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Peer Review Report for "Responses of Visfatin and Resistin Concentration to Different Aerobic Training Intensities Protocols"

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Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) — 3 Apr 2020

Dear AE,
the authors should rewrite the article under the supervision of a person familiar with writing the article and familiar with the English language.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 17 Apr 2020

Dear AE,
With thanks to the worthwhile effort of the authors, the following comments are proposed.
1- The results of the study show that there is a significant difference between the high intensity and control groups, but there is no difference between the other groups. In conclusion, the authors explained both exercises (moderate and intensive) are effective but I think according to the results of the study, this conclusion cannot be made. It seems just the intensive protocol is effective in this study. I think it is better for authors to change the conclusion.
Thank you for your attention.

Parvin Zareian: Associate Editor | **Revision** (0) 17 Apr 2020

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

Iraj Mirzaii-Dizgah: EIC | **Revision** (0) 27 Apr 2020

Dear Author,
Your manuscript primarily accepted. However, there was some error in the text that has been corrected in the attached file. Please edit it according to reviewer comments and resubmit it.
Thanks.

OPEN PEER REVIEW

Revision (1)

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Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Responses of Visfatin and Resistin Concentration to Different Aerobic Training Intensities Protocols

Running title:

Different Aerobic Training Intensities on Visfatin and Resistin

Abstract

Background: Visfatin and Resistin are adipokines involved in metabolic regulation and physiological processes.
Objective: This study aimed to investigate the effects of eight weeks of aerobic training with different intensities on serum levels of resistin and visfatin in obese male rats.
Methods: 24 adult obese rats (weight: 250 to 300 gr, BMI >30g/cm2) divided into three groups: aerobic training with 28 m/min (moderate intensity), aerobic training with 34 m/min (high intensity) and, control group. All training groups carried out exercise training for 8 weeks (5 sessions/per-week for 60 min per session). 48 hours after the training period, the level of serum visfatin and resistin levels was measured.
Results: There is a significant differences in levels of resistin concentration (P=0.001) in different groups. There was no significant difference between visfatin levels in all three groups. Resistin concentration was not significantly changed in moderate intensity group compared to the control group, the change is not statistically significant (185.10±12.85 vs 202.76±17.39) (P=0.05). There was a significant difference between the high intensity and control groups (p= 0.001). There was no significant difference in visfatin concentration in MI and HI groups compared to the control group, the change is not statistically significant (P>0.05).
Conclusion: There is a significant difference in levels of resistin concentration in different groups. There was no significant difference between visfatin levels in all three groups. Therefore, it seems that aerobic training with high intensity has a better effect on the prevention of obesity and cardiovascular disease.

Keywords: Obesity, Aerobic training, Resistin, Visfatin

1. Background

Obesity is caused by fat deposition. Adipose tissue, except lipid storage, plays an essential role in regulating the energy homeostasis, insulin sensitivity, carbohydrate and lipid metabolism (1). The World Health Organization (WHO) report, 2005 indicates that there are 1.6 billion and 400 million obese people who their body mass index is above 25 kg/m^2 and 30 kg/m^2, respectively. According to this report, the prevalence of overweight and obesity in Iran among the demographic profile of 15 – 30 years old is 22% and 16%, respectively (2). The adipose tissue is the largest endocrine organ which exudes hundreds of hormones and cytokine. It affects the processes in the local and environmental systems. This tissue also produces a variety of pro-inflammatory and anti-inflammatory hormones including resistin, visfatin, adiponectin, as well as other cytokines such as interleukin 6, and Tumor Necrosis Factor-α (3, 4).

Resistin is a peptide hormone and rich in cysteine which contains 108 amino acids (5). In fat people with cardiovascular disease, the level of this hormone is high (6). Resistin is primarily made in adipose tissue. It has a direct relationship with the risk of arteriosclerosis and C-reactive protein levels (6). Resistin increases the risk of arteriosclerosis through disrupting glucose and lipid metabolism. It also increases the vulnerability of platelets in atherosclerosis through stimulating pro-inflammatory cytokines (7). Resistin can also be considered as a link between obesity, diabetes, and insulin resistance. Some of the results indicate that plasma levels of resistin in obese people will increases (3).

The results show that there is a relationship between the obesity and the increased levels of visfatin (8). Visfatin is a 25 kDa adipokine which exudes from adipose tissue and is known as phosphoribosyl transferase. Visfatin has an insulin-like function and stimulates the glucose uptake in the adipose tissues and myocytes, obstacles the release of glucose from the liver, and is accompanied by weight loss and reduced waist-hip ratio (9).

However, the importance of resistin and visfatin resulting from exercise is recognized as a therapeutic objective for obesity, but changes in the level of blood resistin and visfatin pursuant to various exercises is not completely evaluated (10, 11). The intensity, duration, and type of exercise has different effects on the resistin and visfatin concentration; so that short term trainings, resistance exercises, and high intensity exercises compared to the low intensity exercises and aerobic exercises have different effects on reducing these values (12-15).

In this regard, Abedi et al. (2017) evaluated the effects of aerobic exercise with 55 to 65% intensity of heart rate reserved in resistin levels and insulin sensitivity during eight weeks (3 sessions per week). They concluded that there is a significant decrease in resistin levels, BMI, and insulin resistance (12)(12). On the other hand, Jorge et al. (2011) reported that after aerobic exercise during 12 weeks there is no significant change in resistin levels and insulin resistance (16). Ghafari et al.

(2019) studied the effect of continuous training during eight weeks (20 minutes activity, 60% of maximum speed) and high-intensity interval training (2 minutes activity, 80% of maximum speed; 2 minutes recovery, 30% of maximum speed) on resistin and insulin levels, and insulin resistance in male Wistar rats with diabetes mellitus type 2. They concluded that interval training lead to significant changes in all the factors except resistin gene expression. There is a significant relationship between changes in insulin resistance and resistin gene expression (13).

Exercise is considered as an effective therapeutic manner to reduce metabolic diseases, including obesity. According to the limited studies concerning the effect of exercise on resistin and visfatin levels, especially in obese people, and the inconsistent of findings due to different training methods, and conducting aerobic training as an effective exercise for prevention and treatment of obesity (13, 16), examining the various intensities of these training on resistin and visfatin levels is necessary. Therefore, the present study is aimed at a comparison the effects of aerobic training with various intensities on serum level of resistin and visfatin in obese male Wistar rats to examine which of above-mentioned intensities of aerobic exercise (various intensities or both of them) can probably stimulate the changes concerning the serum levels of resistin and visfatin on obese male Wistar rats. Thus, this study was carried out to determine the effect of moderate and high-intensity aerobic exercise on the serum levels of resistin and visfatin in obese Wistar rats during eight weeks.

3. Methods

3.1. Animals

A total of 24 healthy male Wistar rats (eight-week-old, 250 to 300 g weight with body mass index (BMI)>30 g/cm2) were used in this experimental study. These animals were purchased from Razi Vaccine & Serum Research Institute of Iran and transferred to animal science laboratory of Physical Education and Sport Sciences at Ferdowsi University of Mashhad, Iran. The rats were kept for 2 weeks in a cage made of polycarbonate under controlled conditions, i.e. average ambient temperature 23±1 ° C, humidity 50 ± 3% and 12-h light/12-h dark cycles with free access to ad libitum food and water. The cage was disinfected 3 times a week with 70% alcohol. After two weeks of familiarity with lab environment, animals were randomly divided into three groups:1) moderate-intensity aerobic exercise (n= 8), 2) high-intensity aerobic exercise (n=8) and control (n=8) groups. It should be noted that the principles of Helsinki Declaration and the opinions of the Ethics Committee of Research were respected at all stages of the research. Also, the steps for tests were approved at the Ethics Committee of Medical Research at the Faculty of Veterinary Sciences of Ferdowsi University of Mashhad under the Code IR.MUMS.REC.2016.131 at Ferdowsi University of Mashhad.

3.2. Induced obesity Rat

The obese group ate a high-fat diet, a high-fat diet containing more calories and fat than standard food (energy of 4.8 vs. 3.9 kcal in g and fat of 39 vs. 3.5%). All rats were fed this way for 14 weeks and had free access to water and food throughout this phase of the study. (Table 1).

3.3. Obesity criteria

The obesity criteria in Wistar rats are body mass index. The body mass index of normal rats is 0.45 to 0.68 g / m2 (17). At the age of 14 weeks (at the end of the obesity phase and before the training) the amount reached 0.84 g / cm 2.

3.4. Familiarization Stage and exercise protocol

The training groups were exercised on a rodent motor-driven treadmill for 60 min/day, 5days/wk for 8 weeks (Table 2). After an acclimatization period to the aerobic exercise protocol, they were placed on the treadmill to walk at a speed of 10 m/min with a 0° slope for 15 min for one week. During the second and third weeks, the speed and duration of the exercise were gradually increased, so that the final speed of running of a moderate-intensity group on the treadmill was 28 m/min～70-75% VO_{2max} and the speed of high-intensity group on the treadmill was 34 m/min～80–85% VO_{2max}. The exercise volumes in moderate- and high-intensity groups were 11.76 km/week and 14.28 km/week, respectively(18).Upon completion of the exercise program, in order to cool down, the speed of the treadmill was reduced gradually until it reached zero. The entire exercise protocol is illustrated in (Figure 1).

3.5. Sample collection

48 hours after the last exercise session and 12-h fasting period, the rats of all groups were transferred to the laboratory were sacrificed. At first, animals were anesthetized in a special sampling space (sterile environment) by a combination of Ketamine (30-50 mg/kg of body weight) and Xylazine (3-5 mg/kg of body weight). After confirmation of anesthesia, 5 ml of blood was taken by syringe from the right ventricle of each rat and immediately poured into non-anticoagulant test tubes (19). The blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C. For measurement of resistin and visfatin levels were measured by a special Rat ELISA Kit (EASTBIOPHARM, licensed by the United States).

3.6. Statistical Analysis

The data are presented as the Mean±SD. The collected data were analyzed by SPSS 16.0 (SPSS Inc., Chicago, IL, USA). After ensuring the normal distribution of the data, using the Shapiro-Wilk statistical test and the homogeneity of variances by Levene's test, paired sample t-test and one-way analysis of variance ANOVA with Tukey's post hoc test was used to evaluate the differences between groups. Furthermore, significance was established at the alpha level $p < 0.05$

4. Results

According to the information in Table 3, a significant difference was observed between moderate, high-intensity aerobic exercises and control groups in the serum of resistin concentration (P=0.001 and F=3.00). According to the findings, the levels of serum visfatin levels has not changed between moderate, high-intensity aerobic exercises and control group(P=0.18 and F=1.68) (Figure 2).

According to the results of Tukey's post-hoc test, a significant differences were not observed in intra-group mean changes between the moderate-intensity aerobic exercises and control group in terms of the resistin concentrations (P=0.05) and a significant differences was denoted between high-intensity aerobic exercises with control groups (P=0.01). In addition, significant different was not observed in the visfatin serum mean changes between the moderate-intensity aerobic exercises with control group (P=0.14). However, there was no significant difference between high-intensity aerobic exercises with control group (P=0.42) (Figure 3). According to Table 4, at the end of period of the eight weeks aerobic training, body weight of rats in the control group increased (p=0.001). There was a significant difference was denoted in the means reduces in both the training groups moderate- intensity and high-intensity training with control groups in the variables of weight (P=0.01). According to the results of Tukey's post-hoc test, the intra-group differences in mean body weight have significant differences between the moderate-intensity and control groups (P=0.001) and between the high-intensity and control groups (P=0.001).

5. Discussion

The purpose of this study was to compare the effect of aerobic training with different intensities on serum levels of resistin and visfatin in obese male rats. Based on the results of the present study, a significant difference was observed between moderate, high-intensity aerobic exercises and control groups in the serum of resistin concentration. These findings are consistent with the results of Halanin et al. and Duzova et al. (20, 21). But it is inconsistent with the findings of Hornik et al. and Vardar et al. (22, 23). Changed serum resistin levels despite weight loss in obese individuals have also been observed in other studies(24). The roles of endocrine glands are effect on adipose tissue, which are known to secrete large amounts of hormones. Among the hormones, resistin is a new signal molecule that reduces the adipogenesis process. Resistin is expressed in white adipose tissue in females with the highest levels in adipose tissue (25). Studies have shown that resistin is a hormone secreted by adipose that has a positive association with body composition index such as weight, body mass index and body fat mass(26). There was a significant association between levels of resistin, obesity, and insulin resistance(27). There is also a direct relationship between changes in resistin values with changes in body mass index, body fat, glucose and insulin in obese individuals (28). Possible mechanisms of resistin reduction include pro-inflammatory cytokine changes such as

interleukin-1, interleukin-6, and donor tumor necrosis factor-alpha, that if these cytokines are reduced, the levels of resistin will decrease (29), and since there are conflicting results about There is an effect of regular physical activity on alpha-donor factor levels (30), which the change in resistin levels can be attributed to cytokines. It is also produced in humans in addition to adipose tissue in lymphocytes and leukocytes (31).

Based on the results of this study, aerobic exercise program with two moderate and high intensity compared to control group resulted in a decrease in serum visfatin concentration in obese male Wistar rats, but these changes were not statistically significant. These findings are consistent with the results of Matinhomaee et al. and Hidayat et al. (32, 33). But it is inconsistent with the findings of Taghian et al., Soltani et al. and McKenzie et al. (34-36). It should be noted that visfatin also acts as a nicotinamide amid phosphoribosyl transferase (Nampt). Nampt plays an important role in regulating cellular energy as well as in the control of NAD-dependent enzymes(37). Visfatin regulates the intracellular activity of NAD / NADH-dependent enzymes that are critical for glucose-stimulated insulin secretion in pancreatic beta cells (38). Circulating visfatin levels are closely related to white adipose tissue accumulation and its synthesis is regulated by several factors including TNF-a, glucocorticoids, interleukin-6, and growth hormone (39).

Investigating the insulin-like function of visfatin indicated that this protein causes an increase in glucose uptake in muscle cells and adipose tissue as well as a decrease in glucose production in liver tissue through attachment and activation of insulin receptors in a different location other than insulin binding site(40). It has a pro-inflammatory and anti-apoptotic potential and plays an important role in inflammatory and infectious diseases (41). The decrease in plasma visfatin concentration after aerobic exercise also strengthens the hypothesis of increased visfatin uptake by subcutaneous adipose tissue. This hypothesis comes from the negative correlation between plasma visfatin concentration and its expression in subcutaneous adipose tissue (42). Another factor affecting visfatin depletion is growth hormone secretion, which can significantly decrease adipocytes (43). Another reason for such inconsistent findings may be due to differences in the duration, intensity, and level of training of the subjects.

5.1. Conclusions

In summary, based on the results of the present study, serum concentrations of resistin and visfatin decreased in the both of the training groups. However, the level of resistin only in the high-intensity aerobic training group compared to the control group reduced significantly. Therefore, it seems that performing moderate and high-intensity aerobic exercise may have a good effect on reducing the incidence of obesity and related diseases. Therefore, it is recommended that both of the training can prevent the adverse effects of increased obesity related metabolic disease.

Footnotes

Authors' Contribution: Contribution of the authors is in accordance with the research regulations.

Conflict of Interests: The authors declare no conflict of interests.

Ethical Approval: The present study was approved by the Ethics Committee of Ferdowsi University of Mashhad under the Code IR.MUMS.REC.2016.131 at Ferdowsi University of Mashhad.

Funding/Support: This paper was not sponsored by any organization.

Patient Consent: Written consent was received from the participants.

Disclosure of interest: The authors declare that they have no competing interest.

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Table 1. High-fat and standard food content

Contents	Protein	Fat	Carbohydrate	Fiber	Ash	Calcium	Phosphorus	Salt	Humidity	Lysine	Methionine	Methionine + cysteine	Reunin + Tryptophan	Other materials	Kcal energy in grams
High fat (%)	18	39	20	2	1	1	0.7	0.5	5	1.15	0.33	0.63	0.95	10	4.8
Standard (%)	20	3.5	25	14.5	10	1	0.7	0.5	10	1.15	0.33	0.63	0.95	11	3.9

Table 2. Moderate and high-intensity aerobic exercise protocol on treadmill

Groups/Weeks		1	2	3	4	5	6	7	8
MI	Duration (min)	15	27	34	40	46	52	58	60
	Speed (m/min)	10	15	20	21	23	24	26	28
HI	Duration (min)	15	27	35	45	54	59	60	60
	Speed (m/min)	10	15	20	22	24	27	31	34

MI: Moderate-intensity aerobic exercise, HI: high-intensity aerobic exercise

Table 3. The variation of visfatin and resistin levels different groups

Variable	C (M±SD)*	MI (M±SD)*	HI (M±SD)*
Visfatin (ng/ml)	859.56±68.46	780.41±74.81	804.74±88.96
Resistin (ng/ml)	202.76±17.39	185.10±12.85	174.81±15.08‡

*: Data are presented as Mean±Standard Deviation; ‡: The mean difference is significant compared to control group at 0.05. C: control, MI: continuous moderate exercise, HI: high-intensity aerobic exercise

Table 4. The variation of weight in experimental and control groups

Variable	Stages	C (M±SD)*	MI (M±SD)*	HI (M±SD)*
Weight (g)	Pre-test	295.75±1.81	295.16±1.40	295.41±2.15
	Post-test	302.58±1.16‡	287.41±4.25‡	287.08±4.23‡

*: Data are presented as Mean±Standard Deviation; ‡: The mean difference is significant at 0.05. C: control, MI: continuous moderate exercise, HI: high-intensity aerobic exercise

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Iraj Mirzaii-Dizgah: EIC | Revision (1) 6 May 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.