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RESEARCH ARTICLE OPEN ACCESS

PHOTOBIOMODULATION THERAPY IN NONALCOHOLIC FATTY LIVERDISEASE

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ABSTRACT

Introduction: Photobiomodulation Therapy (PBMT) can be safely employed in the treatment of liver diseases, such as Non-Alcoholic Fatty Liver Disease (NAFLD). **Materials and Methods**: 32 individuals with a mean age range between 51.03 ± 9.58 years, suffering from NAFLD diagnosed by ultrasonography, were randomized into 2 study groups: Placebo's Group and PBMT's Group. Before and after the analysis period given to each group, the aforementioned individuals underwent liver ultrasonography aswell as BMI calculation and their blood samples were submitted to the following laboratory tests (plasma concentrations): Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Bilirubin (total and fractions) (BILI), Gamma-Glutamyl Transpeptidase or Gamma-GT (GGT), Prothrombin Time Activity (PT or PTA), Total Cholesterol and Fractions (TC - HDL, LDL) and Triglycerides (TG). **Results:** The PBMT's Group demonstrated improvement in steatosis status in 93.8% of patients whereas the Placebo's Group showed improvement in the percentage of 37.5%. Reductions in Triglycerides, Total Cholesterol, LDLand GGT levels were also observed in the PBMT's Group**. Discussion:** There was a significant enhancement in steatosis grade in the group that underwent treatment with PBMT, indicating it as a safe and effective method for treating patients with NAFLD.

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INTRODUCTION

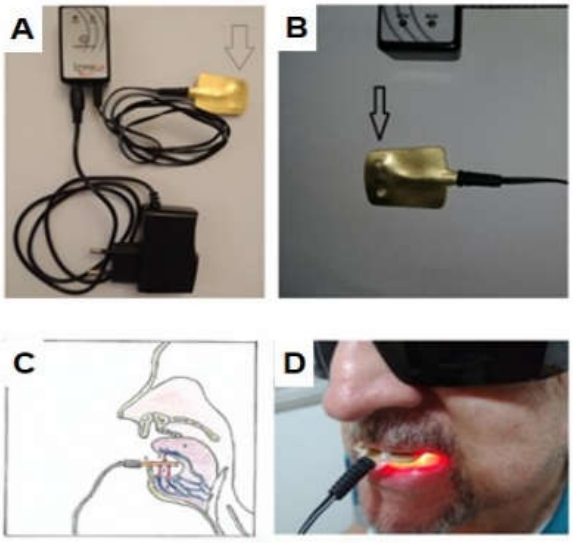
NAFLD is a truly silent epidemic that affects at least 30% of the world populationin the current age[5].Over one third of the adult Brazilian population has steatosis, which can be associated with other liver diseases (such as viral hepatitis, alcoholic liver disease) or be associated with secondary factors (such as medications, chemical agents), but without a doubt, steatosis has its main etiology in NAFLD. Thus, NAFLD is an adaptive response from the liver to insulin resistance[9]. It's an increasingly widespread condition that has a high ubiquity among patients diagnosed with obesity or Diabetes Mellitus (DM). Therefore, NAFLD can be regarded as the hepatic manifestation of Metabolic Syndrome[5]. It's described as the build up fat located in the liver in the absence of ethanol ingestion[14], mainly in the form of triglycerides, exceeding 5% of the organ's actual weight[12]. It covers a wide spectrum of liver lesions, ranging from benign steatosis to nonalcoholic steatohepatitis (NASH), denoting a high risk progression to cirrhosis and hepatocellular carcinom[9;13;14]. In order to achieve the definition of NAFLD, there should be (1) evidence of hepatic steatosis, either by diagnostic imaging or histopathological examination, and (2) absence of secondary underlying causes of liver fat accumulation, such as high alcohol consumption (defined as more than 21 drinks in men and 14 drinks in women per week during a 2-year period), long-term use of steatogenic medications (mainly corticosteroids, amiodarone, methotrexate, and tamoxifen), or monogenic inherited disorders[5]. To this date, no pharmacological treatment has been established for NAFLD. Lifestyle interventions based on exercises and well-balanced diets are seen as important keystones for the treatment of nonalcoholic fatty liver disease, but are poorly followed by the majority of patients[1;8]. For such reasons, several studies have been pursued in order to identify potential alternative therapies that act directly against pathogenic targets of NAFLD. However, the drugs employed for this purpose are very expensive and have numerous side effects.Photobiomodulation Therapy has proven to be an excellent therapeutic tool, possessing biostimulatory capacity, as well as being part of modern therapies such as Laser Therapy, which use Low-Level Laser (LLLT) or LED Therapy.Chavantes(2009) described the ILIB technique (*Intravascular Light Irradiation of Blood*), which involves the irradiation of blood with red or infrared light for anti-inflammatory action, cell activation, antioxidant effect and increased blood circulation that reverberates in the prevention and treatment of several inflammatory and autoimmune diseases, such as arthritis, arthrosis, inflammation and muscle tension, as well as diabetes, cholesterol, hypertension, among other cardiovascular diseases, and can also be directly applied on the blood vessels. Peculiarly, the liver has been an important target for these latest and advanced techniques. A number of them are still under experimental discussion, some clinical trials

have been undertaken, and others have already been incorporated into normal practice. The use of light, whether via Laser or LED, as a biostimulating device for liver regeneration has extensive backing in the literature[3;4;10;11;15]. Regarding its action in the liver parenchyma, it's assumed that the Laser or LED light leads to conformational changes in the structure of hepatocyte mitochondrial cytochrome, so that there would be an enhanced ATP production, expressing an increase in energy metabolism[11]. To this date, there is no research that has used transvascular sublingual LED therapy for the treatment of NAFLD.

Objective: *To evaluate the therapeutic response and safety of sublingual transvascularPBMT via Light Emitting Diode (LED) therapy in patients diagnosed with NAFLD by using liver biomarkers, lipid profile and Body Mass Index (BMI) as study variables.*

MATERIALS AND METHODS

The present research was undertaken after its approval by the Research Ethics Committee of the University Nove de Julho (Opinion Nº. 2,213,462) and registration on the Brazilian Platform of the Ministry of Health, in June 2017 (CAAE: 72551417.8.0000.5511). A prospective randomized clinical study with 32 patients of both genders, aged from 35 to 70 years old, with NAFLD diagnosed by ultrasonography. These patients were randomized into 2 groups: Placebo's Group (GP - n = 16) and Photobiomodulation Therapy's Group (PBMT), (GPBMT – n = 16), which received irradiation (*Linealux Laser Therapy*™) Continuous Wave (CW) Diode LED (λ - 660 nm, in red), through transvascular sublingual, at 3 points, on the mucosa over the sublingual vessels, with the following dosimetry: Power = 5 mW per spot; Power Density = 5 mW/cm²; Total Application Time = 7 minutes; Beam area = 1 cm², Fluence = 2.1 J/cm². Administered once a week for a total of 16 weeks, with a follow-up of 1 month after the end of the PBMT, accounting for a total of 20 weeks.Pre and post study period, all patients underwent liver ultrasonography, BMI calculation and blood samples were collected and subjected to the following laboratory analyses (plasma concentrations):Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Bilirubin (total and fractions) (BILI), Gamma-Glutamyl Transpeptidase or Gamma-GT (GGT), Prothrombin Time Activity (PT or PTA), Total Cholesterol and Fractions (TC - HDL, LDL) aswell as Triglycerides (TG).Thus, all patients received the standard nutritional counseling, normally applied to NAFLD patients, which was individually tailored for adequate caloric intake, and it was also recommended for all of them to practice walking on flat surfaces for 30 minutes three times a week; both supervised.



Source: Oliveire et al, 2019

Figure 1. (A) and (b) Linealux laser Therapy™ device with 3 application points; (c) lllustration of the ILIB technique in the sublingual vessels; (D) LED's application via transvascular sublingual route

Inclusion Criteria: Adult patients of both sexes, aged from 35 to 70 years old, asymptomatic or not, with NAFLD graded from I to III, diagnosed by abdominal ultrasonography, overweight or obese (Body Mass Index equal to or higher than 26 kg/m²), complying with diet and exercise recommendations, with no comorbidities, with AST/ALT ratio < 1. Their liver's ultrasonographic examinations were performed to confirm the presence of NAFLD.

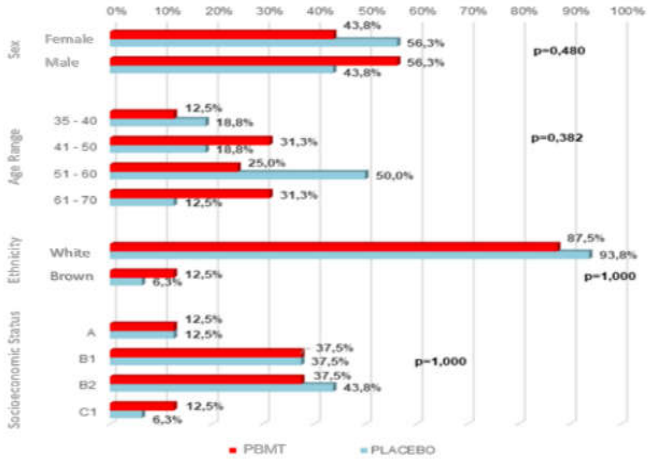
Exclusion Criteria: Patients with advanced liver disease, thyropathies, neoplasms, diabetes mellitus types I and II, history of alcoholism (ethanol use > 20 g/day in women and > 40 g/day in men). Patients who are seropositive for hepatitis B or C and HIV, taking drugs known to cause and treat steatosis, with renal insufficiency or who have recently used the medication Metadoxine. Individuals with collagenoses and autoimmune diseases were also excluded, as were patients who didn't adhere to the diet and exercise recommendations. After 30 days from the end of the treatment period (*follow-up period*), new serum samples were collected and a new inspection by ultrasonography was performed.

Statistical Analyses

The associations' existences between two categorical variables were verified using the Chi-Squared Test. Comparisons of means between both groups were made using the Student's T Test for independent samples. The comparison of means per group (PBMT and Placebo) between two time points was accomplished by using the Analysis of Variance (ANOVA) with repeated measures. The linear association between two variables of numerical nature was evaluated via Pearson's correlation and, for all statistical tests, a 5% significance level was employed. Statistical analyses were performed using SPSS 20.0 and STATA 12.0 statistical softwares.

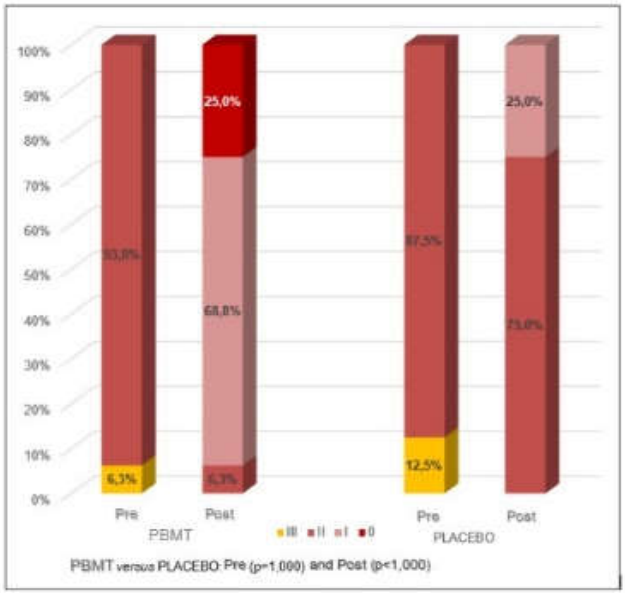
RESULTS

The 32 individuals, as patients, included in the present study werefirst categorized according to sex, age range, ethnicity, and socioeconomic status. This classification is shown in GRAPH 1downbelow:

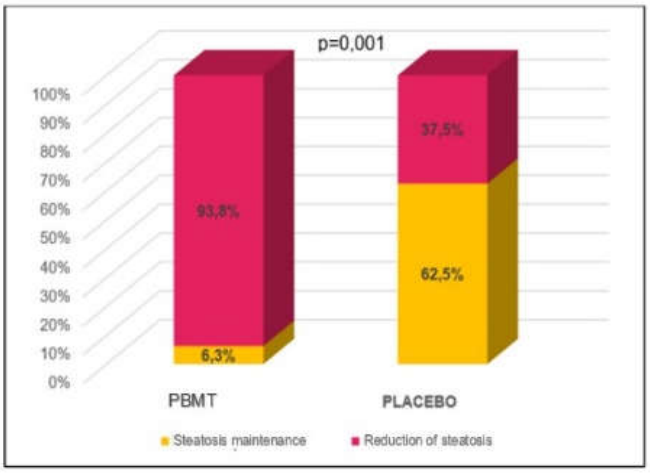


Graph 1. Patients' distribution by socio-demographic characteristics (sex, age, range, ethnicity, and socioenomic status), according to both groups

Concerning the results obtained from the reduction in steatosis grade, it was observed that, 11 patients (34.4%) from the total number of 32, maintained the initial grade of steatosis and 21 patients (65.6%) had a reduction in theirgrade of steatosis. However, this distribution was not homogeneous between the groups (p = 0.001). The results showed that 93.8% of the patients in the PBMT's Group had a significant reduction in the steatosis grade, compared to the Placebo's Group, which had a reduction of 37.5% (GRAPHS 2 and 3). The chance of reduction in steatosis grade in the PBMT's Group was 25 times higher than in the Placebo's one.

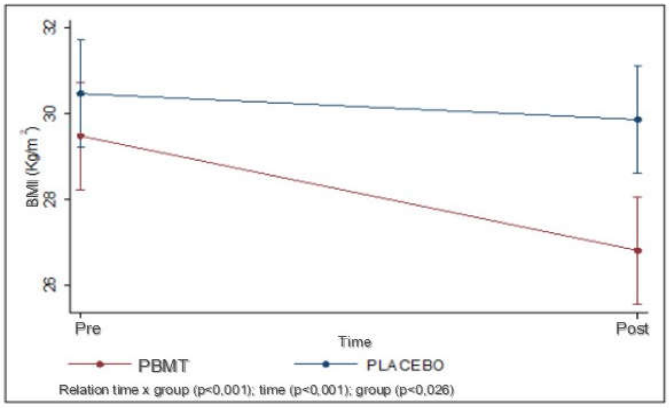


Graph 2. Patients' distribution according to its steatosis grade (absence =0; steatosis grade I, II or III) in both groups, Pre- and post- Treatment

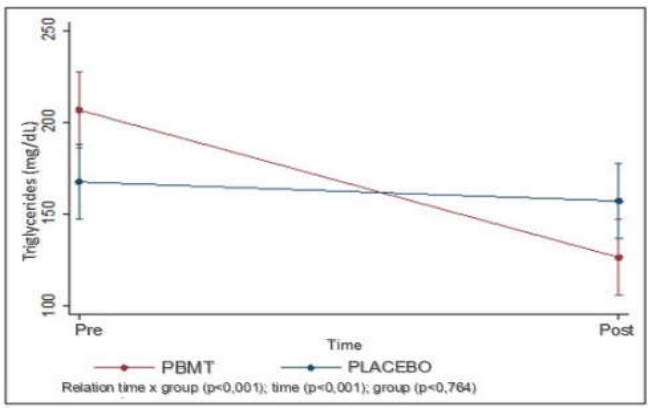


Graph 3. Patients' distribution by steatosis Grade (maintenance or reduction), according to both groups

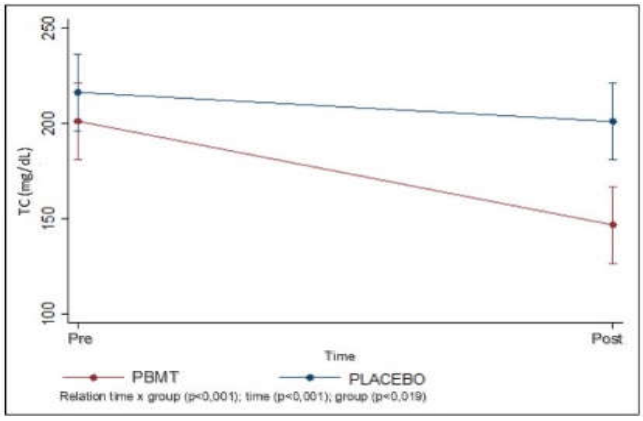
The variables' evolutions involved in this study are shown from GRAPH 4 to 18. Photobiomodulation Therapy was able to decrease, with statistically significant response, the levels of Triglycerides ($p < 0.001$), Total Cholesterol ($p < 0.001$), LDL ($p < 0.001$) and GGT ($p = 0.005$), without promoting pathological changes in other liver biomarkers. Likewise, there was a significant reduction in BMI in the PBMT's Group ($p = 0.003$), whilst in the Placebo's Group the aforementioned reduction wasn't that relevant ($p = 0.508$).



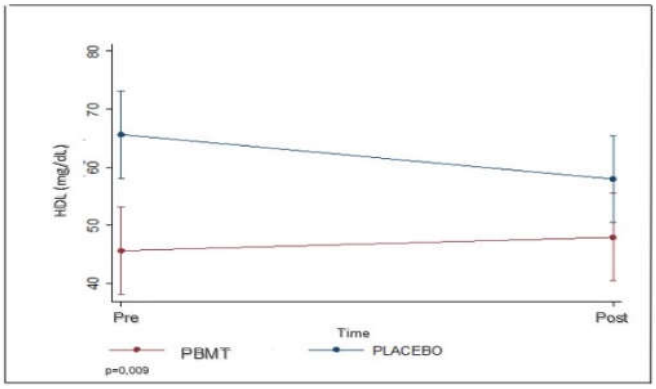
Graph 4. Mean and 95% Confdance Interval of BMI over Time, according to to both Groups



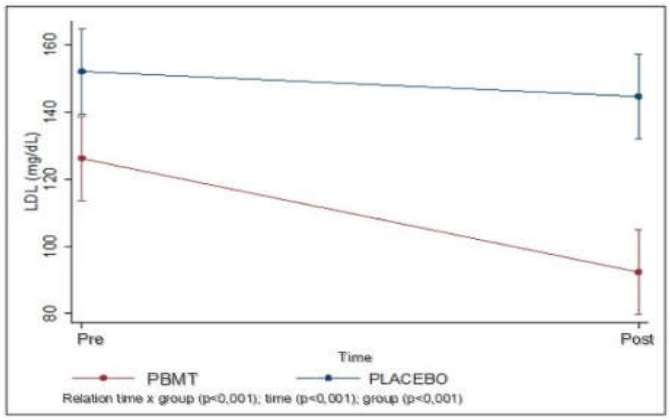
Graph 5. Mean and 95% Confidance Interval of Triglycerides over Time, according to both groups



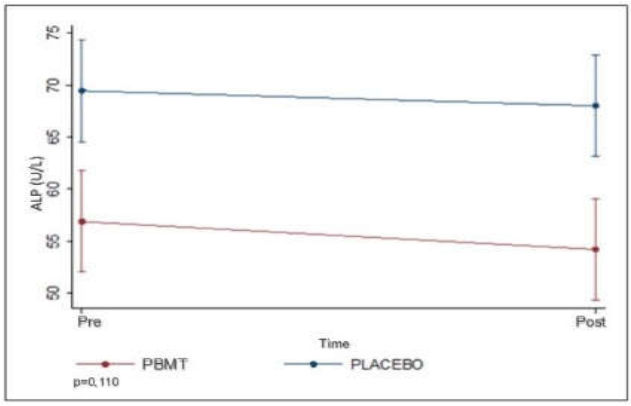
Graph 6. Mean and 95% confidence Interval of Total Cholesterol (TC) over Time, according to both groups.



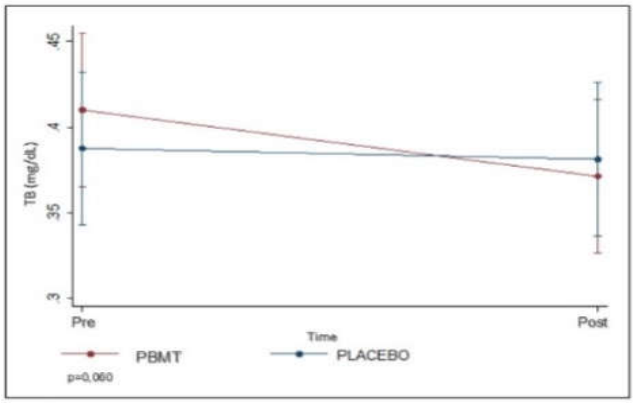
Graph 7. Mean and 95% confidance Interval of HDL Cholesterol over Time, according to both groups



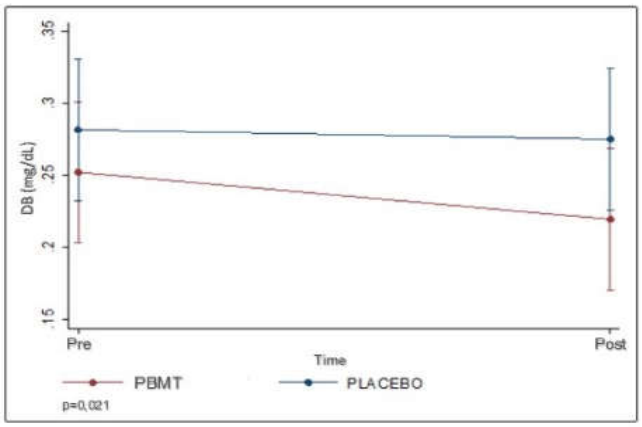
Graph 8. Mean and 95% confidance Interval of LDL Cholesterol over Time, according to both groups



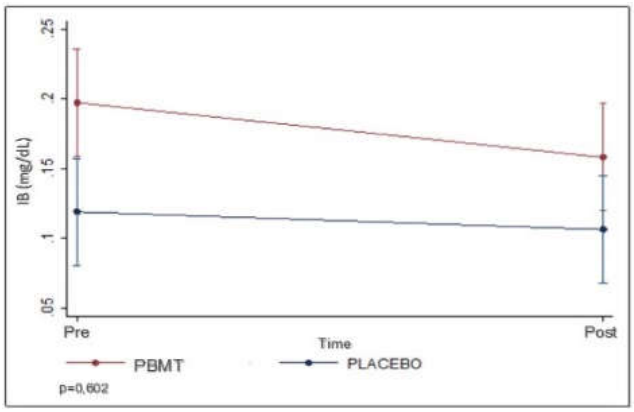
Graph 9. Mean and 95% Confideance Interval of Alkaline Phosphatase (ALP) over Time, according to both groups



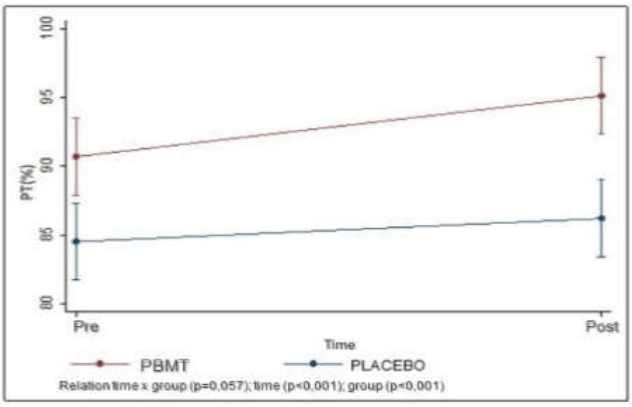
Graph 10. Mean and 95% Confidence Interval of total Bilirubin (TB) over Time, according to both groups



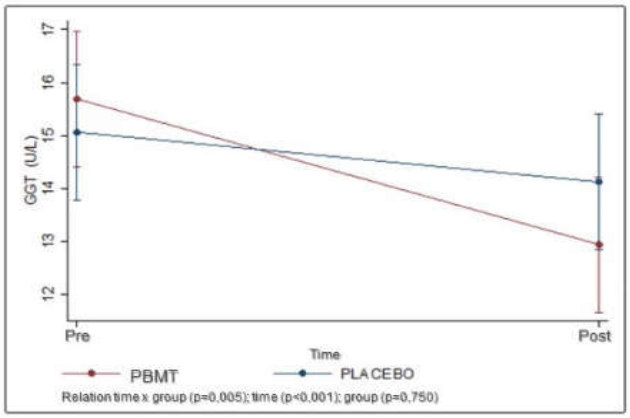
Graph 11. Mean and 95% Confidence Interval of Direct Bilirubin (DB) over Time, according to bith groups



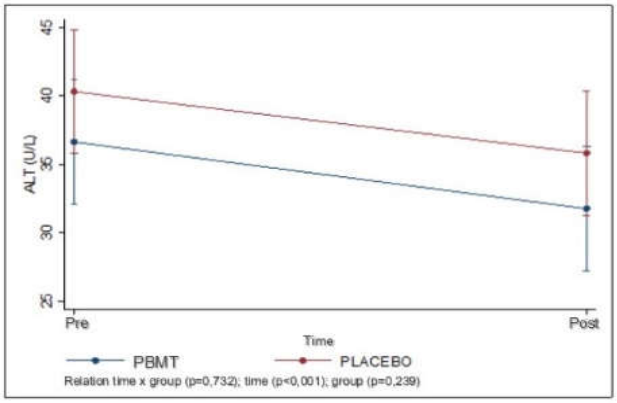
Graph 12. Mean and 95% Confidence Interval of Indirect Bilirubin (IB) over Time, according to both groups



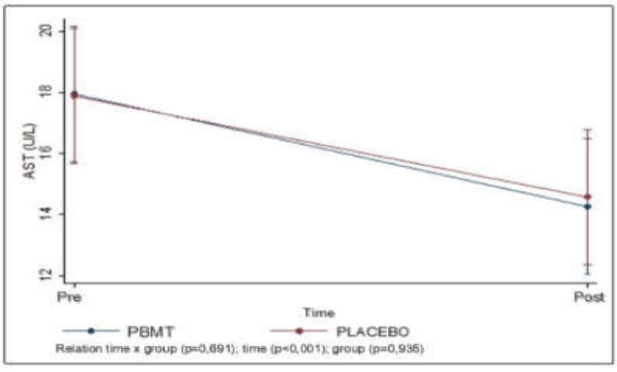
Graph 13. Mean and 95% Confidance Interval of Prothrombin Time Activity (PT or PTA) over Time, according to both groups



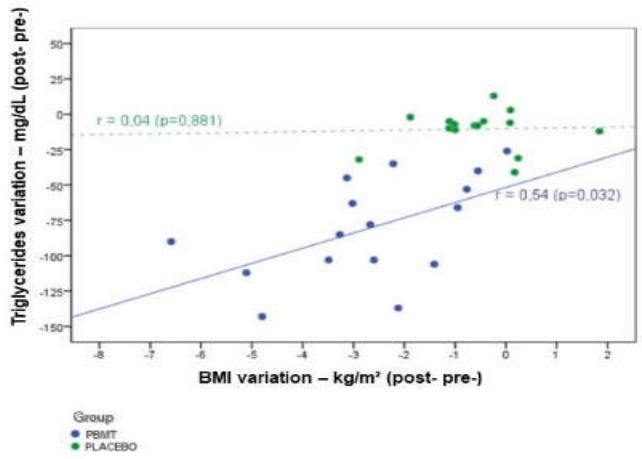
Graph 14.Mean and 95% Confidence Interval of Gamma-Glutamyl Transpeptidse or Gamm GT (GGT) over Time, according to Both Groups



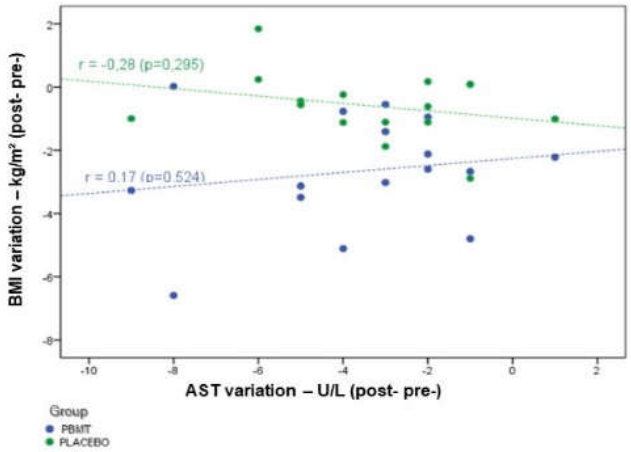
Graph 15. Mean and 95% Confidence Interval of Alanine aminotransferase (ALT) over Time, accordinh to Both Groups



Graph 16. Mean and 95% confidence Interval of Aspartate aminotransferase (AST) over Time, According to both groups



Graph 17. Scatter Plot between Triglycerdes (TG) variation and BMI variation per group



Graph 18. Scatter plot between Aspartate aminotransferase (AST) variation and BMI varation per group

DISCUSSION

NAFLD is a major public health issue due to its high prevalence, its potential progression to serious liver diseases such as steatohepatitis, cirrhosis, and hepatocarcinoma. Besides, it's linked to cardiometabolic diseases, including type 2 diabetes mellitus, metabolic syndrome, and heart disease. NAFLD is the most common chronic liver disease in the world, affecting about 25 to 35% of the population[5]. Accordingly, in the present study, the 32 patients were classified as overweight or obese. At the moment, the most accurate noninvasive imaging method to diagnose and quantify hepatic steatosis is Nuclear Magnetic Resonance Imaging (NMR), which is the Gold Standard Test. However, NMR suffers from several limitations, including its high cost, contraindications, and low availability. Liver ultrasonography can accurately evaluate the detection and staging of steatosis, with a sensitivity of 89% and specificity of up to 100%, which is why it was the diagnostic method used in this research. The use of US in the identification and classification of NAFLD may demonstrate a sensitivity of 89% and specificity of 93%, according to some authors, and according to others, a sensitivity of up to 94% and specificity of up to 100%[9;16]. As a standard treatment for NAFLD, proper nutrition education and a controlled exercise's regimen are widely used as non-pharmacological and noninvasive treatment methods. Thus, aside from reducing the grade of steatosis of NAFLD, there is also a consequential decrease in body weight, with improvement in dyslipidemia and insulin resistance[10]. Even though it was noticed, in this study, a low adherence by patients, where from the initial sample of 69 patients, only 43.37% complied with the recommendation of diet plus exercise. In relation to the practice of exercises, this research has indicated that moderate intensity cardiorespiratory exercise training (30 minutes, 3 to 5 times a week) may produce an positive impact on reducing the steatosis grade. Exercise interventions that met these guidelines demonstrated a reduction in liver fat from 10% to 43% in patients diagnosed with NAFLD[10].

In the light of current knowledge, some drugs have been used, but with modest levels of scientific evidence on their efficacy, and with many side effects, some of them of great magnitude[8]. No pharmacological treatment has yet been found to be truly effective in treating NAFLD. While there are many promising drug therapies in phases II and III clinical trials, treating a large portion of the world's population with long-term medications would be an expensive treatment option in widespread level[10]. New therapies with fewer side effects and more effective are urgently needed for the treatment of both NAFLD and NASH to further improve the prognoses of these diseases. *In vitro, in vivo* and clinical scientific research with PBMT, in the latest decades, has led to the recognition of this therapy by scientific groups around the world. While no consensus has been reached as to the exact dosimetry to be administered in each case, the employment of PBMT has been increasingly done in the therapeutic arsenal by many health professionals[6]. In recent years, the use of PBMT has been employed for a variety of liver diseases. Numerous experimental studies have been carried out in the last decade and some clinical studies have been performed with satisfactory results[4;10;11;15]. In our study, we used the ILIB technique directly on the sublingual vessels, which consists of irradiating the blood with red light (via transvascular in the lingual mucosa), for cell activation through anti-inflammatory action, antioxidant effect and increased hepatic blood circulation[6]. Regarding the purpose of using ILIB in this study, we took into account that all of the patients were considered overweight or obese by BMI calculation. We do believe that the absorption of LED sublingually was more effective because it didn't suffer interference from the skin and subcutaneous tissue, as occurs in the case of radial ILIB, which also requires a much longer time than the one used in transvascular sublingual form[7].

In this research, when it comes to the effects of PBMT on the lipid profile of patients in this group, there were significant results in the decrease of triglyceride levels, total cholesterol, LDL and increase of HDL, with total fluence of 33.6 J/cm², when compared to the Placebo's one. These results are due to the hemorheological action of PBMT. Such results were similar to the ones achieved through experimental research, employing total fluence of 45 J/cm². The adhered cholesterol to the erythrocyte membrane is one of the main factors that maintains the increased adhesiveness/aggregation of erythrocytes and cholesterol balance into the serum. This balance can be shifted by irradiation with phototherapy in the blood, with high levels of total cholesterol and fractions, thereby providing a lower rate of erythrocyte aggregation and deformation. Therefore, persistent laser irradiation may lead to a more efficient rotation of blood cholesterol and ultimately result in lower serum cholesterol level[15]. The evaluation tests for hepatocellular injury are the serum levels of aminotransferases: Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT); the tests for evaluation of bile flow and bile duct injury are the measurement of Alkaline Phosphatase, Gamma-Glutamyl Transferase (GGT) and Bilirubin[5;10]. The results of the analysis of liver biomarkers, in the present study, indicated the safety and efficacy of PBMT for patients, as the results showed that this therapy does not present hepatotoxicity, and can be applied in patients with other liver diseases, such as chronic hepatitis, cirrhosis and hepatocarcinoma[3]. The effectiveness of laser phototherapy in NAFLD has recently been demonstrated in a randomized controlled pilot study. In this study, the total energy delivery in patients was 92.16 J/cm^2 subcutaneously in 4 points (abdomen, quadriceps, gluteal muscles, and biceps femoris). The results have suggested that the use of PBMT provided significant improvement in anthropometric, biochemical, and enzymatic parameters and reduced the steatosis grade[2]. Moreover, the sublingual LED therapy was employed, with total energy of 33.6 J/cm^2, significant improvement in the group of BMTF in anthropometric, biochemical and enzymatic parameters, as well as significant reduction in the steatosis grade. The author

employed an amount of energy almost three times higher than the one employed in our study, with half the time period. Thus, it is necessary to mention that the use of the ILIB technique via transvascular sublingual route indicated excellent results, although it's important to determine the dose needed for each case, avoiding insufficient dosimetry for the treatment, as well as excessive dosimetry, which may modify the expected result. By understanding the physiology, anatomy and pathology not only of the disease, but, above all, of each patient (from the physical, psychic and social points of view), the most suitable dosimetry must always be aimed for in each case, facilitating cellular, tissue and organic homeostasis.

CONCLUSION

The results of the presentpilot study evidenced a statistically significant reduction in the grade of hepatic steatosis in patients of the PBMT's Group through the ILIB technique via transvascular sublingual route. In terms of the lipid profile, there was a statistically significant reduction in the levels of triglycerides, total cholesterol, LDL, and a significant positive increase in HDL in the aforementioned group. No side effects on the hepatic function were identified in the group that received PBMT. Futhermore, PBMT was found to be safe and nonhepatotoxic, as serum levels of liver enzymes did not change. There was a reduction in BMI levels in the PBMT's Group in contrast to the Placebo's Group, which did not demonstrate such relevant changes. Thus, it can be stated that PBMT effectively acted systemically on NAFLD, and can be used in patients with other hepatopathies.

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