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Regression of Non-Alcoholic Fatty Liver by Metabolic Reduction: Phototherapy in Association with Aerobic Plus Resistance Training In Obese Man – A Pilot Study

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Abstract

The excessive body fat, one of the results of obesity, brings with it comorbidities such as lipid changes, insulin resistance, diabetes mellitus type 2 and non-alcoholic fatty liver disease. In this controlled and randomized pilot study, as a non-pharmacological and non-invasive strategy, we consider two groups during 8 weeks: the use of moderate intensity physical exercise and nutritional education, as control group (n=10) and moderate intensity physical exercise, nutritional education and phototherapy (n=10), as phototherapy group. The used phototherapy parameters were: laser Ga-Al-As, wavelength 808 nm, continuous mode, output power 100 mW, and total energy delivery 92.16 J. Selected patients were men with age between 20 and 40 years old, primary obesity, body mass index (BMI) between 30 and 34.9 kg/m^2. The special device as described in the text was applied, allocated in the anterior region and posterior region of body during 5 minutes each side, totalizing 10 minutes of application of light, always at the end after session of exercise. Comparing the control group in relation to the phototherapy group, the better results were obtained for the phototherapy group, with statistical difference in all anthropometric variables, such as the increase of 3.54% ($p<0.007$) in total skeletal muscle mass; as well as, 2.77% ($p<0.005$) in the basal metabolic rate body; 5.47% ($p<0.04$) for metabolic progress; reduction of 4.67% ($p<0.007$) for body mass and reduction was also observed for total body fat, total trunk fat and visceral fat of which the phototherapy group showed the following reduction percentages: 14.3% ($p<0.01$), 14.7% ($p<0.005$) and 16.4% ($p<0.03$), respectively. A significant improvement was also observed in all the biochemical parameters and enzymatic analyzed, such as total cholesterol, triglyceride, the basal insulin, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and gamma-glutamyl-transpeptidase. Therefore the proposed treatment in this work suggests that the association of physical exercise, the nutritional education and phototherapy applied in obese men for two months caused great improvement in all anthropometric parameters, as well as, in all biochemistry and enzymatic parameters indicating that phototherapy is a potential instrument in the treatment of non-alcoholic fatty liver disease, being able to reverse the degree of steatosis in 8 weeks, besides it can be a new non-invasive treatment to obesity and its comorbidities.

Keywords: Non-alcoholic fatty liver disease; Obesity; Physical exercise; Phototherapy; Visceral fat

Introduction

Overweight is one of the greatest public health problems in contemporary society. In this context, obesity as a chronic subclinical inflammatory disease carries with it a huge range of diseases that are installed through the process of gaining body weight, through the increase of total body fat [1]. Diseases such as severe alterations in the lipid profile, insulin resistance, diabetes mellitus type 2 and non-alcoholic fatty liver disease (NAFLD) are some of the diseases that are installed in the body with the appearance of the inflammatory framework coming from obesity [2,3]. Currently, it is considered that 20% to 30% of the general population has fat in the liver [4]. In the same context, according to the literature [5], individuals in the range of body mass index established as obese of degree I, already have a high degree of possibility, about 80%, to develop fat in the liver. The chronic development of this alteration can result in severe inflammatory process, generating posterior consequences, like non-alcoholic steatohepatitis (NASH), fibrosis and cancer [6].

As standard treatment for the fat accumulation in the liver, the appropriate nutritional education and controlled physical exercise are widely used, as methods of treatment non-pharmacological and non-invasive [7,8]. Its functionality is based on the adequacy of the energy balance, making it negative, due to the decrease in caloric intake in relation to the increase in energy expenditure [9]. The beneficial process unleashed by moderate intensity physical exercise is well defined in the literature [1,10,11]. Thus, besides reducing the level of non-alcoholic fatty liver [12,13], there is also a consequent reduction of body weight [12,14], total body fat [14] and visceral fat area [15], and improvement in dyslipidemia and insulin resistance [16]. Moreover, there is an increase in the uptake of glucose for a better glycemic control [16,17], which are vital parameters for the improvement of life quality.

The non-pharmacological and non-invasive standard treatment is the use of the most varied physical exercise protocols, as a direct focus on caloric expenditure and, on the other hand, nutritional education, with a focus on reducing excessive caloric intake [2,7,10]. Recently in experimental [18-20] and clinical [21-25] studies of our group, it was established the conjugated use of physical exercise, nutritional education and phototherapy (with infrared lasers or LEDs). Thus, it was observed that, both experimental and clinical character, the administration of physical exercise, nutritional education and phototherapy protocols, besides reducing the anthropometric parameters (body weight, fat depots, circumferences and skeletal muscle mass), marked improvement of the lipid profile, reversing dyslipidemia, reducing insulin values, insulin resistance, besides enabling hepatic alterations, found in experimental studies [18-20]. The objective of this pilot study was to evaluate the enzymatic alterations of the liver through the use of the standard non-pharmacological technique in relation to the treatment conjugated with phototherapy in the reversal of non-alcoholic fatty liver disease (NAFLD).

Materials & Methods

Patient

The present pilot study, controlled and randomized, involved 20 adult obese men. Ethics committee on human research at Federal University of Sao Carlos (number 237.050) and Clinical Trials.gov (231.286) approved this study. All participants signed the informed consent form. Electronic media was used to recruit the volunteers, according to the following inclusion criteria: men, at age between 20 and 40 years old, primary obesity, body mass index (BMI) between 30 and 34.9 kg/m^2. The exclusion criteria were of continuous drugs and alcohol intake. The initial condition to participate this study was approbation in treadmill submaximal test. The evaluations were performed in two occasions: In the beginning and in the end of treatment (8 weeks).

Groups

The treatment protocols involved exercise combined with nutritional education (control group) and exercise combined with nutritional education and phototherapy (phototherapy group). The 20 men were randomly assigned Control Group (n=10) or Phototherapy Group (n=10). The control group was also placebo for phototherapy, where volunteers received non-active light treatment to mimic the psychological effects.

Nutritional education intervention

Nutritional lectures were carried out to adjust the caloric intake of the patients. The evaluation of habitual food consumption was carried out through a three-day food registry. The food data obtained were analysed using the AVANUTRI software, quantifying the caloric values, before and after the proposed treatment [26]. During all period of study, the patient did not intake alcoholic drinks.

Exercise intervention

The exercising protocol used included 30 minutes of aerobic training followed by 30 minutes of resistance training three days per week. The aerobic training consisted of running on a treadmill (Pro Fitness AP8500 Plus) with intensity of maximal heart frequency between 70 and 85%, the same as established previously by treadmill submaximal test, performed prior to the study. The part of resistance exercise training consisted of specific exercises for the main muscular groups : bench press (Biceps, Triceps, Pectorals Major and Rectus Abdominals), lat pull-down (Biceps, Teres Major and Latissimus Dorsi), Straight-Bar Cable Curl (Biceps), triceps pushdown (Triceps), hamstring curls (Semitendinosus, Biceps Femoris and Semimembranosus), calf raises (Gastrocnemius), leg press and sit-ups (Gluteus Maximus, Quadriceps Femoris, and Gastrocnemius). The loads of training were adjusted in a successive form, in each session and according to individual capacity, with inversion of volume and intensity in relation to number of repetitions, ranging from 6 to 20 repetitions in three sets and conducted using maximal repetitions (Rm) [10,23,27]. This model of training was conducted based on the guidelines of the American College of Sports Medicine [7].

Phototherapy intervention (Phototherapy Group)

In the Laboratory of Technological Support (LAT) of the São Carlos Institute of Physics, University of Sao Paulo (IFSC-USP), specifically for this research, four plates (20 × 20 cm each) made of rubberized material [21-23] were used for phototherapy. Each plate containing 16 diode lasers arranged in 4 lines distant 2.5 cm from each other, and each laser emitting in continuous mode, with 100 mW of output power through a 0.0169 cm^2 elliptical spot.

Phototherapy was performed with the plates in contact with the volunteers' skin, allowing the application of the laser perpendicularly to the skin. Each volunteer was first irradiated in the anterior region (abdomen and quadriceps) for 5 minutes, and then in the posterior region (gluteus and femoral biceps) for 5 minutes. Phototherapy was always applied right after the exercise training, so it means that the volunteers received phototherapy 3 days per week. The control group underwent the same procedure; however, the laser remained off. The parameters of irradiation was: type of diode Ga-Al-As, wavelength 808 nm, continuous mode, 16 emitters by plate with total of 4 plates, 2 box controls, spot diameter 0.3692 (horizontal) and 0.0582 (vertical), spot area 0.0169 cm^2, output power 100 mW, total energy by session 3.84 J (128 points of irradiation) and 92.16 J total of energy delivered (24 sessions).

Analysis of body composition

Through an electronic scale, all volunteers were properly weighed. The respective heights were obtained by stadiometer. After obtaining these primary data, a bioelectrical impedance analysis was carried out by means of a body composition analyzer (In Body model 720, Biospace Co. Ltd.; Seoul, Korea), using 6 different frequencies (1, 5, 50, 250, 500 and 1000 kHz), to evaluate the evolution of the volunteers during the treatment [22]. Thus, the following parameters were evaluated: body mass (kg); total body fat (kg); total trunk fat (kg), visceral fat (cm^2); total skeletal muscle mass (kg), and basal metabolic rate (BMR) (kcal).

Body metabolic progress

The development of a quantification method to measure the evolution of the metabolism through the action of a certain therapy transcends only the use of the basal metabolic rate. Thus, the use of bioelectrical bio impedance, body mass (kg), skeletal muscle mass (kg) and basal metabolic rate (kcal) variables were organized in order to allow a more accurate analysis of body metabolic progress. Thus, as the basal metabolic rate is considered the basal amount of calories for the maintenance of basal body functions and skeletal muscle, in an amount and functionality, determining the variation of the basal metabolic rate [28], we propose:

"Body metabolic progress (kcal) = [body mass (kg)/basal metabolic rate (kcal)] × skeletal muscle mass (kg)".

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Biochemical analysis

The biochemical analyses were realized after 12 hours of fasting, in specialist outpatient clinic (UNILAB/Sao Carlos) and methods for *in vitro* diagnostic were used for each measurement of specific form. The concentrations of lipid profile (total cholesterol, LDL-Cholesterol and triglyceride), insulin and the hepatic enzymes, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and gamma-glutamyl-transpeptidase (GGT) were collected in the beginning and end of the study.

Statistical analysis

Statistical analysis was performed using the software Instat 3.0 for Windows 7 (Graph Pad, San Diego, CA, USA, 1998). All data were expressed as mean and standard deviation. The significance level was set at p<0.05. The Kolmogorov–Smirnov test was used to analyse the normality of data. To compare the delta values between the groups an analysis was performed by one-way ANOVA with a post-test, using Student-Newman-Keuls for parametric data. The Person correlation was calculated between hepatic enzymes versus visceral fat. In order to better compare the obtained results, the variation, Delta, of each evaluated parameter was calculated as follow:

"Delta Value (Δ) = (final value - initial value)/ final value × (100)"

Where Δ corresponds to the evaluated parameters: anthropometric parameters, lipid profile, basal insulin, hepatic enzyme.

Results

The delta of energy intake was represented in Table 1. It is possible to observe the decrease of energy intake in both groups, possibly related to the patient's adherence to nutritional education. The delta of anthropometric parameters (Table 1) shows that the phototherapy led to an improvement in all parameters.

Delta of Energy Intake and Anthropometric Parameters				
Energy Intake	**Control Group Percentage (%)**	**Phototherapy Group Percentage (%)**	**Relation BetweenGroups**	**P Value**
	-44.13	-42.69	-	-
Total Skeletal Muscle Mass	-1.78 ± 2	+1.76 ± 2.6	3.54	0.007
Basal Metabolic Rate	-1.44 ± 1.3	+1.33 ± 2.3	2.77	0.005
Body Metabolic Progress	-0.94 ± 3.6	+4.53 ± 3.2	5.47	0.04
Body Mass	-1.55 ± 1.4	-6.22 ± 3	4.67	0.007
Total Body Fat	-3.6 ± 4.8	-17.9 ± 10	14.3	0.01
Total Trunk Fat	-2.72 ± 4.7	-17.5 ± 8.5	14.7	0.005
Visceral Fat	-3.45 ± 5.6	-19.9 ± 12	16.4	0.03

Table 1: Values of energy intake, total skeletal muscle mass (p<0.007), basal metabolic rate (p<0.005), body metabolic rate (p<0.04), body mass (p<0.007), total body fat (p<0.01), total trunk fat (p<0.0.05) and visceral fat (p<0.03) express in mean ± standard deviation of percentage. Control Group=exercise + nutritional education (n=10) and Phototherapy Group: exercise + nutritional education + phototherapy (n=10). The statistical difference found according to Student "t" test of comparison p<0.05 between groups.

Figure 1 shows the delta of lipid profile (total cholesterol (p<0.03), LDL (p<0.04), triglyceride (p<0.03) and basal insulin (p<0.02). One can observe that the phototherapy group presented a significant decrease in these parameters when compared to the control group.

A comparison of hepatic enzymes analysis are presented in Figure 2 for both control and phototherapy groups. The glutamic oxaloacetic transaminase-GOT (p<0.0009), glutamic pyruvic transaminase-GPT (p<0.002) and gamma-glutamyl-transpeptidase-GGT (p<0.001) showed significant decrease when patients received phototherapy.

Table 2 presents the correlation values of persons, correlating liver enzymes with visceral fat. It is possible to notice higher correlation values of these variables for phototherapy group.

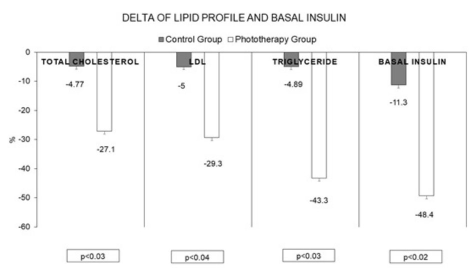

Figure 1: Values of total cholesterol (p<0.03), LDL (p<0.04), triglyceride (p<0.03), basal insulin (p<0.02) expressed in percentage, for control group (n=10) and phototherapy group (n=10). The statistical difference found according to Student "t" test of comparison p<0.05 between groups.

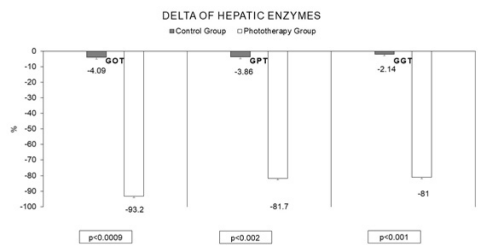

Figure 2: Values of GOT – (glutamic oxaloacetic transaminase) - ($p<0.0009$), GPT (glutamate pyruvate transaminase) - ($p<0.002$) and GGT (gamma glutamyl transferase) - ($p<0.001$) express in percentage, for control group (n=10) and phototherapy group (n=10). The statistical difference found according to Student "t" test of comparison $p<0.05$ between groups.

Persons correlation between hepatic enzymes and visceral fat		
Parameters	**Visceral Fat**	
	Control Group	Phototherapy Group
Glutamic oxaloacetic transaminase (GOT)	0.17	0.96
Glutamic pyruvic transaminase (GPT)	-0.74	0.82
Gamma glutamyl transpeptidase (GGT)	0.31	0.9

Table 2: Persons correlations between glutamic oxaloacetic transaminase (GOT) versus visceral fat, glutamic pyruvic transaminase (GPT) versus visceral fat and gamma glutamyl transpeptidase (GGT) versus visceral fat in relation to control group and phototherapy group.

Discussion

The process unleashed by physical inactivity and inadequate feeding, over time, causes changes in body composition that lead to the development of diseases and comorbidities associated with them [6,9,29,30]. In this way, the excess of fat, dyslipidemias and insulin resistance can promote the accumulation of fat in the liver, known as non-alcoholic fatty liver disease [4,31].

The importance of the standard treatment, involving nutritional education and physical exercise, is due to the major efficiency of these treatments when performed together. An example is the reduction of body weight solely through nutritional education, which can affect the patient, promoting loss of skeletal muscle mass, since the protein content may be insufficient [32]. Thus, standard non-pharmacological therapy, adopted for the treatment of this disease, is composed of physical exercise combined with nutritional education [10,27,33,34].

However, in recent studies, it has been possible to verify that by means of a process called amplification of metabolic activity or metabolic rehabilitation, it is possible to obtain better results. This process demonstrates the action of using low level laser associated with moderate intensity exercise to promote enzymatic modulations [19,35] and mitochondrial alterations [19,36] that potentiate the beneficial effect of physical exercise [18-23,37,38].

In the present study, the adequacy of caloric nutritional education was performed through nutritional lectures with the objective of raising awareness of volunteers about the importance of choosing healthy food. The calories were quantified by software AVANUTRI [26]. Table 1 shows the accentuated reduction of energy intake in both groups, indicating that the volunteers changed their nutritional habits over the 8 weeks of treatment.

We believe the nutritional lectures and the process of reporting their meals in details for calories quantification helped the volunteers to become more aware of the quality of the food they were ingesting during their meals. In both groups, the energy intake decreased more than 40%, showing the efficiency of the process adopted for nutritional instruction.

In Table 1, we observed an increase in total skeletal muscle mass, which is directly responsible for the uptake of energy substrates for the production of ATP [28], in which the phototherapy group showed increase in relation to the control group. This fact is even more important in view of the increase in skeletal muscle mass, as well as an increase in the basal metabolic rate (Table 1).

Consequently, there was an increase in the daily consumption of calories to produce energy, helping to reduce body weight more sharply, when comparing phototherapy group with the control group. However, it is convenient to state that the training model adopted is not specific for hypertrophy, because it is an undulatory training. This training aims to reduce body weight and body fat, and not increase skeletal muscle mass [10,11]. Thus, the significant increase in body muscle volume can be directly related to the joint action between the training methodology used and the action of phototherapy [37].

When the variables total body fat, trunk fat and visceral fat were analysed (Table 1), it was possible to observe their decrease in both groups, however, this decrease was more pronounced for the phototherapy group. Thus, it is possible to observe that the combination of moderate intensity exercises, nutritional education and low level laser therapy, was more efficient, as confirmed by previous studies [21-25,37,39]. These reductions may lead to the decrease in the likelihood of comorbidities, such as hypertension [8,40], various cardiovascular problems [3,40] insulin resistance and diabetes mellitus type 2 [3,41].

In addition, the reduction of the visceral fat (Table 1) is directly related to the decrease in basal insulin (Figure 1), factors that have already been correlated in the literature [5,6,12]. In our study, it was possible to verify the reduction of basal insulin when the values of the phototherapy group were compared with the control. It was possible to observe greater effectiveness of the new therapy and a new possibility of treatment of insulin resistance, considered a step for diabetes mellitus type 2, without the use of medications or reducing the use of drugs established to control it.

Thus, through an increased metabolic capacity by the combined action of moderate intensity exercise and phototherapy [18,21,37], it was possible to generate an amplified metabolic demand [19], conditioning an intensified oxidative capacity of the organism [19,22], providing greater reduction of body weight, anthropometric and biochemical variables. This form, it is possible to notice the significant difference between groups (Table 1), when the phototherapy group showed better performance in relation to control group, showing a better body metabolic progress (BMP).

A change usually found in situations of overweight and obesity is dyslipidemia [3,14,42], where the lipid profile is above the ideal, what may increase the risk of developing cardiovascular diseases, such as hypertension [3,14], atherosclerosis [3] and other cardiovascular changes [3,8]. In our study, the decrease in this risk factor was observed in Figure 1, since the lipid variables, like total cholesterol, LDL-cholesterol and triglycerides were significantly reduced. Our previous experimental study corroborates our current results [18], where the results jointly point to the increase of the oxidative capacity [19,43], besides the probable enzymatic modulation [19,35] of the enzymes lipases hormone sensitive and lipase lipoprotein.

During moderate intensity exercise, triglyceride hydrolysis promotes its fragmentation into 3 fatty acids and glycerol molecules. This latter substrate, in the biochemical process of gluconeogenesis, conditions the production of glycogen and its consequent storage in the muscles and in the liver, initiated during the training. In this context, as attributed in experimental work [18], the association between moderate intensity exercise and phototherapy promoted an increase in hepatic glycogen concentration and a consequent decrease in liver fat. The high concentration of liver fat is a long-term cause of non-alcoholic hepatic steatosis and cancer [5,6].

In our study, our results were corroborated by the previous experimental work [18], although using different support variables, with a marked reduction of hepatic transaminase enzymes (Figure 2), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and gamma glutamyl transferase (GGT), when comparing the values of the phototherapy group and the control group.

The importance of improvement of these parameters is translated when looking at the Table 2 with value of Person`s correlations. Those results show the values of hepatic enzymes versus visceral fat in phototherapy group condition, showing that the greater decrease in visceral fat, the greater decrease in liver enzymes analysed.

On the contrary, the correlation of these same variables does not show the same representativeness in control group condition. In this way, it is possible to affirm that the association of methods (moderate intensity exercise, nutritional education and low-level laser) is an efficient methodology for the control and reduction of non-alcoholic fatty liver disease, without the use of medication.

This decrease can be associated with 4 factors that, when added, can cause this effect. In first, the adequacy of energy balance, from positive to negative, as described in previous studies [9,33,44,45]. In second, restructuring of the energy composition ingested inhibits the storage of lipids in the liver [46].

In third, the systemic enzymatic modulation promoted by the exercise and the laser action, both in relation to the lipases enzymes in direct action in the hydrolysis of circulating and intracellular triglycerides, as well as the increase of Citrate Synthase, the main enzyme in the Krebs Cycle described in the literature [18,19,35,43]. Finally, the decrease in the area of visceral fat, a factor directly related to fat storage in the liver [5,6]. Figure 3 shows the summary of key findings related to the study.

Thus, even in previous studies, experimental and clinical [18-23,32] corroborate the results of the present study, making it necessary to increase the sample size, age group and gender, thus allowing greater safety in a future clinical application.

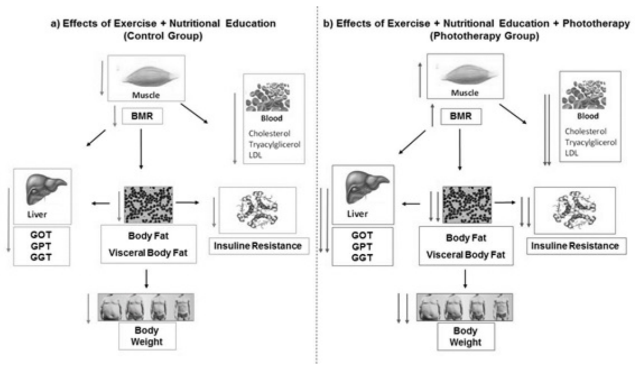

Figure 3: The summary of key findings related to kind of control group (A) and phototherapy group (B). It is possible observe the great difference in phototherapy group in relation to control group.

Conclusion

In the present study, we were able to show that combining physical exercise, nutritional education and phototherapy for 8 weeks to treat obese men provided a great improvement in the anthropometric parameters, in lipid profile, basal insulin and hepatic enzymes. The found results show that phototherapy is a promising technology to associate to standard methodology (physical exercise and nutritional education) to the treatment of obesity and its comorbidities, mainly without use of medicines and invasive procedures. However, further studies should be conducted to better explore this potential instrument.

Conflict of Interest

The authors declare no conflict of interest.

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