

The Role of Chemerin and Myostatin after Physical Activity

M. J. Pourvagar, M. E. Bahram

Abstract—Obesity and overweight is one of the most common metabolic disorders in industrialized countries and in developing countries. One consequence of pathological obesity is cardiovascular disease and metabolic syndrome. Chemerin is an adipocytokine that plays a role in the regulation of the adipocyte function and the metabolism of glucose in the liver and musculoskeletal system. Most likely, chemerin is involved in obesity-related disorders such as type 2 diabetes and cardiovascular disease. Aerobic exercises reduce the level of chemerin and cause macrophage penetration into fat cells and inflammatory factors. Several efforts have been made to clarify the cellular and molecular mechanisms of hypertrophy and muscular atrophy. Myostatin, a new member of the TGF- β family, is a transforming growth factor β that its expression negatively regulates the growth of the skeletal muscle; and the increase of this hormone has been observed in conditions of muscular atrophy. While in response to muscle overload, its levels decrease after the atrophy period, TGF- β is the most important cytokine in the development of skeletal muscle. Myostatin plays an important role in muscle control, and animal and human studies show a negative role of myostatin in the growth of skeletal muscle. Separation of myostatin from Golgi begins on the ninth day of the onset period and continues until birth at all times of muscle growth. Higher levels of myostatin are found in obese people. Resistance training for 10 weeks could reduce levels of plasma myostatin.

Keywords—Chemerin, myostatin, obesity, physical activity.

I. INTRODUCTION

CHEMERIN is a new adipokine, which has recently been discovered. Chemerin is a chemical absorbing protein, which acts as a ligand for a G protein-coupled receptor CMKLR1 (Chemokine-like-receptor-1). Chemerin plays an important role in innate and adaptive immunity [1]-[3]. Research in the past decade shows that chemerin has a significant biological impact on the formation of white adipose tissue during both normal development and pathological conditions (e.g., obesity) [4]. Bad configuration of chemerin (dysregulation of chemerin) during maturation of fat cells results in the low expression of adiponectin, leptin and glucose transporter -4 (GLUT4) by mature fat cells [5]-[7].

Research has shown that there is a correlation between the increases in the chemerin rate and coronary artery disease in people having problems with metabolic syndrome [7]. It seems that adipokines have systemic effects in the brain, liver,

muscle, beta cells, organs and lymph vessels [8]. Chemerin supply in blood circulation is currently unknown. The highest expression of chemerin can be seen in the liver, adipose tissue and the kidneys. Chemerin is a pro-inflammatory cytokine that activate immune cells and may have a role in the inflammation of fat in obese people by calling in macrophages in adipose tissue [9].

Chemerin also play an important role in metabolic syndrome [10]. It seems that chemerin has local effects on adipogenesis. Also, it stimulates insulin and increases the absorption of glucose in adipocytes [11]. Expression and secretion of chemerin are significantly increased by adipogenesis. The studies have shown that chemerin levels have a direct relationship with obesity and metabolic syndrome; therefore, it may be one of the metabolic syndromes [10].

II. CHEMERIN AND STUDIES

The results of the study done by Sherafati and colleague showed, that there were no significant differences in chemerin serum between mice that received an 8-week intensive speed training program and those in the control group [12]. The studies done by Fadaei and colleagues showed that eight weeks of aerobic training significantly reduced chemerin resting levels, body fat percentage, body mass index and waist-to-hip ratio in women with excess weight [13]. Saremi and colleagues, in their study, reported that following an aerobic exercise program caused a significant reduction in chemerin [14].

Khademosharie and colleagues reported that exercise every other day for 10 weeks significantly reduced the concentration of chemerin in women with type 2 diabetes [15]. It is reported that after 12 weeks of resistance training, adiposity indicators such as weight, body mass index, waist circumference and abdominal fat did not change significantly; but visceral fat and total abdominal fat mass decreased with chemerin levels [16]. On the other hand, the results of the study done by Zolfaghari and colleagues showed that 12 weeks of aerobic exercise with green tea extract had no significant effects on chemerin levels, weight, body fat percentage, BMI and WHR in obese women [17].

Pourvagar and Bahram, in their study, showed that adiposity indicators such as weight, body mass index, waist circumference and abdominal fat did not change significantly; but visceral fat and total abdominal fat mass were significantly reduced [16]. Also, in a study, it has been shown that there is a positive correlation between chemerin levels and body mass index, waist circumference, blood pressure, triglycerides,

M. J. Pourvagar (Associate prof.) is with the Department of Physical Education University of Kashan, Kashan, Iran (phone: 0098 21 77897752, fax: 009831555333, e-mail: vaghar@kashanu.ac.ir).

M. E. Bahram is with the Faculty of Physical Education, University of Isfahan (phone: 0098 9132627940, fax: 0098 3155912543, e-mail: bahramsport2010@gmail.com).

cholesterol - LDL and insulin resistance. However, there is a negative relation between chemerin levels and HDL cholesterol and adiponectin (adipokine sensitizers of tissues to insulin) [18]. Sell and colleagues, in a study, revealed that chemerin secretion in adipose tissue was higher in obese women than thin women [19]. It has been reported that there is a negative correlation between the plasma concentration of chemerin and TC and LDL-c levels; however, there is a negative relation between chemerin levels and HDL-c; but, this relationship is not clear and more research is needed in the area. Therefore, probably, chemerin has profound effects on hemostasis and inflammation [14]. It is reported that chemerin levels are associated with coronary artery disease [9].

III. CHEMERIN RESPONSE TO PHYSICAL ACTIVITY

Overweight and obesity is a disorder of the heterogeneous group of disorders with multiple causes which has a direct connection with the incidence of metabolic and cardiovascular diseases. So, obesity as an inflammatory disease plays a key role in the beginning and development of atheroma processes by secretory function of adipose tissue in the synthesis and release of cytokines [20], [21]. Evidence and various surveys have shown that chemerin is mainly originated from adipose tissue which can affect the development of atherosclerosis as paracrine and create the mobilization of macrophages and inflammatory responses in atherosclerosis plaques created [22], [21].

Pourvaghari and Bahram did a study entitled "the evaluation of three months of high-intensity interval training on the levels of plasma chemerin and factors related to body composition on overweight males". The results of this study showed that three months of high-intensity interval training caused a significant change in chemerin levels, weight, body fat percentage, BMI and WHR in overweight students in the experimental group compared to the control group [23], [24]. In the study done by Saremi and colleague, it was reported that there was a significant decrease in plasma concentration of chemerin in obese men following aerobic exercise. In another study, Saremi and colleagues reported that there was reduction in plasma chemerin after 12 weeks of strength training in patients with metabolic syndrome [14], [5]. Fadaei Reihan Abadi and colleagues also reported that there was reduction in chemerin resting levels, weight loss and fat in overweight women after aerobic training [13].

The researchers found a significant relation between a significant decrease of the chemerin level of overweight and obese participants, as well as a decrease in body fat levels and weight loss [23], [11], [13]. The reduction in plasma concentration of chemerin shows that changes in abdominal fat, BMI, WHR after three months of high-intensity interval training can play an important role in improving the secretion of macrophages in adipose tissue and inflammatory markers such as chemerin and features of metabolic syndrome. Since chemerin in the process of adiponectin is secreted in greater amounts, it may reduce it due to reduction in fat synthesis and speed of its entry into metabolic cycles [21], [16]. It is reported that high intensity training increases the capacity of

skeletal muscle to use fat which may play a role in weight control in obese and overweight people and a reduction in cardiovascular risk factors. It seems that in the present study, chemerin levels can be reduced by reducing fat percentage, BMI and WHR [24]. On the other hand, one of the mechanisms, that can be invoked, is the increase of GLUT4 in high-intensity activities, which facilitates the entry of glucose into fat cells through GLUT4; and it increases the glucose uptake in adipocytes and regulates insulin sensitivity in adipose tissue [25]. The study done by Fadaei and colleague confirmed that in addition to reducing chemerin, the indicator of body composition was reduced after eight weeks of aerobic training [13]. On the other hand, it can be justified that much of the fatty acids required for the working muscles is supplied by 3-4 times more increase in triglyceride lipolysis in adipose tissue. High intensity exercise results in a two-fold increase in the level of blood flow to adipose tissue; while, it increases the blood flow to active muscles of the body at a rate of 10 times more, which results in a decrease in body fat, decrease in WHR, and the improvement of body composition because of the imbalance between energy intake and energy consumption, and a negative caloric balance that may result in the reduction in plasma chemerin after training [26].

Another possible mechanism is that high intensity interval training associated with an increased caloric consumption may reduce the route of adipogenesis. Since the values of chemerin increase with hyperlipidemia, this reduction represents a decrease in the speed of adipogenesis due to intensive exercise [27].

However, the result of the present study is not consistent with the results of the study done by Zolfaghari and colleague. The difference between these studies can be due to age, sex, type and intensity of the exercise. The study by Zolfaghari and colleague was done on men over 40 years whose serum chemerin was higher compared to younger people, which may be decreased to a lower level by high intensive exercise. This, in turn, can be effective in reducing weight and fat percentage. In the previous study, green tea extract was used as a supplement that could affect the results of the study [17]. Since there is not enough information and chemerin action is not fully understood and only few studies have been done in this area, it is not possible to properly explain the conflicting results of the research. However, more research is needed to confirm this.

IV. MYOSTATIN

Myostatin is a member of TGF- β family which negatively regulates skeletal muscle growth. After expression in skeletal muscle, myostatin releases into circulation; this it is done by binding to Activin IIB which increases the expression of 21P (inhibitor of cell cycle) and inhibits myogenic regulatory factors including myogenin and ultimately decreases the proliferation and differentiation of satellite cells [28]. Therefore, the main objective of myostatin messaging is the suppression of cell proliferation and differentiation, which can ultimately inhibit muscle growth [29]. It has been found that inhibition of myostatin can increase muscle mass and strength

[30]; and, inactivity is associated with increased expression of myostatin and muscle atrophy. It seems that resistance training leads to reduction in the expression of myostatin.

V. MYOSTATIN AND RESPONSE TO PHYSICAL ACTIVITY

The results showed that 10 weeks of resistance training reduces the level of myostatin in obese young men. Assad and colleagues, in a study, investigated the effect of eight weeks of resistance training on plasma myostatin levels of 19 obese male non-athletes. The results showed that the plasma levels of myostatin in the experimental group compared with the control group decreased significantly [31].

It has been reported that the amount of testosterone in men is 10 times higher than women. Given the role of testosterone in anabolic processes and increase of muscle mass in men, using male participants in the study resulted in a reduction in the levels of myostatin. Testosterone, growth (GH) and IGF (Insulin-like growth factors) by activating different signaling pathways, especially the signaling pathway activator of transcription b5, as well as a complex series of cellular cascade routes, leads to a negative regulation of expression of myostatin in muscle cells, and as a consequence, a reduction in the secretion of blood [32].

Coffey and Hawley showed that resistance exercise decrease the FOX1 (Forkhead box1) and increase MTOR (Mammalian target of rapamycin); as a result, plasma myostatin is reduced [33]. It is argued that myostatin variations take place in response to confounding factors such as changes in the frequency and level of physical activity in skeletal muscle receptors. Due to an increase or decrease of some factors, variations in the number and level of activity of myostatin receptors in skeletal muscle play an important role in the regulation of the number and the activity of myostatin receptors and their binding to this receptor. It has been seen that after physical activity and exercise, increased performance of additive regulators especially decorin and the number of serine/activated kinase protein receptors α II and β II (especially β II), increase myostatin binding to the receptors in muscle. This eventually leads to decrease in plasma myostatin [34]. One of the mechanisms that can be invoked is mechanical stimulation; sarcolemma injury and interpose of FGF-2 secretion (Fibroblast growth factor-2) are considered as an important autocrine mechanism for guiding mechanical load stimulation toward the response of skeletal muscle [35].

VI. CONCLUSION

Accordingly, it can be concluded that high intensive exercise, by regulating chemerin, can act as an effective method to reduce weight and body fat, as non-invasive and non-pharmacological methods.

In conclusion, the study showed that resistance training for 10 weeks could reduce levels of plasma myostatin. It seems that resistance training can reduce atrophy and increase muscular strength; and it plays role as an autocrine mechanism to guide the growth of skeletal muscle in response to mechanical stimuli times. Due to the limited number of studies

done and different physiological mechanisms in the plasma myostatin, it is necessary to do multiple studies with different samples for more decisive comment. It is suggested the effects of different resistance training protocols on the levels of myostatin with muscular resistance measurements to be conducted on participants with muscular atrophy in order to infer and generalize the effect of myostatin on increasing muscle strength more confidently.

REFERENCES

- [1] C. Martins, MD. Robertson, LM. Morgan, "Effects of exercise and restrained eating behaviour on appetite control," *Proc Nutr Soc.*, 67 (1): 28-41. 2008.
- [2] Y.J. Hah, NK. Kim, MK. Kim, HS. Kim, SH. Hur, HJ. Yoon, et al. "Relationship between chemerin levels and cardiometabolic parameters and degree of coronary stenosis in Korean patients with coronary artery disease," *Diabetes and Meta J.*, 35(3): 248-54. 2011.
- [3] E. Maury, SM. Brichard, "Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome," *Mol Cell Endocrinol.*, 314:1-16. 2010.
- [4] M. Saghebjo, R. Fathi, E. Talebi-Ghorghani, A. Hosseini-Kakhak, A. Ghanbari-Niaki, M. Hedayati, "Obestatin and the regulation of energy balance in physical activity," *Iranian Journal of Endocrinology and Metabolism.*, 12 (6): 647-55. 2010.
- [5] A. Saremi, M. Moslehabadi, M. Parastesh, "Effects of twelve-week strength training on serum chemerin," *TNF- α And CRP Level in Subjects with the Metabolic Syndrome. Iranian Journal of Endocrinology and Metabolism.*, 12 (5): 536-43. 2011.
- [6] D. Stejskal, M. Karpisek, Z. Hanulova, "Chemerin is an independent marker of the metabolic syndrome in a Caucasian population--a pilot study," *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.*, 152: 217-21. 2008.
- [7] B. Dong, W. Ji, Y. Zhang, "Elevated serum chemerin levels are associated with the presence of coronary artery disease in patients with metabolic syndrome," *Inter Med.*, 50 (10): 1093-97. 2011.
- [8] C. Matthew, J. Ernst Christopher, "Chemerin: at the crossroads of inflammation and obesity," *Trends In Endo And Meta.*, 21(11): 660-67. 2010.
- [9] MC. Ernst, CJ. Sinal, "Chemerin: at the crossroad of inflammation and obesity," *Trends Endo Meta.*, 21: 660-7. 2010.
- [10] OA. Mac Dougald, CF. Burant, "The rapidly expanding family of adipokines," *Cell Metab.*, 6: 159-61. 2007.
- [11] S. Mora, IM. Lee, JE. Buring, PM. Ridker, "Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women," *JAMA.*, 295(12):1412-1419. 2006.
- [12] M. Sherafati-Moghadam, F. Daryanoosh, M. Mohammadi, M. Kooshki Jahromi, H. Alizadeh-Palavani, "The effect of eight-week intense sprint exercise on plasma levels of vaspin and chemerin in female Sprague-Dawley rats," *Scientific-Research Journal of Shahed University.*, 21(107):1-9. 2013.
- [13] S. Fadaei Raehanabadi, R. Fathi, B. Nokhostin Rohi, "Effects of aerobic training on resting levels of chemerin and plasma lipids in overweight women," *Exercise physiology.*, 18, 121-136. 2011.
- [14] A. Saremi, N. Shavandi, M. Parastesh, H. Daneshmand "Twelve-week aerobic training decreases chemerin level and improves cardiometabolic risk factors in overweight and obese men," *Asian Journal of Sports Medicine.*, 1(3): 151-158. 2010.
- [15] Khademosharie T, Amiri Parsa MR. Hamedinia MS, Hosseini-Kakhk SAR. "Effects of two aerobic training protocols on Vaspin, Chemerin and lipid profile in woman with type 2 diabetes," *ISMJ.*, 17(4): 571-81. 2014.
- [16] M. J. Pourvagh, "Impact of a 2-month aerobic exercise on CRP of overweight female students," *Feyz.*, 17(4): 380-386. 2013.
- [17] M. Zolfaghary, F. Taghian, M. Hedayati, "The Effects of Green Tea Extract Consumption, Aerobic Exercise and a Combination of These on Chemerin Levels and Insulin Resistance in Obese Women," *Iranian Journal of Endocrinology and Metabolism.*, 3(15): 253-261. 2013.
- [18] K. Bozaoglu, D. Segal, KA. Shields, N. Cummings, JE. Curran, AG. Comuzzie, et al. "Chemerin is associated with metabolic syndrome phenotypes in a Mexican-American population," *J Clin Endocrinol Metab.*, 94: 3085-8. 2009.

- [19] H. Sell, J. Laurencikiene, A. Taube, K. Eckardt, A. Cramer, A. Horrigs, "Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary Human skeletal muscle cells," *Diabetes.*, 58(12): 2731-40. 2009.
- [20] T. J. Sledzinski, A. Korczynska, L. Hallmann, M. Kaska, T. Proczko-Markuszewska, M. Stefaniak, "The increase of serum chemerin concentration is mainly associated with the increase of body mass index in obese, non-diabetic subjects," *J. Endocrinol. Invest.*, 36: 428-434, 2013.
- [21] P. Poirier, TD. Giles, GA. Bray, Y. Hong, JS. Stern, FX. Pi Sunyer, "Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss," *Arterioscler Thromb Vasc Biol.*, 26(5): 968-76. 2006.
- [22] KB. Goralski, TC. McCarthy, EA. Hanniman, BA. Zabel, EC. Butcher, SD, Parlee, "Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism," *J Biol Chem.*, 282 (38): 28175-88. 2007.
- [23] J. Kaur, R. Adya, BK. Tan, J. Chen, HS. Randeve, "Identification chemerin receptor (ChemR23) in human endothelial cells: Chemerin-induced endothelial angiogenesis," *Biochem Biophys Res Commun.*, 391(4): 1762-8. 2010.
- [24] M. J. Pourvaghari, M. E. Bahram, M. Sayyah, Sh. Khoshemehry, The Effect of a Three-Month Intensive Intermittent Training on Plasma Chemerin and Factors Related to Body Composition on Overweight Males," *Armaghan Danesh.*, Vol. 20 , Number 5 (100); Pp. 381-392. Aug. 2015.
- [25] SE. Wozniak, LL. Gee, MS. Wachtel, EE. Frezza "Adipose tissue: the new endocrine organ? A review article. *Digestive Diseases and Sciences.*, 54 (9): 1847-56. 2009.
- [26] F. Yamaner, T. Bayraktaroglu, H. Atmaca, MA. Ziyagil, K. Tamer, "Serum leptin, lipoprotein levels, and glucose homeostasis, between national wrestlers and sedentary males," *Turk. J Med Sci.*, 40 (3): 471-77. 2010.
- [27] JM. Bruun, JW. Helge, B. Richelsen, B. Stallknecht, "Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects," *Am J Physiol.*, Vol. 290 no. 5, Apr. 2006.
- [28] E. Cadore, R. Pinto, F. Lhullier, C. Correa, C. Alberton, S. Pinto, "Physiological effects of concurrent training in elderly men," *Int J Sports Med.*, 31 (10): 689. 2010.
- [29] A. Matsakas, A. Friedel, T. Hertrampf, P. Diel, "Short-term endurance training results in a muscle specific decrease of myostatin mRNA content in the rat," *Acta physiologica scandinavica.*, 183 (3): 299-307. 2005.
- [30] RS. Taipale, K. Häkkinen, "Acute hormonal and force responses to combined strength and endurance loadings in men and women: the order effect," *Plos one.*, 8 (2): 55051. 2013.
- [31] MR. Asad, J. Vakili "Effect of resistance training on plasma myostatin level in overweight untrained men," *Applied research of sport management.*, 1 (1): 75-80. 2012.
- [32] TR. Lundberg, R. Fernandez-Gonzalo, T. Gustafsson, PA. Tesch "Aerobic exercise alters skeletal muscle molecular responses to resistance exercise," *Medicine and Science in Sports and Exercise.*, 44(9):1680-8. 2012.
- [33] VG. Coffey, JA. Hawley "The molecular bases of training adaptation," *Sports Medicine* 2007; 37(9): 737-63.
- [34] A. Bonniou, G. Carnac, B. Vernus "Myostatin in the pathophysiology of skeletal muscle. *Current genomics.*, 8 (7): 415-22. 2007.
- [35] MS. Clarke, DL. Feedback "Mechanical load induces sarcoplasmic wounding and FGF release in differentiated human skeletal muscle cultures," *FASEB J.*, 10(4): 502-9. 1996.