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The effect of two intensities resistance training on muscle growth regulatory myokines in sedentary young women

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1. Introduction

The skeletal muscles are vitally important for preserving and developing health. In this respect, muscle is considered as an important endocrine organ (Broholm and Pedersen, 2010). More than 40% of body weight of a normal person is skeletal muscle that includes a major part of the body's metabolism; therefore, most metabolic diseases are related to muscles, directly or indirectly (Broholm and Pedersen, 2010; Roca-Rivada et al., 2012). A sedentary lifestyle is the most important factor in muscle atrophy in healthy and mature individuals (Pedersen and Febbraio, 2012); therefore, atrophy and muscle development depend on the balance between developer and inhibitor factors of muscle growth. According to research, Myostatin (GDF-8) and Follistatin are the most important inhibitors and developers of muscle growth (Migliaccio et al., 2014; Juhas and Bursac, 2014). Myostatin, a cytokinetic inhibitor factor of muscle growth, was introduced in 1997 by Mc Pherrone (Kandarian and Jackman, 2006). This cytokines is a new member of the large family of TGF-β[1]. Myostatin is primarily released by muscle cells and, in smaller amounts, by various tissues such as brain and fat tissue (Juhas and Bursac, 2014; Lutosławska et al., 2012) and is responsible for inhibiting the hypertrophic growth of muscle cells and preventing cell proliferation (growth inhibition of Hyperiolasic) (Lee et al., 2010). Myostatin functions may be influenced by interactive factors such as Follistatin, FLRG[2], GASP-1[3] and Myostatin receptors (Activin IIb). Among these, Follistatin is the most important inhibitor factor (McPherron and Lee, 2002).

Follistatin is a glycoprotein which is released in almost all tissues of mammals and, in particular, by skeletal muscles. The most important task of Follistatin is neutralizing functions of the TGF-β family proteins, including Myostatin. In the presence of Follistatin, Myostatin is not able to bind to self-receptors and its function will be impaired (Juhas and Bursac, 2014; Bradley et al., 2008). In addition, the type of training and energy intensity involved in activities can cause different adaptations in muscle through different changes in muscle growth regulation factors (Elkina et al., 2011). In general, most studies show that resistance training (after one session or a prolonged period) reduces the level of Myostatin (Elkina et al., 2011; Fedoruk and Rupert, 2008) and increases Follistatin expression (Hiroki et al., 2011; Hittel et al., 2010), however there are also conflicting results (Bradley et al., 2008; Hiroki et al., 2011).

Resistance training increases muscle growth factors and inhibits negative adjustment factors by increasing the muscle hypertrophy and hyperplasia (Bellamy et al., 2014; Sharp et al., 2014). However, it is known that exercise pattern and intensity in resistance training as well as the role of gender are very effective for the development of muscle (Saini et al., 2009). According to different hormonal and metabolic characteristics and patterns of gain power, muscle mass is naturally less in adult women than in adult men (Juhas and Bursac, 2014; Gundersen, 2016). Nevertheless, more research has been done on males (Allen et al., 2011; Schoenfeld, 2010), and different patterns and different intensities of resistance training exercises have been less studied. On the other hand, deleting the Myostatin gene in animals doubled muscle growth, while in animals that received Follistatin, the muscle growth increased fourfold. Therefore, Follistatin, in addition to its effect on the Myostatin, can affect the other members of the TGF-β family (Bradley et al., 2008; Elkina et al., 2011). Thus, the positive and negative regulatory factor interactions in muscle growth also seem useful.

2. Material and methods

2.1. Subjects

This semi-experimental research included two phases which were performed before and after 8 weeks in two experimental

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[1] Transforming Growth factors β (TGF-β).
[2] Follistatin-Related Gene (FLRG).
[3] Growth and Differentiation Factor-Associated Serum protein-1 (GASP-1).

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groups. A total of 24 sedentary young women aged over 20 years (mean age 24.42 ± 2.95 years, and mean body mass index 23.77 ± 1.54 kg/m^2) were recruited for this study. All of the volunteers completed the exercise program during 8 weeks. Based on the demographic and medical records questionnaires, the subjects had not done regular exercise over the prior six months and did not have a history of coronary artery diseases, kidney failure, or hypothyroidism. Furthermore, calorie intake was estimated using the dietary questionnaire in order to monitor the energy balance in each week. Based on the collected data, daily calorie intake of subjects varied between 1600 and 1900 kcal.

2.2. Measurement of anthropometric characteristics

BMI was measured using a body composition analyzer device (Inbody-720 Body Composition Analyzer, Japan) while height was measured with a stadiometer (SECA, Germany).

2.3. 1RM testing

In this study, prior to the 1RM testing session, subjects were given three familiarization sessions to ensure proper lifting techniques and testing procedures. During these sessions, the load was gradually increased to allow the estimation of a proper starting point for the test session. Before performing the actual tests, subjects were given a 10-min low-intensity warm-up and 3-min rest between test efforts. They were instructed to refrain from food intake 2 h prior to the test session but were allowed to drink water.

2.4. Resistance training protocol

Twenty four young, sedentary women were assigned to either an 8-week high or low intensity resistance training program in a circular shape, involving 3 training sessions per week. Based on the equation of one repetition maximum (1RM), the training program for both groups was isocaloric. In each training session, subjects were given a 10-min general and specific warm-up (low speed running, stretching exercises, and weightlifting movements with light weight) and 10-min cool-down exercise. The training protocol consisted of four lower body exercises (leg extension, leg flexion, squat, and standing calf raise) and three upper body exercises (high pull, elbow flexion, and elbow extension) performed at both low intensity (40%–60%1RM and 20–30 repetition in each station) and high intensity (70%–90% 1RM and 5–15 repetition in each station). In the low-intensity exercise group (n = 12), the time of activity in each training station was 45 s. There was a resting period of 30 s between training stations and 2 min between the seven-station training rounds. In the high-intensity exercise group (n = 12), the time of activity in each training station was 20 s. The subject had a resting period of 30 s between training stations and 2 min between the seven-station training rounds. Moreover, the number of training rounds was three. To observe the principle of overload and the regulation of practice pressure, Borg questionnaires were completed by the individuals at the end of the third session of each week. The following equation was used to determine the progressive increase in overload at each station in the first week and at the end of the fourth and sixth weeks (Murach and Bagley, 2016).

$$1RM = W/ [1.0278-(0.0278.r)]$$

2.5. Collection and analysis of blood samples

Blood samples were taken before and after eight weeks of resistance training. The procedure was performed by standard antecubital venous puncture. Blood samples were collected after 12 h fasting, and then the samples were clotted for two hours at room temperature before centrifugation for 15 min at 1000 × g. Serum was stored at −20 °C for 2 months until the time of analysis. Serum Myostatin concentrations were determined using Human Myostatin (MSTN) ELISA Kit (CK-E11241), and Serum Follistatin concentrations were determined with Human Follistatin (FS) ELISA Kit (CK-E10682).

2.6. Statistical analysis

All statistical analyses were performed with SPSS version 22. The average and standard deviations of data were calculated after checking the normal distribution using Shapiro-wilk test. Levene test was also used to ensure the homogeneity of variances. Moreover, one-way ANOVA was conducted for determining the homogeneity of the groups before starting the exercise program, and repeated measure analysis of variance method was implemented to compare the means between the groups, and to compare the means within the groups as well. For all analysis, statistical significance was assigned at $P < 0.05$.

3. Results

As seen in Table 1, in the low-intensity RT group, no significant changes were observed in Follistatin serum ($P = 0.649$), whereas it increased significantly ($P = 0.040$) in the high intensity RT group. Nevertheless, the variance between groups in Follistatin was not significant ($P = 0.086$).

In the high intensity RT group, Myostatin serum decreased significantly ($P = 0.041$), whereas the ratio of Follistatin to Myostatin increased dramatically ($P = 0.951$). In this case, the variance between the groups was not significant for both Myostatin ($P = 0.211$) and the ratio of Follistatin to Myostatin ($P = 0.060$).

4. Discussion and conclusion

Statistical analysis showed that eight weeks of high intensity resistance training significantly increased both Follistatin and the ratio of Follistatin to Myostatin. It also significantly reduced the amount of Myostatin in sedentary young women. Raue et al. (2006) reported that one high-intensity resistance training session caused a 50% reduction in Myostatin mRNA levels in young and old women (Moienneia and Attarzadeh Hosseini, 2016). Kim et al. (2005) examined the effect of a resistance training session on Myostatin levels in young and old women and men (Tay et al., 2015). Results showed a significant reduction in Myostatin levels. Roth et al. (2003) reported that nine weeks of heavy training consisting of only knee extensions has led to a significant decrease of Myostatin levels in men and women (Ost et al., 2016). Results are almost in line with the results of the high-intensity resistance training group. Nevertheless, the low-intensity resistance training could not make a statistically significant change in the mentioned variables. Furthermore, there was not a significantly meaningful comparison between changes in Follistatin, Myostatin, and Follistatin to Myostatin ratio in the two groups (after the intervention).

Comparing this study with previous research seems quite difficult because the effects of resistance training on myokines of regulatory muscle growth often have been assessed in either tissue samples or male samples (Schiffer et al., 2011; Jensky et al., 2010). However, research by Schiffer et al. (2011) examined the effect of twelve weeks of resistance and endurance training on Myostatin gene expression. The results showed a lack of any meaningful difference in Myostatin muscle after the post-test (Raue et al., 2006). Also Jensky et al. (2010) examined the effect of introvert and

Table 1
The compression of mean changes of variations within and between-groups.

		M ± SD		F	p-value [a]	F	p-value[b]
		Pre test	Post test				
Follistatin (ng/l)	LRT	61.08 ± 37.46	63.03 ± 39.58	0.219	0.649	3.23	0.086
	HRT	60.78 ± 48.52	78.15 ± 66.22	5.401	0.040[c]		
Myostatin (ng/l)	LRT	295.25 ± 151.90	279.25 ± 137.13	1.518	0.244	1.660	0.211
	HRT	278.91 ± 164.61	231.75 ± 119.32	5.339	0.041[c]		
Follistatin/myostatin (ng/l)	LRT	0.2016 ± 0.0730	0.2224 ± 0.1283	0.893	0.365	3.931	0.060
	HRT	0.2007 ± 0.0565	0.3185 ± 0.1697	7.253	0.021[c]		

Data are presented as mean ± standard error of the mean (SEM) or absolute numbers.
Abbreviations: LRT, low -intensity resistance training; HRT, high-intensity resistance training.
[a] Within group comparison.
[b] Between groups comparison.
[c] Significant correlation ($p < 0/05$).

extrovert resistance training (on one foot), in both one and seven sessions, on expression of Follistatin and Myostatin genes in women. Biopsy results of Vastus lateralis muscles revealed that both one and seven sessions of concentric and eccentric resistance training had no statistically meaningful effect on expression of either gene in young women (Kim et al. 2005). So these results were in part similar to the results of the low intensity resistance training.

According to studies, it seems that Myokines' release rate and regulate factors of muscle growth depend on the exercise intensity and the volume of muscles involved (Roth et al., 2003; Winbanks et al., 2012). The initial signaling that stimulates muscular hypertrophy results from tension of contraction proteins (Motevalli et al., 2015). Due to muscle contraction and stretching these proteins, a set of signals are activated, which results in a positive balance of myogenic factors such as Follistatin, Myo-D, c-fos, and the negative balance of Myostatic factors such as Myostatin, and eventually leads to a positive balance of the hypertrophic process by increasing the synthesis of contractile proteins, absorption, and proliferation of satellite cells (Schoenfeld, 2010; Motevalli et al., 2015).

Moreover, the intensity and level of resistance affect the activation of involved moving units so that the amount and type of involved moving units in exercises affect the released myokines levels and their Autocraine and Paracrine performance (Allen et al., 2011). According to research, an increase in muscular hypertrophy has been reported through a rise in ratio of fast-twitch muscular tissues to slow-twitch muscular tissues (by exogenic increase in the levels of Follistatin or suppressing the Myostatin gene expression). It seems that the recall of more fast-twitch moving units (which happens as a result of high intensity exercises than to low intensity ones) has higher impact on both muscular Myokines levels and the signaling of myogenic factors (Allen et al., 2011; Sandri, 2008).

An important point of interest is that an increase in the Myostatic factors, such as Myostatin, and a decrease in myogenic factors, such as Follistatin, not only have been reported in long periods of inactivity, but also in some cases such as long-term hunger, low calorie diet and sarcopenia. It has also been confirmed that the level of myogenic factors in women is lower than in men (Tay et al., 2015). It seems that, in addition to inner-muscular mechanisms, the control of signaling in muscular hypertrophy is a function of other powerful factors such as hormonal factors, so the share of each of these factors in muscle hypertrophy is debatable (Schoenfeld, 2010). According to research, signaling of muscular hypertrophy (resulting from activities) can be influenced by the levels of hormones such as GH[4], IGF-I[5], testosterone, and cortisol, depending on intensity of exercises (La Colla et al., 2015). Growth hormone level increases in response to high intensity exercise, and the pattern of its release depends on the nature, intensity, size, and group of involved muscles (La Colla et al., 2015; Barbé et al., 2015). Increased levels of GH decreases protein catabolism and increases protein synthesis (as a result of an increase in IGF-I) (La Colla et al., 2015). IGF-I activates a set of signals of intracellular anabolic through activating the anabolic routes such as PI3K and IRS-1.2 (zakavi i, 2015; La Colla et al., 2015). Additionally, increased levels of androgens such as testosterone have been reported in the intense resistance training and the intense aerobic exercise; however, this rate of increase depends to LH and it is higher in men than in women (Jensky et al., 2010; zakavi i, 2015).

It is known that the promoter of the Myostatin gene has both a testosterone receiver and a cortisol receiver, so increasing the testosterone levels and binding to this receptors reduces Myostatin expression. In addition, an increase in cortisol levels will result in Myostatin gene expression. In this case, it has been specified that in resistance trainings, the level of testosterone to cortisol will increase (Allen et al., 2011; Jensky et al., 2010). Testosterone not only decreases the levels of Myostatin factors, but also increases the levels of myogenic factors such as the Follistatin (Allen et al., 2011). Therefore, an increase in levels of both Follistatin and the ratio of Follistatin to Myostatin, and a decrease levels of Myostatin in the high-intensity resistance training are, in part, a result of these factors. Moreover, the high-intensity resistance training increases the activation of signals for contractile proteins stretch which increases the levels of Myokines (Allen et al., 2011; Schoenfeld, 2010; La Colla et al., 2015).

Based on research, muscular hypertrophy (resulted from resistance training) is likely to happen by changing the balance of muscular protein synthesis through increasing the molecular stimulation of signaling routes of protein synthesis such as Akt/mTOR[6], MAPK[7], route-dependent to calcium (Ca + 2), suppressing the routes of protein degradation, and cellular apoptosis such as FOXO[8] (Allen et al., 2011; Barbé et al., 2015; Pedersen, 2011). The key role of Myostatin and Follistatin in these processes are quite significant.

Follistatin is necessary for the formation, growth and development of muscular fibers. Follistatin is a powerful factor that stimulates the all signaling routes of protein synthesis and suppresses routes of protein degradation (Pedersen, 2011). In addition, Follistatin is the most important factor contributing to stimulation of satellite cells that are vitally important in restoration and

[4] growth hormone (GH).
[5] insulin-like growth factor (IGF-I).
[6] Mammalian target of rapamycin (mTOR).
[7] Mitogen-activated protein kinase (MAPK).
[8] Forkhead box.

development of muscular tissue (Schoenfeld, 2010). One of the important parts of the Follistatin myogenic mechanism results from its functionality in suppressing TGF-β family members, especially Myostatin. Follistatin directly impairs its performance by decreasing the levels of a free Myostatin protein and binding to its specific receptor. It also, indirectly reduces the performance of other members of the TGF-β family through activation of some of the intermediate elements (Pedersen, 2011).

Similarly, Myostatin has a two-way mechanism. From one hand, it damages the all routes of intercellular anabolic and protein synthesis by activating a set of SMAD proteins and from the other hand, it accelerates all catabolic processes through activating the signaling routs of protein degradation and cellular apoptosis such as FOXO. Finally, it causes atrophy of muscle tissue (Sandri, 2008). Accordingly, it seems that small changes in the values of these Myokines can play a role in the muscular development process and body metabolic balance (Schiffer et al., 2011; Gilson et al., 2009). In addition, it has been determined that Myostatin is effective in increasing the insulin resistance and progression of metabolic diseases such as diabetes.

Hence, recently, changes in the ratio of Myostatin to Follistatin have been considered as an indicator contributing to activation of the majority of development mechanisms of positive anabolic processes such as increased protein synthesis in tissue especially in muscular and bone tissues as well as increasing the catabolic process of fat tissues (Pedersen, 2011). In this case, the meaningful increase of this ratio in the high intensity training group is quite important. It is highly recommended to conclude more cautiously because this study has some limitations such as varied diet, different adaptation responses to resistance trainings, lack of control of resting and sleeping, and other individual differences.

5. Conclusion

Overall, according to our findings, it seems that low-intensity resistance training does not provide adequate mechanism to enable the most important factors of Myostatic and myogenic in sedentary women. Moreover, high intensity resistance training develops their muscular tissue through increasing the Follistatin levels and decreasing the Myostatin levels in sedentary women, and probably by enabling the powerful mechanisms of protein synthesis and breakdown of fatty tissue.

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