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Effect of laser biostimulation and a low-calorie diet *vs.* a low-calorie diet alone on insulin resistance, inflammatory biomarkers, and depression among obese postmenopausal women: a randomized controlled trial

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Abstract. – OBJECTIVE: Postmenopausal women are significantly predisposed to a multitude of disorders. Laser biostimulation (LB) and a healthy diet have been linked to multiple health benefits. This study aimed to investigate the effect of a combined LB and balanced low-calorie diet (LCD) *vs.* an LCD alone on insulin resistance (IR), inflammatory biomarkers, and depression score in obese postmenopausal women.

PATIENTS AND METHODS: In the present study, a total of 66 postmenopausal women, with a mean age of 66.61 ± 4.80 years and a body mass index (BMI) of 35.93 ± 2.67 kg/m^2, were randomized into two equal groups. The experimental group received LB and LCD (including 50-60% carbohydrates, 15-20% protein, 20-35% fat, and 25 g of fiber/day plus a restriction of 500-1000 kcal/d), while the control group followed the same diet program only for 12 weeks. Before and after the intervention, IR [measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA–IR index)], inflammatory biomarkers [C-reactive protein (CRP), white blood cells (WBCs), lymphocytes, and erythrocyte sedimentation rate (ESR)], and depression level [as assessed by the Hamilton Depression Rating Scale (HAMD-17)] were all measured.

RESULTS: Using an intention-to-treat analysis for 60 women who completed the study, the body weight average reduction was -13.14% for the experimental group (p<0.001) *vs.* -6.36% for the control group (p<0.001). BMI, IR, inflammatory markers, and depression levels were also similarly changed.

CONCLUSIONS: In postmenopausal obese women, adding LB to a suitable dietary program provides the most significant benefit in terms of lowering IR, metabolic inflammation, and depression.

Key Words:
Anti-inflammatory agents, Blood sedimentation, Caloric restriction, Low-level light therapy, Post-menopause, Risk factors.

Introduction

Globally, women after menopause are more likely to develop metabolic and psychiatric illnesses, which are linked to increased mortality and morbidity rates[1]. In Egypt, because of a lack of health facilities, women have a higher rate of menopause-related conditions[2]. For instance, obesity, which is associated with higher insulin resistance (IR) and inflammatory markers [C-reactive protein (CRP), white blood cells (WBCs)[1], lymphocytes, and erythrocyte sedimentation rate (ESR)][3]. Moreover, psychiatric disorders are common in postmenopausal women, which reduce immune system response and promote inflammation[4].

These comorbidities are pervasive in obese postmenopausal women[1] and are associated with elevated drug consumption, thus increasing the risk of adverse events[3]. Consequently, it is critical to investigate potential non-pharmacological safety interventions that reduce multimorbidity associated with obesity.

Laser biostimulation (LB) and dietary restriction demonstrated more desirable changes in body composition[5,6]; LB has achieved remarkable results in obesity management[6], being a non-invasive, quick, and safe intervention that stimulates conventional acupoints[7]. Many studies[8,9] have identified the role of LB in weight loss.

Furthermore, LB has multiple significant health benefits[10], such as changing cellular metabolic processes and regulating inflammatory mediators[11]. One of the most recent LB applications is the Laser Watch, which provides laser blood

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irradiation[7] and has been revealed to improve microcirculation, insulin secretion, lipid profile, and body composition[10].

A well-balanced diet is a crucial component of lifestyle adjustments to lower BMI[5], inflammatory and metabolic indicators, and cardiovascular risks[12]. Accordingly, the current study's purpose was to determine whether a combined LB and low-calorie diet (LCD) demonstrate better outcomes than LCD alone to reduce IR, inflammatory markers, and depression in postmenopausal obese women.

Patients and Methods

Study Design and Ethical Approval

According to the latest CONSORT statement and the Helsinki Declaration, this 12-week parallel randomized clinical trial was conducted on postmenopausal women from January 2020 to January 2021. After fully demonstrating the study's objectives and voluntary purpose, each participant provided written informed consent. Faculty of Physical Therapy Ethics Committee, Cairo University, Egypt approved the study under No. P.T.REC/012/002677.

Study Setting and Participants

A group of eligible postmenopausal women was assessed and enrolled by physicians (MR, HA, and NA; co-authors) from the Internal Medicine Department, outpatient clinic, Cairo University Hospital, Egypt. The participants were recruited in the study based on the following inclusion criteria: selected women had not menstrual cycle for an average of 11.05 ± 2.13 years, had a BMI of 35.93 ± 2.67 kg/m^2, and were 66.61 ± 4.80 years old. They had moderate depression [8–16 on the Hamilton Depression Rating Scale (HAMD-17)] and a sedentary lifestyle (less than 14 units defined by the Godin leisure time questionnaire) with a mean score of 10.99 ± 1.38.

Participants were divided into two equal groups: the experimental group (n=33) received LB with an individualized LCD program and the control group (n=33) followed the same diet program alone for 12 weeks. Insulin resistance was assessed by the HOMA-IR index; anthropometric measures [weight, BMI, and waist circumference (WC)]; inflammatory biomarkers (CRP, WBCs, lymphocytes, and ESR), and depression (recorded by the HAMD-17 scale) were assessed before and after the intervention.

Exclusion Criteria

Women were excluded from this study if they were: smokers, diabetics, alcoholics, uncontrolled hypertensives, receiving hormonal therapy, following weight reduction or exercise program at least six months prior to participation in this study, on medications known to affect their psychological states or bodyweight, phototherapy sensitive, having cognitive impairment, having malignant diseases or any cardiovascular disease, and having any additional factors that might affect our outcome measures or the intervention progression.

Randomization

Sixty-six eligible postmenopausal women were randomly assigned (1:1) to either the experimental group (LB with LCD) or the control group (LCD program only), utilizing block randomization with block sizes of 2, 4, and 6 *via* the R Software (version 2.11) to obtain balanced groups. The study statistician created the randomization list, which was then concealed in numbered envelopes in a blinded manner. Hence, both the participants and the clinician were unaware of the assigned intervention.

Eligibility

Initially, a total of eighty postmenopausal women were evaluated for eligibility; approximately fourteen women were excluded (ten met the exclusion criteria, two refused to participate, and two for other reasons). Six women were lost to follow-up for personal reasons, and only sixty women completed the trial and were included in the statistical analysis (Figure 1).

Intervention

LB

The experimental group received LB *via* a non-invasive laser watch that radiated photobiology infrared laser waves through bilateral nasal probes and specific wrist acupuncture point stimulation without registering any identified hazards after the intervention, which was operated according to the parameters[7] shown in Table I.

Diet Program (LCD)

During the first six weeks of the study, both groups' diets were restricted by 500 kcal/d, and the mean energy intake was 1773.62 ± 41.70 kcal/d. In the final six weeks of the study, the diet was restricted to 1000 kcal/d of daily calorie requirements[13], which were cal-

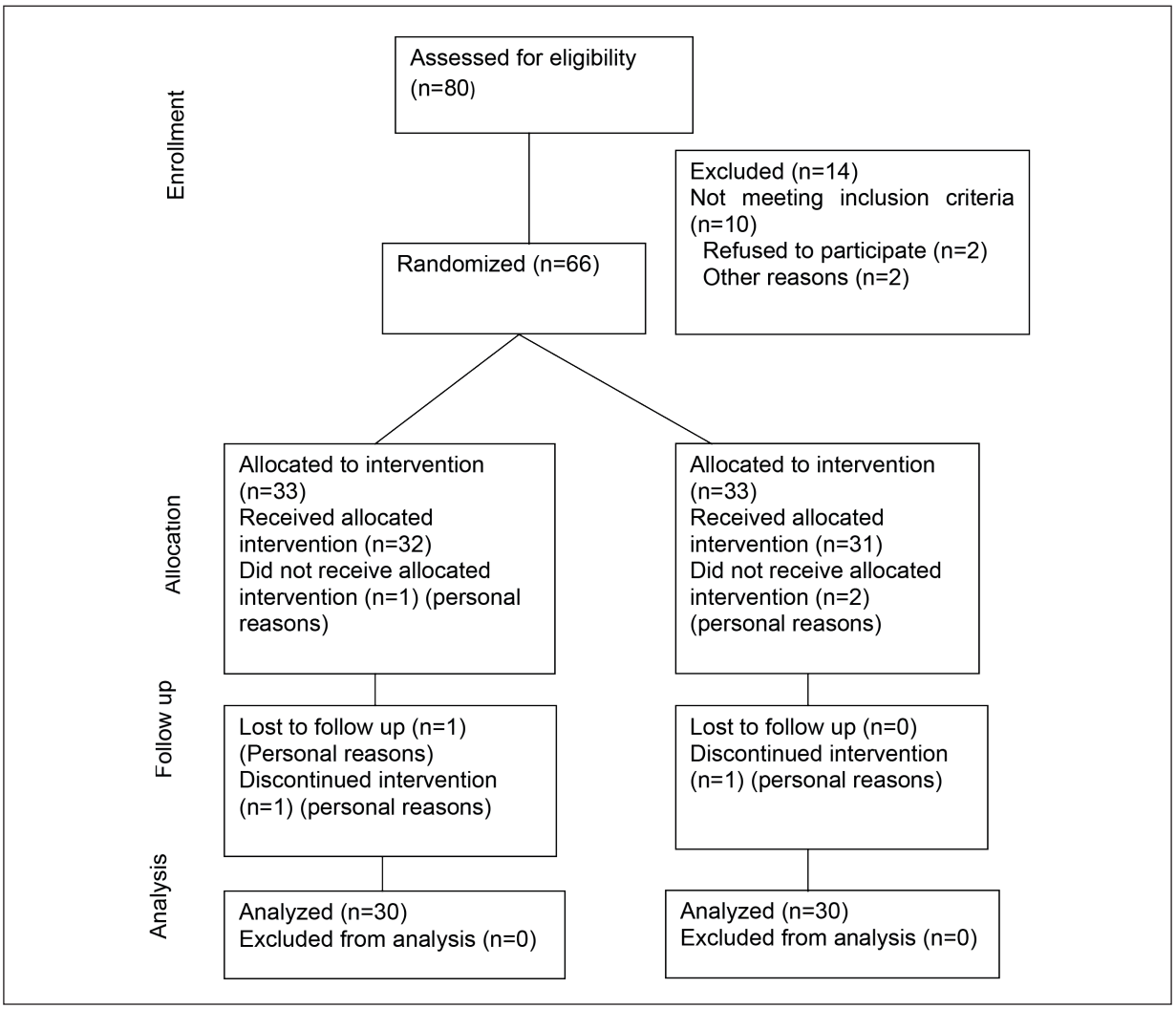

Figure 1. Consort flow diagram of this study.

culated using the Harris-Benedict equation for daily energy expenditure estimation[14], and the mean energy intake was 1276.70 ± 41.93 kcal/d[15]. The prescribed restricted balanced diet included 50-60% carbohydrates, 15-20% protein, 20-35% fat, and 25 g of fibers per day[16]. A nutritional consultant and a physiotherapist regularly contact participants on a regular basis to ensure their adherence to the prescribed diet program, avoidance of unsafe eating patterns, and maintenance of the same level of daily physical activity.

Primary Outcome Measures

Venous blood samples were collected at the beginning as well as the end of the 12-week study period in the outpatient clinic (nearly at 9:00 am after at least 12 hours of fasting) to analyze blood glucose and insulin levels in order to calculate insulin sensitivity using the HOMA-IR index formula [fasting plasma glucose (mmol/l) × fasting serum insulin (mU/l)/22.5] and to measure the inflammatory biomarkers (WBCs count, lymphocytes, ESR, and CRP levels).

Depression

A depression assessment scale (HAMD-17-item scale) was applied in our study with a maximum score of 52 to categorize the participants as normal, mild, moderate, or extreme depression based on scores of 0-7, 8-16, 17-23, and over 24, respectively.

Secondary Outcome Measures

All participants' BMI (kg/m^2) was calculated by dividing their body mass (kg) by their heights

Table I. Baseline characteristics of study participants mean ± standard deviation (SD).

Characteristics		Experimental group (n =30)	Control group (n =30)	*p*-value
Age (yrs)	Mean ± SD	66.10 ± 4.56	67.12 ± 5.06	0.482
	Range	60.00-75.00	60.00-75.00	
Physical activity units	Mean ± SD	10.90 ± 1.45	11.07 ± 1.31	0.642
	Range	9.00-13.00	9.00-13.00	
Menstrual cycle absences (yrs)	Mean ± SD	10.83 ± 2.00	11.27 ± 2.26	0.435
	Range	7.00-15.00	8.00-15.00	
Energy intake (kcal/d)	Mean ± SD	2277.50 ± 45.69	2276.40 ± 37.99	0.920
	Range	2200.00-2360.00	2230.00-2350.00	
Height (cm)	Mean ± SD	153.21 ± 3.83	152.89 ± 3.24	0.725
	Range	147.00-161.00	148.00-160.00	
Weight (kg)	Mean ± SD	84.93 ± 9.04	83.97 ± 8.59	0.674
	Range	70.40-100.60	67.70-98.30	
BMI (kg/m^2)	Mean ± SD	35.99 ± 2.68	35.86 ± 2.71	0.849
	Range	30.80-39.90	30.10-39.70	
Waist circumference (cm)	Mean ± SD	104.62 ± 9.47	104.15 ± 8.79	0.843
	Range	88.60-120.60	88.70-120.50	
Insulin resistance	Mean ± SD	2.96 ± 0.72	3.01 ± 0.66	0.792
	Range	1.97-4.99	1.96-4.90	
CRP (mg/L)	Mean ± SD	4.80 ± 0.63	5.08 ± 0.67	0.109
	Range	3.70-6.00	3.71-6.01	
ESR (mm/hr)	Mean ± SD	16.60 ± 5.16	17.37 ± 4.86	0.556
	Range	7.00-25.00	8.00-25.00	
WBCs (10^9/L)	Mean ± SD	9.19 ± 1.02	9.24 ± 1.03	0.851
	Range	7.50-11.20	7.40-11.10	
Lymphocytes (10^9/L)	Mean ± SD	36.00 ± 5.85	37.73 ± 6.31	0.274
	Range	27.00-47.00	28.00-48.00	
Depression scale	Mean ± SD	11.93 ± 0.40	11.83 ± 0.48	0.482
	Range	10.89-13.14	10.88-13.13	
Education level				
1st	N (%)	4(13.3%)	4(13.3%)	0.998
2nd		3(10.0%)	3(10.0%)	
3rd		8(26.7%)	8(26.7%)	
4th		7(23.3%)	8(26.7%)	
5th		8(26.7%)	7(23.3%)	

†BMI, Body mass index; CRP, C - reactive protein; ESR, Erythrocyte Sedimentation Rate; WBCs, White Blood Cells.
Data represented as mean ± standard deviation (SD) and range (min-max) for continuous data and N (%) for categorical data.

(m^2). Furthermore, WC was estimated during full expiration using an elastic tape midway between the last rib and the upper iliac crest border.

Estimation of Sample Size

With a 95% confidence interval, a total required sample size of 30 women in each group was calculated. A type I error rate of 0.05, and a type II error rate of 80% statistical power, a two-tailed *t*-test (i.e., the difference between two independent means of two groups) was assumed to estimate moderate effect size, Cohen's d (0.5), and a drop-out rate of 5%.

Statistical Analysis

With sixty-six women enrolled in this study, we had 91% retention at 12 weeks, with sixty of the sixty-six women completing final evaluations (Figure 1). For subjects who had withdrawn, an intention-to-treat analysis was performed. The last observation carried forward method was used for data filling. Statistical analysis was conducted with SPSS 25 statistical software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether the data were normally distributed. Continuous data were described as mean ± standard deviation (SD). The categorical

data were expressed as absolute frequencies and percentages. Unadjusted comparisons of baseline characteristics were performed using independent samples *t*-test for continuous data and Chi-square tests for categorical data.

A mixed-repeated-measures analysis of variance (ANOVA) was applied to compare the mean values of variables between the experimental and control groups and between pre-and post-intervention in each group. Huynh-Feldt was undertaken when Mauchly's sphericity test denied the assumption of sphericity. The partial eta-squared ($\eta^2 p^2$) effect size was calculated to assess the differences between and within the experimental and control groups. Bonferroni's test was used as a post hoc test to follow significant interactions or main effects, mean values of dependent variables for both groups, and pre-and post-intervention outcomes in each group. *p*-values lower than 0.05 were considered statistically significant.

Results

A total of sixty obese postmenopausal women were included in this study, with a mean age of 66.61 ± 4.80 (ranging between 60.00-75.00 years), a mean weight between 84.45 ± 8.76 kg (ranging between 67.70-100.60 kg), and a mean BMI of 35.93 ± 2.67 kg/m^2 (ranging from 30.60-39.80 kg/m^2). Thirty women received LB combined with LCD (the experimental group), while the remaining thirty women, serving as the control group, received LCD alone.

As displayed in Table II, there were no statistically significant differences between the experimental and control groups regarding qualitative and measured variables at baseline ($p>0.05$).

Table III demonstrates a significant difference within the experimental and control groups in all dependent variables before and after the intervention ($p<0.001$), along with a significant interaction between intervention type and time, Wilks' lambda ($p<0.001$) for all variables.

There was a significant interaction between intervention type and time regarding weight and BMI ($p < 0.001$, η^2 $p = 0.684$ and 0.938, respectively) and a significant main effect of the intervention ($p < 0.001$, η^2 $p = 0.212$ and 0.291, respectively). In the experimental group, we observed a significant decrease in weight and BMI after 12 weeks of follow-up by 13.14 kg and 11.28 kg/m^2, respectively, compared to the control group, whose levels decreased by 6.36 kg and 6.41 kg/m^2, respectively ($p<0.001$, η^2 $p=0.947$ and 0.995, respectively).

With respect to WC and IR, there was a significant interaction between intervention type and time ($p<0.001$, η^2 $p=0.962$, $p<0.001$, η^2 $p=0.676$, respectively). Also, there was a substantial main effect of time ($p<0.001$, η^2 $p=0.997$, $p<0.001$, η^2 $p=0.918$, respectively) and a significant main effect of intervention ($p=0.023$, η^2 $p=0.225$, $p=0.012$, η^2 $p=0.240$, respectively).

Regarding the CRP and ESR levels, there was a significant interaction between intervention type and time ($p<0.001$, η^2 $p=0.904$, $p<0.001$, η^2 $p=0.791$, respectively) and a substantial main effect of intervention ($p<0.001$, η^2 $p=0.201$, $p<0.001$, η^2 $p=0.147$, respectively). Time also had a substantial main effect ($p<0.001$, η^2 $p=0.979$, $p<0.001$, η^2 $p=0.962$, respectively).

In terms of WBCs and lymphocytes concentrations, a statistically significant reduction in the experimental group was observed (MD=-1.84 ± 0.23 10^9/L and MD=-8.13 ± 1.43 10^9/L, respectively), compared to the control group (MD=-0.67 ± 0.11 10^9/L and MD=-3.27 ± 0.74 10^9/L, respectively) after 12 weeks of follow-up ($p < 0.001$). Additionally, WBCs and lymphocytes concentrations ($p<0.001$) with a large effect size (η^2 p = 0.914 and 0.825, respectively) revealed a significant main effect of time ($p<0.001$) with a large effect size (η^2 $p=0.980$ and 0.963, respectively) and a significant main effect of intervention ($p=0.015$ and 0.008, respectively) with a large effect size (η^2 $p=0.219$ and 0.116, respectively).

For the depression scale, there was a significant interaction between intervention type and time ($p<0.001$, η^2 $p=0.803$) (Table III). Time ($p<0.001$, η^2 $p=0.932$) and group ($p<0.001$, η^2 $p=0.297$) had the main significant effect. Additionally, the experimental group experienced a significant reduction in the depression scale over time when compared to the control group (MD=-2.25 ± 0.50 *vs.* MD = -0.66 ± 0.27; $p<0.001$).

Discussion

The current study aimed to compare the effect of LB combined with a balanced LCD *vs.* LCD alone on IR, inflammatory biomarkers, and depression levels in obese postmenopausal women. The results showed an average reduction of the body weight -13.14% for the experimental group ($p<0.001$) *vs.* -6.36% for the control group. There

Table II. Comparison of all measured variables before and after 12 weeks, in both experimental and control groups mean ± standard deviation (SD).

Variables		Pre-intervention	Post-intervention		% of improvement	Interaction (Group X Time)		Within groups (Time)		Between groups (groups)		*p*-value[b]
					p-value[a]	η^2 p	p-value[a]	η^2 p	p-value[a]	η^2 p		
Weight (kg)	Experimental group	84.93 ± 9.04	73.77 ± 8.94	-11.04 ± 2.78	↓13.14%	<0.001*	0.684	<0.001*	0.947	0.040*	0.212	<0.001*
	Control group	83.97 ± 8.59	78.63 ± 8.64	-5.33 ± 0.20	↓6.36%							<0.001*
BMI (kg/m^2)	Experimental group	35.99 ± 2.68	31.93 ± 2.71	-4.06 ± 0.30	↓11.28%	<0.001*	0.938	<0.001*	0.995	0.029*	0.291	<0.001*
	Control group	35.86 ± 2.71	33.56 ± 2.78	-2.30 ± 0.13	↓6.41%							<0.001*
Waist circumference (cm)	Experimental group	104.62 ± 9.47	90.09 ± 9.28	-14.52 ± 0.51	↓13.89%	<0.001*	0.962	<0.001*	0.997	0.023*	0.225	<0.001*
	Control group	104.15 ± 8.79	96.27 ± 8.88	-7.87 ± 0.81	↓7.56%							<0.001*
Insulin resistance	Experimental group	2.96 ± 0.72	2.26 ± 0.58	-0.70 ± 0.20	↓23.65%	<0.001*	0.676	<0.001*	0.918	0.012*	0.240	<0.001*
	Control group	3.01 ± 0.66	2.73 ± 0.62	-0.28 ± 0.06	↓9.30%							<0.001*
CRP (mg/L)	Experimental group	4.80 ± 0.63	3.72 ± 0.55	-1.09 ± 0.13	↓22.5%	<0.001*	0.904	<0.001*	0.979	<0.001*	0.201	<0.001*
	Control group	5.08 ± 0.67	4.66 ± 0.63	-0.42 ± 0.08	↓8.267%							<0.001*
ESR (mm/hr)	Experimental group	16.60 ± 5.16	11.80 ± 4.50	-4.80 ± 0.92	↓28.92%	<0.001*	0.791	<0.001*	0.962	0.046*	0.147	<0.001*
	Control group	17.37 ± 4.86	15.23 ± 4.76	-2.13 ± 0.35	↓12.32%							<0.001*
WBCs (10^9/L)	Experimental group	9.19 ± 1.02	7.35 ± 0.84	-1.84 ± 0.23	↓20.02%	<0.001*	0.914	<0.001*	0.980	0.015*	0.219	<0.001*
	Control group	9.24 ± 1.03	8.57 ± 1.05	-0.67 ± 0.11	↓7.25%							<0.001*
Lymphocytes (10^9/L)	Experimental group	36.00 ± 5.85	27.87 ± 5.18	-8.13 ± 1.43	↓22.58%	<0.001*	0.825	<0.001*	0.963	0.008*	0.116	<0.001*
	Control group	37.73 ± 6.31	34.47 ± 6.16	-3.27 ± 0.74	↓8.64%							<0.001*
Depression scale	Experimental group	11.93 ± 0.40	9.68 ± 0.63	-2.25 ± 0.50	↓18.86%	<0.001*	0.803	<0.001*	0.932	<0.001*	0.297	<0.001*
	Control group	11.83 ± 0.48	11.16 ± 0.53	-0.66 ± 0.27	↓5.66%							<0.001*

‡BMI, Body mass index; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; WBCs, White Blood Cells.
Δ: Mean difference of post-pre value (MD). $\eta^2 p$, Partial Eta-Squared ranges from 0 to 1 (0.01=small, 0.06=medium, and 0.14=large effect-size).
[a], Mixed repeated-measures ANOVA.
[b], Post hoc using paired sample *t*-test.
*, Statistically significant at $p < 0.05$.

was also a reduction in BMI, IR, inflammatory markers, and depression scores.

The current findings are compatible with previous studies[8,9] which detected a reduction of fat deposits of about 6-12 inches of WC after LB. Jackson et al[17] found that applying LB it resulted in a substantial reduction in body weight and BMI with $p<0.0005$ and $p<0.001$, respectively. Furthermore, in a study of seventy-four postmenopausal women with visceral obesity, Wozniak et al[10] suggested that combining LCD with laser therapy reduced body weight, BMI, and waist-hip ratio (WHR) more than LCD alone. Weight loss has been linked to the LB effect by increasing lipid metabolism[18] and inducing an antioxidant effect on adipocytes, which contributes to the production of adiponectin[19]. In addition, the LCD decreases body weight by reducing the amount of energy input[5].

Our results regarding inflammatory biomarkers (ESR, CRP, and WBCS) were supported by Thomas et al[20], who found a substantial decrease in the inflammatory markers (WBCs, lymphocytes, eosinophils, ESR, and CRP) after LB sessions. LB has also been shown to lower ESR levels in people with inflammatory arthritis[21], possibly due to diminished plasma fibrinogen[20]. It has been shown that after LB intervention, the amount of cyclic adenosine monophosphate (cAMP)[7] increased, which acts as an inflammatory modulator in many cells[22].

The LB could reduce intracellular reactive oxygen species (ROS) by inhibiting prostaglandin production and subsequent biochemical reactions[23]. A low-calorie diet was found to have a greater anti-inflammatory benefit[5], where dietary fibers were inversely correlated with serum CRP concentrations and inflammatory cytokines[10]. Moreover, lower sodium and saturated fat intake improved the lipid profile and blood pressure control[5]. Also, higher fiber consumption and fewer sugary products resulted in lower blood glucose levels[24].

Regarding IR, Sene-Fiorese et al[25] stated that LB combined with LCD diet led to a more significant reduction of the HOMA-IR index ($p<0.0001$), which is congruent with our findings. LB affects insulin sensitivity by reducing the intercellular levels of inflammatory cytokines released from adipocytes and contributes to IR[26]. Additionally, laser therapy improves cation transport across the cell membrane, disrupted in hyperinsulinemia or IR[22]. Accordingly, a calorie-reduced diet strongly correlates to weight loss and enhanced insulin sensitivity[27].

As a result of mitochondrial malfunction, postmenopausal women are more susceptible to depression, as evidenced by lower energy levels[4]. LB enhances the mitochondrial activity and adenosine triphosphate (ATP) generation, which can help alleviating depression symptoms[26]. Furthermore, a well-balanced diet rich in fruits and vegetables increases the antioxidant effect, reducing free radicals and protecting brain cells[27].

Morries et al[28] found that LB improves memory and decreases depression, headaches, insomnia, and anxiety in chronic traumatic brain injury patients. Moreover, Cohen et al[29] found that LB lowers postmenopausal women's mental and behavioral difficulties, which is congruent with our findings. Linde et al[30] found a relationship between LCD intervention and improvements in depressive symptoms in obese women.

Limitations

This study evaluated the effect of LB with LCD on the physical parameters and the psychological status in obese postmenopausal women. Moreover, we highlighted the benefits of non-invasive LB in sedentary subjects who did not prefer to exercise or abstain from surgical or pharmacological adverse effects.

Despite the promising results, this research was focused only on one form of LB and one dietary weight loss program in obese postmenopausal women. Future studies are needed to investigate various dietary regimens and LB wavelengths in different populations and health conditions to enhance the generalization of the results. Participants' selection was limited to women with no cardiovascular disorders or medical problems. Women with surgical menopause and those on hormonal therapy were excluded, which may cause a limited variation in the study results.

Conclusions

The current study's findings support the combined effect of LB with LCD in decreasing inflammatory biomarkers, IR, and depression in postmenopausal women, paving the way to apply the current approach to high-risk patients, including diabetic and hypertensive patients.

Contribution Statement

M. M. and E. N. contributed to data curation, methodology, investigation, conceptualization, M. R., H. E., and N. A. participated in methodology, editing, supervision, validation, writing-original draft, and all authors read and approved the final version of the manuscript and agreed with the order of presentation of the authors.

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Conflict of Interest

The authors state that they have no competing interests.

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