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STUDY OF CHANGES IN THE PLASMA LEVELS OF CHEMERIN OF WOMEN WITH OVERWEIGHT AND OBESE DURING A PERIOD OF ENDURANCE TRAINING ON A CYCLE-ERGOMETER USING HYDROALCOHOLIC EXTRACT OF URTICA

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ABSTRACT

Background and Purpose: Adipokine chemerin is a pre-inflammationan associated with obesity and metabolic syndrome. The aim of the present study was to investigate the changes in the plasma levels of chemerin of women with overweight and obese during a period of training on a cycle-ergometer using hydroalcoholic extract of urtica. Materials and Methods: This quasi-experimental study was performed on 44 overweight and obese women (BMI>25Kg/m^2) with age range of 30-45 in Zahedan. Subjects were selected targeted and using permuted block randomization were divided into four groups of 11 subjects including training groups + hydroalcoholic extract of urtica (1), exercise + placebo (2), control + hydroalcoholic extract of urtica (3) and control+placebo (4). Training protocol was performed for 8 weeks (3 sessions per week) by cycling on a cycle-ergometer (60-75% heart rate reserve) and duration of 16 to 30 minutes along with the use of hydroalcoholic extract of urtica (8 ml daily) and placebo (8 ml daily) in different groups. Blood samples were collected in two stages before and after the same conditions in order to measure plasma levels of chemerin. To analyze the results, t-test, ANOVA, covariance and Kruskal-Wallis analysis were used at a significant level of α <0.05. Results: Intra-group comparisons showed that 8 weeks of aerobic exercise along with using hydroalcoholic extract of urtica, in addition to significant reduction of obesity-related factors in groups 1,2,3, significantly reduced plasma levels of chemerin in group 1 (P=0.001) and 2 (p=0.002). In inter-group comparison, there was a significant difference between the changes in plasma levels of chemerin of the studied groups. Conclusion: It seems that training on cycle-ergometer with the use of hydroalcoholic extract of urticacan be considered as a preventive approach in reducing the pre-inflammatory factor of chemerin and obesity-related factors in overweight and obese women.

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Introduction

Obesity and overweight are now a major concern worldwide [1] because obesity is reported to be the cause of diseases such as type 2 diabetes, coronary artery disease, cardiovascular disease [2], and different cancers [3]. Therefore, the development of prevention programs and the fighting obesity are of particular importance. Researchers definitely link obesity with lifestyle variables such as physical activity patterns [4] and factors such as disturbed nutritional behaviors, stress, etc. [5]. Today, adipose tissue, as an active endocrine system, by producing fatty acids and secreting several types of proteins regulates

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hormones of absorbing and consuming energy. Some of the hormones secreted from adipose tissue, which play an important role in the process of inflammation and cardiovascular disease, are calledadipokine [6]. In obese people, the production of most adipokines that contribute to the balance and regulation of energy, immunity, metabolism and fatty homeostasis and angiogenesis [7] has increased or impaired, and all of the above factors increase the risk of cardiovascular disease [7] and disorders such as type 2 diabetes, inflammation, and metabolic syndrome [8]. Chemerin is an adipokinethat is initially secreted as an immature and inactive peptide with 163 amino acids and a molecular weight of 18 KiloDalton (kDa) from white and liver adipose tissue in the form of proxamethrin. Then it turns into mature and active chemerin with 143 amino acids and molecular weight of 16 kDa by extracellular serine protease enzyme and is found in plasma and serum [9]. Chemerin has localized effects on adipogenesis and potentially profound effects on metabolism and inflammation [10]. Due to its role in fat synthesis, energy metabolism, inflammation, and the invocation of immune cells to the site of injury and inflammation have been of great importance [11]. Production of chemerin is associated with the volume of adipose tissue, so that the higher the adipose tissue, the, and this higher chemerin secretion at lipogenesis level is associated with insulin resistance [12]. Based on the results of recent studies, serum level of chemerin in patients with obesity and type 2 diabetes increases. In addition, the amount of chemerin has a positive correlation with BMI, waist circumference, blood pressure, triglyceride, LDL-C, and a negative correlation with HDL-C and adiponectin [13]. As physical inactivity is an important factor in the incidence of obesity [14], one of the methods treatments of obesity has heavily focused on sports activities [15]. This is because exercise has an effect on the amount of adipose tissue that affects adipocytic secretions [16] and along with reducing fat percent decreases levels of inflammation [17]. Given the importance and potential role of sports exercises in reducing weight and complications of overweight, improving cardiovascular [18] and oxidative stress reduction [19] are used today to improve the physical condition of obese and diabetic patients, instead of using chemical drugs- regular exercise, including endurance exercises along with the use of medicinal herbs extracts. One of the medicinal plants is urtica with the scientific name urticadioica, which has been introduced in Iranian traditional medicine as an adjunct to the treatment of diabetes [20]. In European countries, urticais mostly used to reduce inflammation [21], blood pressure, and the treatment of rheumatoid arthritis [22]. Nowadays, exercise on cycle-ergometer is considered as a new exercise among the people of the community. However, the effect of this new exercise on the concentration of adipokinechemerin and the relationship between this type of exercise and the mechanism of this hormone along with the use of urtica extract are not clear due to lack of research history. Several studies have been conducted on the effects of various types of sports activities on chemerin levels and the results have not been consistent due to differences in the type of subjects, intensity, type and volume of exercise. Zolfaghari et al. [23] and Askari et al. [24] reported no significant changes in chemerin levels of their subjects, but Jafari et al. [25] and Sadeghipour et al. [26] reported a significant decrease in chemerin levels in their studies. Therefore, considering the contradictions in the results of the effect of exercise on chemerin levels and the gap of studies in of the effect of training on cycle-ergometer along with the use of urtica extract on the plasma levels of chemerin, conducting this study seems necessary.

Methods

The present study is a randomized clinical trial (RCT) (laboratory) using pre-test and post-test stages along experimental and control groups. At first, with the call of research at the level of the offices of Zahedan, overweight and obese women volunteer to participate were selected in a targeted way. At a briefing session, some explanations were given on the objectives of the plan and how it was going to be performed, then the questions and ambiguities were answered, and the subjects completed the consent form with full knowledge and completed the questionnaire containing personal information, medical-health, physical activity, etc. The inclusion criteria for entering the research were women aged 30-45 years, having a general physical and mental health level BMI>25 (Kg/m^2), lack of participation in regular exercise activities during the past 6 months, lack of cardiovascular disease, diabetes, hormonal disorders, kidney and liver diseases, surgery, tobacco use and any therapeutic intervention affecting laboratory results. Exclusion criteria included not following the diet, participation in other sports activities, illness during exercise, pregnancy, and irregular attendance of subjects in one of the groups tested. To assess physical and mental health, the participants were examined by the physician and accepted in case of proven health. Subjects were selected targeted and using permuted block randomization were divided into four groups of 11 subjects including training group 1 (endurance exercise with cycle-ergometer + hydroalcoholic extract of urtica), group 2 (endurance exercise with cycle-ergometer + placebo), group 3 (control + hydroalcoholic extract of urtica), and group 4 (control+placebo). Then, the individual and physical characteristics of the subjects including age, height in cm (without shoes, legs stuck together, and the buttocks, shoulders and back in contact with Height gauge), weight in kilograms (light clothes without shoes), BMI by dividing body weight in kilograms by squared height in meters, waist circumference in tibia, hip circumference, hip circumference in the most prominent part of the pelvis by the strip meter, WHR from splitting waist circumference to hip and body fat percentage by measuring subcutaneous fat using a calipers model (SAEHAN Made in Korea) at three points, triceps, above pelvis and the thigh on the right side of the body were measured and for calculating body fat percentage were given to Jackson and Pollack formula [27].

All measurements were done one stage before the beginning of the exercise (24 hours before), and the next step after the end of the training (the day after the last training session) in the morning and in the same conditions. To assess the changes in

plasma levels of chemerin, blood samples were taken in the pre-test (24 hours before the beginning of the first session) and post-test (48 hours after the last training session to prevent the effect of acute inflammation induced by exercise) in the same conditions after 12 hours of fasting [28]. In order to prevent the effects of night-daytime oscillations on plasma levels of Chemerin, sampling was performed at a specific time of day (7 to 8 in the morning) at different stages [29]. Blood samples were centrifuged for 5 minutes at a speed of 3000 RPM and stored frozen at -20°C for plasma separation. Eastbiopharm human kit made by a Chinese-American company was used for biochemical analysis and measurement of the plasma levels of chemerin with a sensitivity of 4.99 ng/L. Two weeks before the start of the training, all subjects were asked to take no medication during the study period and refrain from participating in other training programs, and observe the usual diet during the study period. In addition, groups (3) and (4) were also asked to refrain from any physical activity during the study period. The protocol was run for 8 weeks and 3 sessions per week. The training program included 10 minutes of warm-up running at low intensity and tensile strength at the beginning of the session, followed by a specific training protocol and the end of each training session, cooling to 10 minutes by soft running and stretching movements. Specific exercise protocols included cycling on cycle-ergometer (Sport Cross-Life Care model) with a reserved heart rate of 60 to 75% [30]. The Pulse Oximeter A310 fingerprint speedometer made in Germany was used to control the intensity of heart rate during exercise. The intensity of exercise was calculated based on reserved heart rate through Kornen formula [31].

Heart rate during exercise= (maximum heart rate - resting heart rate) × intended heart rate (60% to 75%) + Rest heart rate

The maximum heart rate was calculated from the formula (220-age). The duration of the main training at the start of the course was 16 minutes, which gradually increased to 30 minutes by the end of the training period. In each week of the training, based on the principle of overload, the intensity and duration of the training (2 minutes per week and 5% every two weeks) inceased [30]. In groups (1) and (3), the subjects were asked to maintain a constant diet for 8 weeks and mix 8 cc of urtica extract in a glass of water daily and use it for three consecutive days after the main meals. Similarly, the same eatable color of urtica extract was used as a placebo for groups (2) and (4). For being standard, the urtica used was purchased from the prestigious center of Gorgan Essential Oil.

Statistical method

Descriptive statistics were used to categorize raw data, to determine the mean and standard deviations, and to determine the normality of the data related the subjects of the research groups. Shapiro-Wilk test was used. In order to study the intra-group differences, paired t-test was used, and for inter-group comparison, one-way analysis of variance (ANOVA), covariance, Kruskal-Wallis, and if significant, Tukey's post hoc test was used to determine differences. SPSS 16 was used to perform statistical calculations and the statistical significance level was considered 0.05.

Findings

The mean and standard deviation of subjects' individual characteristics in the pretest phase are presented in Table 1. One-way ANOVA showed that there was no significant difference in the basic levels of personal data ($P<0.05$), but the mean of chemerin before intervention was significantly different between the groups ($P = 0.025$).

Table 1. Descriptive Indices of Individual Characteristics in the Four Study Groups

Group / Variable	(1) M±SD	(2) M±SD	(3) M±SD	(4) M±SD
Age(Year)	34.90±5.97	32.10±4.40	34.54±3.64	36.00±6.24
Height(centimeter)	160.83±3.60	161.55±4.65	163.45±8.51	160.27±4.73
Weight(Kilograms)	83.49±10.88	81.22±8.59	79.52±13.25	77.25±7.89
BMI (Kg / m2)	31.71±5.08	31.15±2.91	29.74±4.27	30.70±3.79

Table 2. The mean and standard deviation (±) of the variables of the research according to dependent t-test, one-way analysis of variance, covariance and Kruskal-Wallis

Variable	Groups	Pre-test	Post-test	Intra-group P	Inter-group P
Weight (Kilograms)	(1) (2) (3) (4)	81.22±12.76 81.22±8.59 79.52±13.25 77.25±7.89	76.90±11.57 77.40±8.56 77.40±13.06 76/79±8.22	*0.001 *0.001 *0.001 0.332	¥ 0.997

Body fat percentage	(1) (2) (3) (4)	41.59±3.89 41.04±3.89 40.13±5.83 39.61±3.34	37.37±3.72 38.41±3.85 37.41±4.72 39.12±3.37	*0.001 *0.001 *0.001 0.066	¥ 0.679
BMI (Kg/m^2)	(1) (2) (3) (4)	31.46±5.08 31.15±2.91 29.74±4.27 30.20±2.58	29.81±4.67 29.80±3.08 28.94±4.17 30.01±2.70	*0.001 *0.001 *0.001 0.319	¥ 0.910
WHR	(1) (2) (3) (4)	0.78±0.05 0.80±0.04 0.78±0.05 0.81±0.08	0.77±0.05 0.80±0.03 0.77±0.05 0.80±0.08	0.111 0.779 0.725 0.242	# 0.486
chemerin (ng/L)	(1) (2) (3) (4)	330.36±54.20 398.08±37.43 360.11±55.09 341.43±61.81	293.86±48.47 375.13±39.12 358.25±47.84 341.71±57.55	*0.001 *0.002 0.624 0.870	*$<0.001

Values are shown as mean ± standard deviation
* Significant statistical significance (P <0.05)
$ Covariance test
# Kruskal Wallis Test
¥ One-way analysis of variance

Table 2 shows that intra-group changes using paired t-test significantly reduced in three groups (1), (2), and (3) in obesity-related factors such as weight, body fat percentage and BMI. Plasma levels of chemerin decreased in three groups (1), (2) and (3), which were statistically significant in groups (1) and (2) (P<0.05). In group 4, weight, fat mass, BMI and chemerin plasma levels did not show significant differences (P>0.05). Based on covariance test, there was a significant difference between the changes in the Chemerin plasma levels in the studied groups (p<0.05). However, the results of ANOVA showed no significant differences between the changes from pre to post-test of other anthropometric variables in the studied groups (P>0.05). The results of Tukey post hoc test showed a significant difference between the changes in the Chemerin plasma levels in the four groups (p=0.003) (Table 3).

Table 3. Comparison of chemerin in the studied groups

Variable	Group		Mean difference	Standard Error	p
Chemerin	(1)	(2)	-82.272	21.348	*0.002
		(3)	-67.054	21.348	*0.016
		(4)	-47.854	21.348	0.130
	(2)	(1)	82.272	21.348	*0.002
		(3)	15.218	21.348	0.891
		(4)	34.418	21.348	0.383
	(3)	(1)	67.054	21.348	*0.016
		(2)	-15.218	21.348	0.891
		(4)	19.200	21.348	0.805

* Statistically significant (P<0.05)

Discussion

Because of the lack of a research background on the effect of training on cycle-ergometer and the consumption of hydroalcoholic extract of urtica on plasma levels of chemerin, in the present discussion, we have used studies related to the subject in some way. In addition, in this study, the effect of endurance training on cycle-ergometer and the effect of the use of hydroalcoholic extract of urtica on plasma levels of chemerin on overweight and obese women were examined from two different perspectives. With this explanation, of the most important findings of the present study, we can refer to the significant reduction of plasma levels of Chemerin in groups (1) and (2) following 8 weeks of training on cycle-ergometer with a 60% to 75% reserved heart rate. Other significant results were significant reduction in weight, fat percentage and BMI in three groups (1), (2), and (3) at the end of the period compared to the base values. However, WHR values did not change significantly in any of the groups compared to baseline values. Adipose tissue plays an important role in the development of metabolic

problems associated with obesity with the production of inflammatory factors [32]. As stated, obesity is one of the factors leading to a rise in chemerin levels in humans, and a decrease in the weight is due to lower levels of serum levels of chemerin [33]. Although the correlation of chemerin with fat accumulation is not known well, the results of the studies show that chemerin concentration is associated with a high fat percentage, WHR [34], BMI, and waist circumference [13]. Shin et al. (2011) examined the relationship between the levels of chemerin and body composition in 173 women, and found it in correlation with BMI, lipid percentage, WHR, visceral fat, fasting insulin, total cholesterol and triglyceride, so introduced chemerin as an indicator associated with visceral obesity in cardiovascular disease [35]. Other studies also show that active lifestyle [36], weight loss due to caloric restriction, obstructive surgery [10], and regular exercise [37] lead to reduction of serum chemerin. Regarding the results of this study denoting a significant reduction in weight, fat percentage and BMI after a training period and consumption of urtica extract in groups (1), (2) and (3) compared with base values, probably we can relate the factors effective in reducing plasma levels of chemerin to these factors. The results are consistent with the results of Saremi et al. [18], Pourvaghar et al. [38], Jafari et al. [25] and Fadaei Raehanabadi et al. [39]. These researchers also attributed a significant decrease in chemerin levels in overweight and obese subjects to lower body fat levels and weight loss following exercise. By exercising, skeletal muscle capacity increases for using fats, which can play an important role in controlling the weight of obese and overweight people and reducing cardiovascular risk factors. It can be justified that a significant proportion of the fatty acids required in the muscles in operation is provided by increasing the lipid triglyceride lipolysis of the adipose tissue 3 to 4 times. Sports activity doubles the amount of blood flow to the adipose tissue and increases the amount of blood to the active muscle of the body. This reduces body fat and improves body composition by eliminating the balance between intake and consumption of energy and creating a negative calorie balance that itself may lead to a decrease in chemerin of plasma after exercise [40].

One of the effective mechanisms for decreasing the plasma levels of chemerin compared to the base levels of groups (1) and (2) in the present study leading to desirable improvement of subjects with obesity following exercise and consumption of urtica hydro alcoholic extract can be better metabolism of visceral fats and creating better conditions in the cardiovascular capacity of the subjects, especially the training groups. This is stated to be because chemerin stimulates the phosphorylation of ERK1, ERK2 and MAPKs (cell mediates involved in lipolysis). Another possible mechanism for decreasing chemerin can be the increase in caloric expenditure after training and its effect on reducing the pathway of adipogenesis. Since with increase in lipogenesis, chemerin values increase, this decrease reflects the reduction in the rate of adipogenicity, which is an important indicator for diabetic and cardiovascular patients. Various studies have suggested the origin of chemerin to be adipose tissue, which can affect atherosclerosis development as paracrine and may result in the call of macrophages and inflammatory responses in atherosclerotic plaques [41]. Saremi et al. (2010) have considered significant reduction in plasma levels of chemerin following endurance training related to weight loss, especially visceral fat in obese individuals. They believe that changes in visceral fat after exercise may have an important role in regulating the secretion of macrophages into fat tissue and inflammatory markers such as chemerin [18]. On the other hand, the results of this study are in conflict with the research by ghanbarzadeh et al (2015) [30], Asgari et al (2014) [42] and Moradi et al. (2014) [43].

In the research by Ganbarzadeh et al., which was performed on elderly women (HRmax intensity of 61-88% in the period of 30 to 16 minutes), despite a significant decrease in weight and BMI, there was no significant change in the plasma levels of chemerin, fat percentage and WHR of the subjects [30]. The reason for the difference in the results of the research mentioned with this study can be at the level of fitness, age, health status of the subjects and other factors. As in the study by Ghanbarzadeh et al. the age range of subjects was 55-70, while the age range of the subjects in this study was 30-45. It is likely that the differences in age and physiological conditions of the subjects in the mentioned studies have had a different effect on the secretion and metabolic systems of these subjects. It seems that the response of chemerin hormone to exercise is different subjects is different due to age. In the study by Asgari et al. [42], the subjects were young girls with an average age of 20 years. The reasons for the inconsistency of the results with this study can be the factorial difference of the subjects' age and differences in the practice protocol. In the study by Moradi et al. [43], which was performed on inactive elderly men, there was no significant change in factors such as weight, fat percentage, BMI and consequently in the plasma levels of chemerin. According to the results of various studies, which have linked the reduction of chemerin to reduction of fat mass, and as Alfadda et al. showed a positive correlation between the serum levels of chemerin in adult women and men with different degrees of obesity with BMI [44], lack of changes in serum levels of chemerin in the subjects of the study by Moradi et al. can be attributed to weight and fat mass remainin constant. In the present study, in the subjects (group 3) that used only hydroelectric urtica extract and did not participate in any kind of exercise activity, weight, fat percentage, and BMI significantly reduced, but the plasma level of chemerin of these patients, despite a decrease, was not significant. Since no research has been conducted on the effect of urtica extract on adipose tissue and adipocytic secretion from it, its effective mechanism in calorie reduction is not clear. The results of studies indicate that the aqueous extract of urtica has high antioxidant properties and prevents phospholipid oxidation of cell membranes, ninoleic fatty acids and diabetes mellitus, which is carried out through active metal oxidizing enzymes [45]. The present study showed that the consumption hydroalcoholic extract of urtica, by reducing the level of mercuric acid, through its anti-inflammatory and antioxidant properties, could improve the complications of obesity in the cardiovascular system. Anthocyanin is a natural bioflavonoid species found in the urtica root extract. The antioxidant has a very strong anti-inflammatory effect and usually does this by neutralizing enzymes effective in inflammation and by preventing

damage of free radicals to connective tissues and repairing damaged proteins of the blood vessel walls [46]. Regarding using urtica extract and serum lipid levels, Shahrakie et al. showed that the use of urtica extract improves serum lipid levels in male rats [47]. Therefore, in this study, probably the use of urtica extract in addition to exercise in group (1) has enhanced the effect of exercise on lipid oxidation and improved the body composition in subjects, which can be considered as a mechanism for decreasing plasma level of chemerin in subjects. Among the limitations of the present study, we can mention the low volume of samples, stressors, endocrine discharges, the genetic characteristics of the subjects and the inability to control the diet of the subjects accurately by the researchers.

Conclusion

It seems that doing eight weeks of endurance training on cycle-ergometer and using the hydroalcoholic extract of the urticacan be considered as a new and effective method for decreasing plasma levels of chemerin and improving the body composition in obese and overweight women. In order to reach the definitive result, given the lack of study in this area, it is suggested that the effect of this exercise along with the use of hydroalcoholic extract of urtica be examined on other humans and obese and overweight men.

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