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Original Article

The Effect of Aerobic Training and Spirulina on Nesfatin-1 and Peptide YY in Overweight Elderly Men: A randomized trial

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Abstract

Background and purpose: Research has shown that aging affects appetite and energy intake. The aim of this study was to investigate the protective effect of aerobic training (AT) and spirulina (SP) on Nesfatin-1 and Peptide YY (PYY) in overweight elderly men.
Materials and Methods: In this clinical trial study, 32 overweight elderly men (age 57.50±4.84 years, Body mass index: BMI 26.90±2.85 kg/m2) in public and administrative centers of Bandar-e-Anzali were selected and randomly divided into four groups including Overweight (OW), Overweight-Aerobic Training (OWAT), Overweight-Spirulina (OWSP), and Overweight-Aerobic Training -Spirulina (OWATSP). AT, including running on treadmill was performed three sessions per week with intensity of 70 - 85% of maximum heart rate for eight weeks. The groups of OWSP and OWATSP were provided two 500 mg SP tablets daily in the morning and evening. Serum Nesfatin-1 and PYY levels were measured using the kit and ELISA method. Data were tested using independent samples t-test and ANCOVA at a significance level of p <0.05
Results: Mean weight and BMI in the groups of aerobic exercise, spirulina and exercise-spirulina decreased significantly (P<0.05). The results showed that exercise, spirulina and exercise-spirulina caused a significant increase in Nesfatin-1 and Peptide YY compared to the pretest and control group (P=0.001). Also, the Nesfatin-1 and Peptide YY level of the exercise-spirulina group was significantly higher than the spirulina group (P=0.003).
Conclusion: AT intervention and daily intake of SP supplement were associated with increase in hormones affecting appetite. It was then recommended that overweight and obese elderly people use this effective combination strategy for its benefits.

Keywords: Aging; Overweight; Exercise; Spirulina; Nesfatin-1; Peptide YY

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1. *Introduction*

Currently, 962 million people worldwide are over the age of 60, and it is estimated that 22% of the world's population will be 60 and older by 2050. A large part of healthcare is spent on the elderly, and this rate will increase due to the projected increase in this population (1). Age has been shown to affect appetite and energy intake; appetite is physiologically regulated by the endocrine nervous system, and several hormones play a role in mediating hunger and satiety (2). Several hormones have been identified to exert appetite suppressant effects, including the peptide YY (PYY) and nesfatin-1. Nesfatin-1, a recently discovered anti-appetite peptide is derived from an 82-amino acid protein called nucleobindin-2 (NUCB2), known as a satiety molecule in the hypothalamus (3). Nesfatin-1 is an anorexic and energy stabilizing agent (4). Nesfatin-1 has been shown to reduce food intake, has an inhibitory effect on food intake, and therefore reduces obesity in a dose- and time-dependent manner after intracerebroventricular and intraperitoneal injection, which indicates a potential therapeutic role in obesity (5). There is also a positive correlation between Nesfatin-1 and BMI in humans (4). PYY also reduces appetite and energy intake in healthy individuals, indicating that PYY is involved in regulating satiety (6). PYY is a 36 amino acid peptide that performs a number of functions including slowing gastric emptying, gastrointestinal motility, inhibiting gastric acid secretion, regulating gallbladder contractions and pancreatic exogenous enzymes, and more importantly regulating food intake (7). Fasting PYY levels are negatively correlated with BMI and waist circumference, indicating a relationship between PYY and energy intake or overall energy homeostasis (8). The effects of age on PYY levels have also been investigated. Aging affects appetite and gastric emptying process. Since PYY may affect both of these, it is to be expected that aging may play a role in circulating PYY levels and nutrient responses (9). Lifestyle intervention with the aim of increasing physical activity and improving eating habits is the most effective treatment strategy in helping to reduce or maintain body weight and improve performance and fitness in the elderly (10). In a study conducted by Faraji et al. (2017), three months of concurrent training increased nesfatin and PYY levels in obese women (11). In another study, Amanat et al. (2020) showed that twelve weeks of AT resulted in an increase in nesfatin-1 in overweight women with metabolic syndrome (12). However, Uğraş and Özçelik (2020) in a study examined the effects of AT on nesfatin-1 in healthy-sedentary man. Serum levels of Nesfatin-1 did not increase significantly (13). Scheid et al. (2011) also showed that fasting PYY did not change after a three-month training intervention in the absence of weight loss (14). On the other hand, the increasing demand for health foods has led to increasing attention to modern natural resources. Microalgae are among the most useful foods due to their unique bioactive compounds. Spirulina (SP) is a small, multicellular, spiral blue-green algae that contains high levels of p-carotene (provitamin A), phycocyanin, and essential unsaturated fatty acids. Apart from the nutritional properties of SP, there have been reports of therapeutic properties associated with this cyanobacterium (15). SP supplementation affects the body composition of overweight and obese people and reduces visceral fat (16).

Maintaining health and nutrition is important to support longevity. At the same time, obesity is a risk factor for age-related diseases. Obesity accelerates cellular processes in a manner similar to aging and shortens life expectancy (17). As obesity has become a global problem in the elderly, mechanisms for its development and the identification of effective prevention and treatment strategies are of high priority. Research findings on the response of hormones involved in the body's energy homeostasis to exercise training are contradictory; SP also has therapeutic effects on the prevention and treatment of obesity;

however, the effects of this herbal supplement along with exercise training on energy balance hormones in elderly subjects are not known. Therefore, the present study intended to investigate the effect of AT with SP on Nesfatin-1 and PYY in overweight elderly men.

2. *Materials and Methods*

The present study was performed in a double-blind manner. The pill containing the spirulina supplement was similar in appearance to the placebo pill, and the study participants in the study groups did not know that the pill they were taking contained spirulina or the placebo. Also, the person in charge of conducting the experiments did not know in which group each participant was examined. In this study, 32 overweight adult men in Bandar-e-Anzali (Gilan, Iran) in the age range of 55-65 years were purposefully selected by a physician after reviewing their files. For this purpose, announcements were made to invite volunteers to participate in the city (parks, shopping and entertainment centers). A total of 32 men who were non-smokers and non-alcoholics with no history of chronic disease volunteered to participate in this study. The sample size was calculated considering $\beta = 0.1$ and $\alpha = 0.05$ using the following formula with 80% power and 5% curvature level and assuming variance heterogeneity, which leads to a higher sample volume than the variance homogeneity condition, and assuming that the standardized value of the effect size was 75 0.75, and also the ratio of variances of the two groups was equal to Z = 1.5, and an equal number of participants were assigned to the control group and the case ($\varphi = 1$). In this formula, α (first type error) is equal to 0.05, and β (second type error) is equal to 0.02:

$$\frac{(\sigma 1 2 + \sigma 2 2)(Z \alpha/2 + Z \beta)2}{\Delta^2}$$

This study was approved by the Research Ethics Committee of the Islamic Azad University, Marvdasht Branch, with the code IR.IAU.M.REC.1400.032 and was registered in the Clinical Trial Center under the number IRCT20140415017288N7. All subjects eligible to take the test, one week before the start of the study, submitted a written consent form and a questionnaire and announced their readiness to begin the training program. Inclusion criteria included the following: age range 65-55 years, BMI more than 25 kg per square meter, inactive lifestyle (exercise less than 1 hour per week), no drug use in the previous six months, and satisfaction with participation in the study. Also in this study, the subjects received a health certificate from a specialist physician (with cardiovascular approach, hypertension and peripheral nerve disorders). Exclusion criteria also included not taking supplements and exercising, diagnosing other underlying diseases during the protocol, such as cardiopulmonary problems, and skeletal and neurological disorders during exercise that prevented the activity, feeling the risk of exercising or taking supplements, and receiving no call from the researcher to follow up. Subjects were asked not to change their diet during the study period. It should be noted that the present study did not have a history of participating in a regular exercise program one year before the start of the study. Subjects were randomly divided into four groups: overweight (OW), overweight-training (OWAT), overweight-spirulina (OWSP), and overweight-training-spirulina (OWATSP). During the implementation of the protocol, the control group was asked to perform their daily activities and to refrain from physical activity. Before starting the exercise, a session was dedicated to adapting people to the equipment and the correct way of doing the exercises. The training groups participated in the training program for eight weeks and five sessions per week (Table 1).

The training sessions were one hour, which included 10 minutes of warm-up and stretching, 40 minutes of AT, and 10 minutes of cooling. Stretching and jogging for 10 minutes were used to warm up. The main stage of training included walking on a treadmill, stationary bike and climbing stairs with an intensity of 65% of the maximum heart rate, which gradually increased to 85% (18).

Table 1. Aerobic exercise protocol for overweight men

Week	1	2	3	4	5	6	7	8
Duration (minutes)	40	40	40	40	40	40	40	40
Intensity (MaxHR)	65	70	70	75	75	80	80	85

SP tablets were purchased from Mehban Daroo Company, and 2*500 mg tablets were taken daily in the morning and evening by the subjects of OWSP and OWATSP groups. The placebo groups also took starch tablets at the same time (19).

Two days before and after the training period (to eliminate the acute effect of the last training session) in the fasting state (12 hours), blood sampling was done from the brachial vein while sitting. The blood samples were transferred to special test tubes for serum preparation (tubes containing sodium citrate) and centrifuged for 10 minutes at 3000 rpm. It should be noted that all stages of the test were performed in the same and standard conditions from 8 to 10 o'clock in the morning. Then the desired indices were measured using kits and special laboratory methods.

Shapiro-Wilk test was used to ensure the normal distribution of variables, and regression slope was used to assume homogeneity. T-test was also used to examine the changes within the group. Meanwhile, to evaluate the significant changes in each of the research variables, between different groups, the method of analysis of covariance (ANCOVA) was used.Calculations were performed using SPSS Software (version 26) and the significance level of the tests was considered to be $p \leq 0.05$.

3. *Results*

Table 2 shows the mean and standard deviation related to the demographic characteristics of the subjects in different groups. There was no significant difference between mean weight and BMI in different groups in the pre-test ($P>0.05$). Mean weight and BMI in the groups of aerobic OWAT, OWSP and OWATSP decreased significantly ($P <0.05$).

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Table 2. Values related to the mean of pre-test and post-test changes in demographic characteristics

Group / Variable		OW	OWAT	OWSP	OWATSP
Age (years)	pre-test	56.75±4.83	55.75±5.6	58.75±4.268	58.38±4.83
Height(meters)	pre-test	1.69±0.07	1.7±0.06	1.69±0.05	1.7±0.07
Weight (kg)	pre-test	77.75±6.67	79.12±4.85	81.75±3.69	82.88±4.64
	post-test	76.94±7.19	76.31±4.79	78.81±3.7	79.69±7.47
	p	0.441	0.001*	0.004*	0.001*
BMI (kg/m2)	pre-test	27±0.99	27.36±2.14	28.59±1.86	28.58±3.22
	post-test	26.71±1.4	26.38±1.99	27.58±2.09	27.49±3.15
	p	0.427	0.001*	0.003*	0.001*

*** Difference with pre-test**

The results of analysis of covariance showed that the pretest was correctly selected as a variable of covariance, and on the other hand, it was clear that there was a significant difference between the mean scores of different groups (Table 3).

Table 3. Results of covariance test related to the amount of Nesfatin-1

Source	sum of squares	degree of freedom	mean squares	F	p
Modified model	314.178	4	78.54	76.239	**0.001**
Tracking	39.730	1	39.730	38.591	**0.001**
pretest	134.200	1	134.200	130.353	**0.001**
group	148.216	3	49.405	47.98	**0.001**
Error	27.797	27	1.030		
Total	7335.87	32			

The results of Bonferroni post hoc test depicted that a significant difference existed between the control and the exercise groups, supplement and exercise and supplement groups, and between the supplement group and the exercise and supplement groups. But there was found no significant difference between supplement with exercise group and exercise with supplement and supplement group (Table 4).

Table 4. Results of Bonferroni post hoc test related to the amount of Nesfatin-1

Group	Mean difference	p
Control-Exercise	-4.607	**0.001**
Control-Supplement	-3.713	**0.001**
Control-Exercise and Supplement	-5.771	**0.001**
Exercise-Supplement	0.894	**0.564**
Exercise-Exercise and Supplement	-1.164	**0.179**
Supplement-Exercise and Supplement	-2.058	**0.003**

The results of analysis of covariance showed that the pretest was correctly selected as a variable of covariance. It was also found that there was a significant difference between the mean scores of different groups (Table 5).

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Table 5. Results of covariance test related to the amount of Peptide YY

Source	sum of squares	degree of freedom	mean squares	F	p
Modified model	285.563	4	71.39	27.660	**0.001**
Tracking	33.550	1	33.550	12.999	**0.001**
Pretest	201.321	1	201.321	78.001	**0.001**
Group	118.339	3	39.446	15.283	**0.001**
Error	69.768797	27	2.581		
Total	7436.64	32			

The results of Bonferroni post hoc test showed that there was a significant difference between the control group and the exercise, supplement and exercise and supplement groups, and between the supplement group and the exercise and supplement groups. But there was found no significant difference between supplement with exercise group and exercise with supplement and supplement group (Table 6).

Table 6. Results of Bonferroni post hoc test related to the amount of Peptide YY

group	Mean difference	p
Control-Exercise	-3.528	**0.001**
Control-Supplement	-2.531	**0.029**
Control-Exercise and Supplement	-5.402	**0.002**
Exercise-Supplement	0.997	**0.989**
Exercise-Exercise and Supplement	-1.874	**0.177**
Supplement-Exercise and Supplement	-2.871	**0.008**

4. *Discussion*

The results of the present study showed that AT increased levels of Nesfatin-1 and PYY in overweight elderly men. These results were consistent with some previous findings (11, 12). Some reports have suggested that changes in cellular energy sources in a positive or negative direction due to fasting or starvation, a low-calorie diet, or re-feeding after food deprivation affected nesfatin and its concentration (20). Improving body composition, especially weight loss and fat, seemed to be one of the main reasons for the change in blood levels of Nesfatin-1. Ramanjania et al. (2010) reported a positive correlation between nesfatin-1 and BMI (21). Also, in connection with the mechanism that causes an increase in nesfatin levels, we can note the increase in insulin levels which then leads to Akt activation. An increase in this enzyme also leads to an increase in PDE-3 activity levels which inhibit the enzyme adenylate cyclase, resulting in preventing the formation of cAMP. As a result of this process, lipolysis stops and the amount of storage in adipose tissue increases and eventually an increase is seen in nesfatin levels (22). It has been suggested that physical activity directly and indirectly affects visfatin levels by altering insulin and blood glucose levels. As a result of increasing nesfatin levels, insulin resistance decreases (23). Meanwhile, increasing the levels of YY peptide as an anti-appetite factor can indicate the desired effect of training on suppressing appetite and desire to eat and is effective in reducing energy intake. Increasing the level of PYY seems to be strongly dependent on training, because higher levels of training lead to higher levels of circulating PYY (24). As mentioned earlier, the increase in PYY depends on the intensity of the exercise activity; however; other

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mechanisms, such as cytokine release, changes in plasma glucose and insulin concentrations, sympathetic nervous system activity, and muscle metabolism may mediate the increase in PYY anti-appetite signals (25). Potential increases in sympathetic nervous system activity can also affect PYY, because catecholamines can stimulate the release of this hormone from intestinal L cells (26). In addition, YY peptide increases after exercise under the influence of signals, such as gastric acid, cholecystokinin and bile salts of lumina, insulin-like growth factor-1, and calcitonin gene-dependent peptide (27). PYY probably exerts its anorexic effects through G protein receptors, which include Y1-Y6, and among them, Y2, which has a greater tendency to bind to PYY in the central nervous system (28). It seems that the increase in PYY concentration following exercise activity is related to the effect of this peptide on hypothalamic Y2 receptors, thereby inhibiting the expression and synthesis of appetite-stimulating hormones such as ghrelin (29). Some studies have also reported no significant change in nesfatin and PYY levels after training (13, 14, 30), which contradicts the results of our study. Mokhtari et al. (2015) in a study examined 12 weeks of resistance training on plasma levels of Nesfatin-1 in elderly women with hypertension. In the experimental group, changes in nesfatin levels were not significant, while in the control group, there was a significant increase in nesfatin levels (30). Also, in a study of obese adults who did AT for 15 days, there was no difference in fasting or postprandial PYY levels before and after training intervention (31). Scheid et al. (2011) also showed that fasting PYY did not change after a 3-month training intervention in the absence of weight loss. The researchers stated that the effect of exercise on PYY is an acute response and that regardless of changes in body weight, PYY levels do not change with chronic training (14). It seems that the response of these hormones in different populations varies according to the type of subjects and the time of measurement requiring more research to be conducted in this field.

The results of the present study also showed that AT with SP supplementation increased levels of Nesfatin-1 and YY peptide in overweight elderly men. The anti-hyperlipidemic and anti-hyperglycemic effects of SP have been reported by lowering blood glucose levels, controlling cholesterol and triglycerides, and improving insulin resistance (32). SP acts as a hypoglycemic agent. The hypocholesterolemic and hyperglycemic effects of SP are associated with obesity and aging in rats, where oral administration of SP in rats reduces serum glucose, cholesterol and leptin levels in obese rats (32). In one study, it was found that taking SP supplement at a dose of one gram per day for 12 weeks was effective in modulating weight and appetite (33). According to the results of our study, the effectiveness of this herbal supplement in reducing obesity and regulating appetite-related hormones was confirmed. In our study, a significant increase in the levels of Nesfatin-1 and YY peptide and thus weight loss in the intervention group can be attributed to the effects of appetite and weight loss of SP. Golestani et al. (2021) in a study investigated the effects of SP and high-intensity interval training (HIIT) on nesfatin-1 levels and lipid profile in overweight and obese women. The HIIT group received 500 mg of SP tablets twice daily for 4 weeks. There was a significant increase in serum levels of Nesfatin-1 in the HIIT-SP, but no significant increase was observed in the HIIT group - placebo. Anaerobic running program was also used for HIIT protocol including six sessions with a maximum speed of 35 meters, with a rest of 10 seconds in each position (3 times a week, 4 weeks). The results also showed that there was a significant difference between the two groups in terms of serum levels of Nesfatin-1 (34). In the present study, eight weeks of AT was performed, so the duration and type of training protocol may be inconsistent with the above findings. In our study, weight loss was also observed in the

OWSP group. These results indicated the regulation of appetite hormones and improved metabolic efficiency in overweight elderly subjects following the use of this herbal supplement. In addition, in our study, the interaction between aerobic exercise and spirulina supplementation in regulating appetite hormones was more effective than exercise and spirulina supplementation alone, possibly due to the support of these two factors in improving these indices in overweight elderly men.

Limitation

There were some limitations in the present study, such as the small number of samples in the current research, so a similar study measuring these indicators in the number of high samples is suggested. Another limitation of this study was the lack of measurement of other appetite hormones and also the amount of fat examined. Also, similar studies to measure plasma glucose and insulin concentration and sympathetic nervous system activity in overweight elderly are recommended.

In summary, the results of this study showed that the intervention of AT and daily consumption of SP supplement was associated with an increase in hormones affecting appetite. Therefore, it is suggested that elderly people with overweight and obese conditions use this effective combination strategy in order to benefit from it.

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Conflicts of Interest

None declared.

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