the cardiopulmonary exercise test (CPET) was performed to determine the gas exchange threshold (GET) and $\dot{V}O_2$ peak. Three independent researchers determined the GET by the ventilatory method.[22,23] The $\dot{V}O_2$ peak was calculated by the mean $\dot{V}O_2$ value of the last 30 s before exercise recovery.[22,24]

In the next four visits, the participants received LEDT or placebo therapy according to the randomization previously described in Francisco et al.[20] The order of the therapies was randomly defined using opaque sealed envelopes. Blocks of 6 opaque envelopes were prepared by an investigator who did not participate in data analysis. All subjects received both therapies (LEDT and placebo); these were alternated in each visit. After the therapy (LEDT or placebo), participants performed a moderate constant workload cycling exercise protocol composed by 3-min freewheel warm-up; 6-min moderate constant exercise at 80% of the workload at GET followed by a 6-min cool-down. The cycling cadence was kept constant at ~60 rpm. The interval between LEDT and placebo therapies was at least 14 days (washout period). All tests occurred in the morning, at the same time of the day. Subjects were asked to avoid caffeine and refrain from exercise for 24 h before all tests.

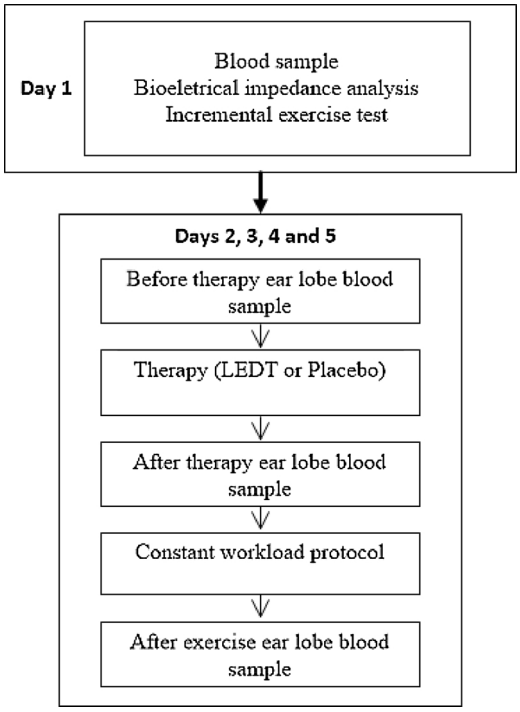

Fig. 1. Experimental protocol flowchart. This figure was adapted from the original publication by Francisco et al. 2015 [20].

2.5. Light-emitting diode therapy (LEDT) and blood sampling

The LEDT was applied with a flexible light-emitting diode array[25] (50 GaAIA LEDs, 850ηm, 75 mW each diode, and 3 J per point) in direct contact over the skin on *quadriceps femoris* and *triceps surae* muscle areas, bilaterally (as described in Table 1). The application time in each

Table 1
LEDT device information and treatment parameters.

Type	Ga-AI-As semiconductor diode
Number of diodes	50
Wavelength	850 ± 20 nm
Frequency	Continuous output
Optical output	75 mW each diode
Spot size	0.2 cm^2
Power density	375 mW/cm^2
Energy density per diode	15 J/cm^2
Energy per diode	3 J
Total energy delivered per muscle group	150 J
Treatment time over each muscle group	40 s
Number of irradiation sites per lower limb	2
Total energy delivered per lower limb	300J
Application mode	Skin contact

muscle was 40 s, delivering 150 J of total energy per muscle. Placebo followed the same procedure, but with the LEDT device turned off.

Blood samples were collected via earlobe puncture to evaluate lactate and glucose levels before and after the therapy (LEDT or placebo) and at the end of the constant workload exercise protocol. The sample measurements were performed using an automated glucose analyzer (YSI 2300 STAT PLUS – Yellow Springs Instruments, USA).

2.6. Measurements

The $\dot{V}O_2$ data were measured breath-by-breath by a computerized metabolic cart (Vmax29c, Sensor Medics, Yorba Linda, USA) calibrated before each testing session following manufacturer's specification.

Arterial pressure, heart rate (HR) and cardiac output ($\dot{Q}$) were measured by a photoplethysmography system (Finometer Pro, Finapres Medical System, Netherlands). The finger cuff was placed on the middle finger of the left hand and a height correction was used as recommended by the manufacturer to correct the hydrostatic pressure changes related to the heart.[26]

The local changes of deoxygenated hemoglobin (HHb) of the *vastus lateralis* was assessed by a near-infrared spectroscopy (NIRS) system (Oxymon, Artinis Medical Systems, Netherlands). The NIRS optode was fixed by tape on the distal part of right *vastus lateralis* muscle belly (approximately 15 cm above the patella proximal border) and then a dark cloth was gently wrapped around the thigh to avoid any influence of motion artifact and ambient light.

2.7. Data analysis procedures

$\dot{V}O_2$, HR, $\dot{Q}$ and HHb data obtained during the two constant workload protocols under the same condition (LEDT or placebo) were time-aligned (zero as the onset of exercise), second by second linearly interpolated and then the ensemble averaged to obtain a single response per condition. The first 20 s of data after the onset of exercise were deleted from $\dot{V}O_2$, HR and $\dot{Q}$ data to remove the effects of the cardio-dynamic phase[27,28] over the data modeling. The remaining data from -60 to 360 s were submitted to time domain kinetics analysis to evaluate the dynamic responses of each variable. For the HHb signal, individual data fitting window was performed following the method described by Murias et al.[28] adopting a fitting window up to 90 seconds. This method was used in order to eliminate the cardio-dynamic phase without lose time-domain information.[28,29] Also, because the HHb has an "exponential-like" time-course, longer fitting window increases the risk of poorer fitting of the early transient.[28]

The $\dot{V}O_2$, HR, $\dot{Q}$ and HHb data were fitted by the following mono-exponential model[9,30–32]: $y_t = a_0 + a_1(1 - e^{-(t-TD)/\tau})$; where y_t represents the $\dot{V}O_2$, HR, $\dot{Q}$ or HHb at any given time (t); a_0 is the baseline value of y before exercise onset; a_1 is the steady-state amplitude of the response above a_0 ; τ is the time constant and represents the time required to attain 63% of the steady-state amplitude after a given time delay (TD). Finally, the mean response time (MRT) that represented the overall description of the dynamics was calculated by the sum of τ and TD.[27,33]

2.8. Statistical analysis

Data were expressed as mean and standard deviation. Comparisons between placebo and LEDT were performed using the Wilcoxon test. For the variables with statistical differences between placebo and LEDT we tested their correlation with HbA_{1C} using Pearson correlation analysis.

The changes in blood lactate and glucose levels measured during each therapy session (placebo or LEDT) were analyzed by repeated-measures One-way ANOVA. When the sphericity condition tested by Mauchly's test was satisfied, the comparison was tested by the F test, otherwise Hotteling's trace was used. Afterwards, the Bonferroni *post hoc* test was performed for both conditions.

The level of significance was set at 5% ($P < 0.05$). All analyses were performed using the SPSS 17.0 for Windows (IBM Company, USA).

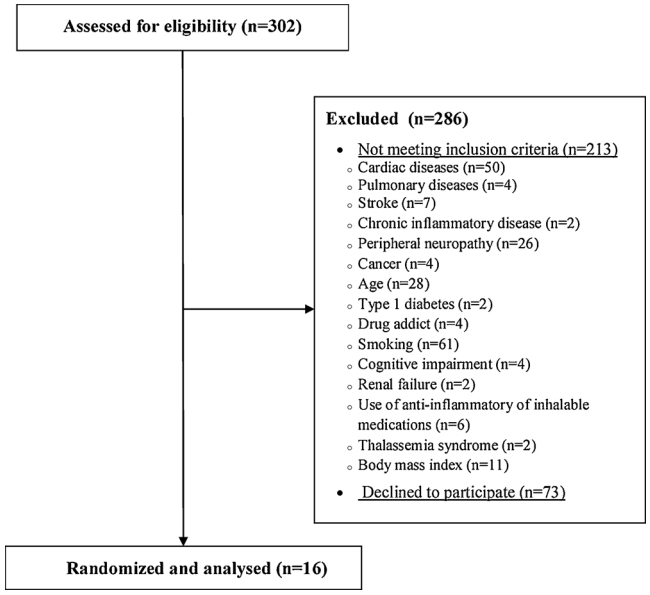

Fig. 2. Flowchart of the study (in compliance with CONSORT statement).

3. Results

From three hundred two volunteers initially evaluated, sixteen were included in this study. The flow diagram with detailed information of the screening process is outlined in the Fig. 2. All participants randomized for the study completed the experimental protocol.

The characteristics of the included participants are summarized in Table 2. Among the participants the duration of diabetes ranged between 2 and 20 years and the HbA_{1C} levels ranged between 5.0 and–10.4%. All participants were receiving medication treatment for hyperglycemia management as follow: one participant (6.3%) was treated with insulin, one participant (6.3%) was treated with gliclazide and fourteen participants (88%) were treated with metformin. Of these 14 participants using metformin, two were also being treated with insulin and two were also being treated with gliclazide. Moreover, seven subjects (43.7%) were under hypertension treatment with angiotensin-

Table 2
Subjects characteristics.

n	16
Age, years	55.1 ± 5.4
Duration of diabetes, years	9 ± 5.3
Weight, kg	84.2 ± 7.7
Body fat, %	26.6 ± 3.6
BMI, kg/m2	28.6 ± 2.3
SBP at rest, mmHg	139.2 ± 18.6
DBP at rest, mmHg	76.0 ± 9.8
HR at rest, bpm	76.5 ± 11.9
HbA_{1C}, %	7.9 ± 1.5
Fasting insulin, μU/ml	17.5 ± 15.4
Fasting glucose, mg/dl	166.6 ± 69.2
Insulin sensivity, %, HOMA	8.4 ± 12.5
$\dot{V}O_2$peak, $L{\cdot}kg^{-1}{\cdot}min^{-1}$	20.5 ± 4.9
Workload peak, W	135 ± 33

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, HbA_{1C} Glycohemoglobin, HOMA homeostasis model assessment of insulin resistance, $\dot{V}O_2$ pulmonary oxygen uptake.

Table 3
Kinetics parameters for, pulmonary oxygen uptake, heart rate, cardiac output, and deoxyhemoglobin.

	Placebo	LEDT	P
Baseline $\dot{V}O_2$, l/min	0.47 ± 0.04	0.48 ± 0.04	0.23
$\dot{V}O_2$ amplitude, l/min	0.49 ± 0.20	0.50 ± 0.20	0.76
$\dot{V}O_2$ MRT, s	49.6 ± 8.3	51.0 ± 8.7	0.26
Baseline HR, bpm	77 ± 10	76 ± 9	0.78
HR amplitude, bpm	20 ± 7	20 ± 8	0.46
HR MRT, s	46.1 ± 12.0	42.7 ± 11.8	0.17
CO MRT, s	45.1 ± 14.1	45.6 ± 12.2	0.58
MRT [HHb], s	22.2 ± 3.6	21.5 ± 3.8	0.25

LEDT light-emitting diode therapy, $\dot{V}O_2$, pulmonary oxygen uptake, τ time constant, TD time delay, MRT mean response time, HR heart rate, CO cardiac output, HHb deoxyhemoglobin. Statistical significance $P < 0.05$ using Wilcoxon test.

converting enzyme inhibitors; four (25%) were taking simvastatin for dyslipidemia; and two (12.5%) were controlling hypertriglyceridemia by using ciprofibrate.

The LEDT did not change any variable related to the cardiopulmonary or hemodynamics adjustments (Table 3) represented by p values higher than 0.05. Similarly, the LEDT did not affect blood lactate concentration. No differences were found in blood lactate concentration within-interventions or between interventions (placebo: 1.9 ± 0.6 mmol/L pre intervention vs 1.9 ± 0.5 mmol/L post exercise protocol; LEDT: 1.8 ± 0.7 mmol/L pre intervention vs 1.9 ± 0.9 mmol/L post exercise protocol).

The baseline levels of glucose were similar between the interventions (181.4 ± 70.2 mg/dl in placebo vs. 173.7 ± 61.0 mg/dl in LEDT, $p > 0.05$). The exercise associated with LEDT decreased significantly the glucose levels ($p < 0.05$), however the magnitude of changes were not statistically different between placebo and LEDT ($p > 0.05$) (Fig. 3). In addition, HbA1c was negatively correlated with changes in glucose levels after exercise on LEDT arm ($r = -0.54$ $p = 0.05$) (Fig. 4B) but not on placebo arm (Fig. 4A).

4. Discussion

The main finding of this study was the significant reduction in blood glucose levels in T2DM subjects after LEDT followed by a moderate cycling exercise without affecting hemodynamic and cardiopulmonary dynamics. To the best of our knowledge this was the first study that evaluated the effect of PBM on the cardiopulmonary and hemodynamic adjustments, and on glucose levels in T2DM.

T2DM is characterized by hyperglycemia[2] and management of blood glucose is a key element in reducing complications and improving the quality of life of this population. Some studies have shown reduction in glucose levels combined with acute effects of moderate physical exercise, probably by decreasing hepatic glucose production, increasing insulin sensitivity, and number and activity of muscle glucose transporter (GLUT4).[6,34,35] However, all these effects were found in a single session of prolonged aerobic exercise (30 to–70 min).[34,35] In the present study, the subjects with T2DM exhibited statistically significant reduction in glycaemia after moderate physical exercise only when combined with LEDT. Furthermore, the present study used a short physical exercise protocol (15 min, including 3 min of warm-up, 6 min of moderate intensity and 6 min of cool down), to which population with T2DM may possibly respond with better adherence.

The position statement of ADA and European Association for the Study of Diabetes (EASD)[36] recommends that the HbA_{1C} should be maintained below 7% and this target can be achieved by maintaining the fasting glucose lower than 130 mg/dl. Moreover, every reduction of 1% in HbA_{1C} may be associated with a 15% reduction in relative risk for non-fatal myocardial infarction.[36,37] In our study, the participants presented similar glucose levels at baseline (181.4 ± 70.2 mg/dl in placebo vs 173.7 ± 61.0 mg/dl in LEDT). Although the changes in glucose levels were statistically similar between the therapies, the higher magnitude of changes after LEDT could be considered clinically relevant (reduction of 21.4 ± 37.3 mg/dl in placebo arm vs reduction of 30.2 ± 33.2 mg/dl in LEDT arm). In addition, HbA_{1C} presented moderate negative correlation with glucose levels only in LEDT arm (Fig. 4B). Therefore, individuals with poor glycemic control could have higher reductions in glucose levels after a short exercise protocols associated with LEDT, indicating an optimized therapeutic strategy for these patients.

Few studies showed the effects of PBM in glucose metabolism. Sene-Fiorese et al.[38] showed in women with obesity that 20 weeks of laser therapy (LLLT) combined with physical exercise (aerobic exercise 3x/week) lead a greater reduction in insulin levels and HOMA-IR compared with exercise combined with placebo LLLT. Silva et al.[39] demonstrated that 4 weeks of PBM improve glucose tolerance in obese mices. Despite these studies evaluated long-term effects of phototherapy, their results corroborates with our results where blood glucose levels decreased by PBM in T2DM patients. Our study demonstrated that glucose homeostasis seems to be affected by PBM, however the pathway by which phototherapy acutely affect glucose metabolism remains unclear.

Although our volunteers received pharmacological treatment for hyperglycemia during the study, the results were consistent in our sample, since all subjects were submitted to both therapies (LEDT and placebo). Moreover, the same drugs were maintained during this

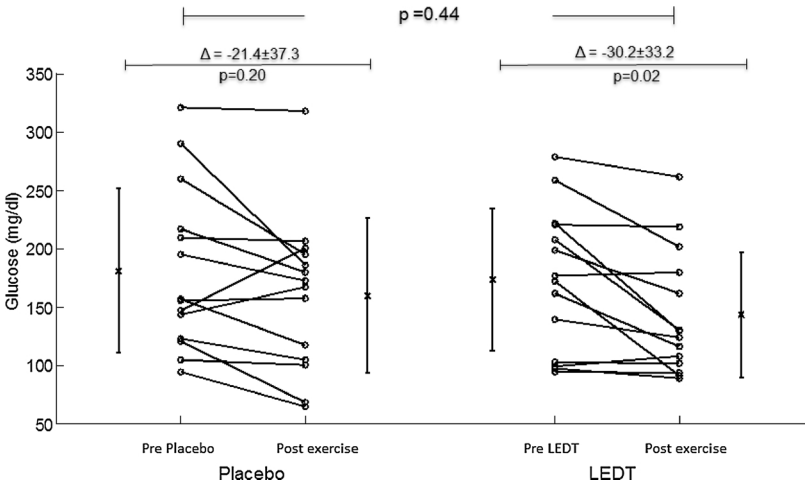

Fig. 3. Glucose levels before intervention and after exercise protocol.

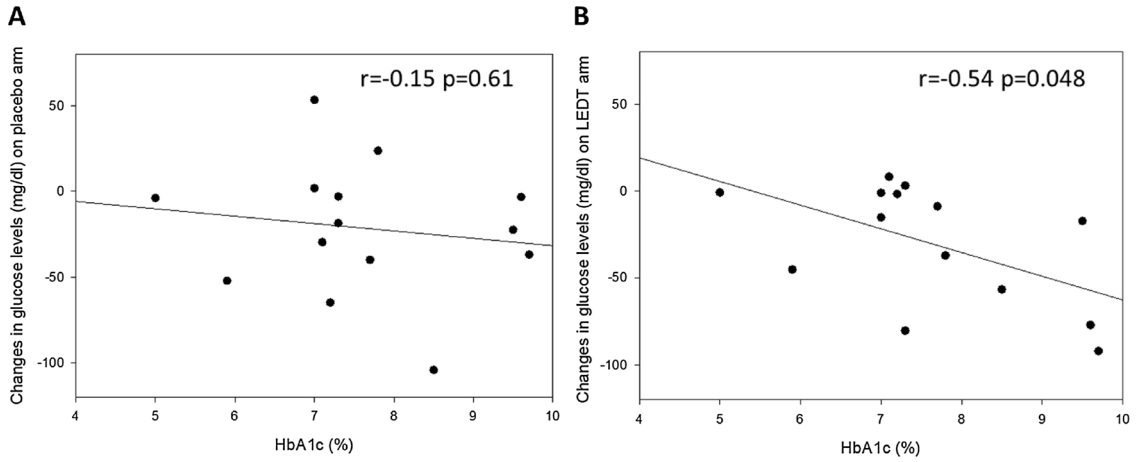

Fig. 4. Correlation between Glicohemoglobin (HbA_{1C}) and changes in glucose levels after placebo combined with physical exercise (panel A) or after LEDT combined with physical exercise (panel B).

clinical trial, and the therapy was applied in randomized order.

Considering the lactate levels, there are conflicting data in the literature. Some studies have shown smaller lactate production in exercise after PBM in healthy subjects.[13,16,25] Our results are in agreement with those that did not find any effects of PBM on lactate levels.[40–42] On the other hand, the studies generally used high-intensity physical exercise[13,16,25,40–42] that significantly increased lactate production. In our study, the lactate levels were similar to the baseline after the moderate exercise protocol. Therefore, the absence of PBM effect on lactate levels could be affected by the exercise intensity. In addition, the lactate levels were lower after both of the therapies (LEDT and placebo), suggesting no effect of the PBM on lactate levels in T2DM patients submitted to short duration, moderate intensity cycling exercise.

Regarding the cardiopulmonary and hemodynamic adjustments, previous studies found no influence of PBM on the GET values during incremental exercise.[13,14] Nonetheless, these same studies showed improvements in $\dot{V}O_2$ peak related to PBM.[13–15] These studies, similarly with our study, applied the phototherapy only in the legs. However, there are methodological differences between these studies[13–15] and the present study as the PBM parameters (42 J to–270 J per site vs 150 J) and the exercise protocol (incremental exercise test vs moderate constant workload). For this reason, it is difficult to address if the absence of changes in cardiopulmonary responses are due these study design differences and/or due to the different LEDT parameters. The optimal parameters of PBM using lasers and LEDs to improve exercise performance in healthy or in T2DM patients are still unknown. In our study, the PMB parameters are in agreement with a recent review with meta-analysis about PBM and muscle performance.[16]

Our research group previously published a case study conducted with an elite runner, in a double-blind crossover trial,[25] that found apparent improvements in $\dot{V}O_2$ dynamics and time of exercise during intense running exercise performed on a treadmill after effective LEDT. In this case study, multiple areas received the irradiation with LED (legs, arms and trunk)[25] while in the present study only legs received the LEDT. This may be a factor related with the absence of changes in the cardiopulmonary and hemodynamic adjustments in the present study. In the other hand, previous studies evaluated the effect of PBM on exercise capacity and found improvements in $\dot{V}O_2$ peak after applying phototherapy only in the legs.[13–15] In spite of the differences in light dose (J) applied on the *quadriceps femoris* muscles among all the aforementioned studies (37.5 J to 270 J),[13–1525] all these studies induced voluntary exhaustion during cardiopulmonary assessments, whereas, the exercise protocol in the present study was in constant workload performed at moderate intensity. Possibly, the effectiveness of LEDT in exercise performance may be dependent on the exercise demand.

Our study has limitations that are important to address. First, we did not measure the thermal effect of LEDT and even a small increment in thermal sensations can be considered a source of bias for blinding of participants. One recent study[44] tested the thermal impact of phototherapy using a multi-diode phototherapy cluster containing four 905-nm super-pulsed laser diodes, four 875-nm infrared-emitting diodes, and four 640-nm LEDs. This study did not find significant temperature increases, but they have important differences with our study. Grandinetti et al.[44] applied in an area 30 times smaller than the area of application of our study (20cm^2 vs. 612 cm^2), a dose 3 times smaller than the dose tested in our study (50 J vs. 150 J) and they used LEDs with optical output 5 times smaller than the LEDs used by our study (15 to–17.5 mW vs. 75 mW). Because the power output in our study was distributed in a larger area, we expect no significant temperature increases similarly with the cited study. Moreover, the investigator did not note any blush or changes in temperature after the LEDT, while attaching the NIRS optode.

Other limitation is the potential effect of medication differences among participants. To clarify the medication effects, one possibility was perform a stratification by medication sub-groups, but our sample size for each medication was small and sub-groups would not have enough statistical power to test it. Nevertheless, our participants did not change their medication during this clinical trial and the crossover design mitigates this issue since each participant acts as their own control.

5. Conclusion

In conclusion, LEDT in combination with moderate exercise acutely decreased glucose levels in adult men with T2DM and did not affect cardiopulmonary and hemodynamic adjustments during transition to moderate exercise. Our results demonstrated, for the first time, the potential therapeutic effect of PBM in combination with a short exercise protocol for the management of hyperglycemia in T2DM. This type of protocol may induce better adherence in the population with diabetes and this result can open a new avenue for diabetes mellitus treatment.

Disclosure

The authors declare have no conflict of interest.

Acknowledgments

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