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OriginalArticle

Effects of Eight Weeks of Resistance Training on Muscle Myostatin Gene Expression and Insulin Resistance in Male Wistar Rats with Type 2 Diabetes

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ABSTRACT

Background and Objectives: Muscular atrophy is one of the indicators of uncontrolled diabetes. The aim of the current study was to investigate effects of eight weeks of resistance training (RT) on myostatin gene expression in soleus muscles and insulin resistance in streptozotocin (STZ)-induced diabetic rats.

Materials and Methods: In general, 14 Wistar male rats weighing 200–250 g and aging 8–10 weeks were selected for the study. Then, a newly prepared diabetic STZ solution was intraperitoneally injected to the rats. Animals were randomly divided into two groups of controls and resistance training diabetes. The resistance training protocol was carried out at ten repetitions as climbing up the ladder with 100% of the body weight for eight weeks, five days a week. Nearly 48 h after the last training session, soleus muscles of the rats were removed and the myostatin gene expression was assessed. Statistical data analysis was carried out using independent t-test at a significance level of P <0.05.

Results: Results of the independent t-test showed that the mean expression rate of myostatin protein genes in rat soleus muscles of the resistance training group was significantly lower than that of the control group (P = 0.013). Furthermore, levels of glucose, insulin and insulin resistance were significantly lower in resistance training group, compared to those in control group (P-values of 0.001, 0.005 and 0.001, respectively). A significantly positive correlation was seen between the mean expression of myostatin protein gene and the blood glucose (P = 0.012, r = 0.539), as well as the expression of myostatin protein gene and the insulin resistance (P = 0.015, r = 0.525).

Conclusions: Results of this study indicated that resistance training decreased myostatin expression and could improve insulin resistance in rats with type 2 diabetes. Hence, targeting myostatin might be a new therapeutic approach for the treatment of metabolic diseases such as obesity, diabetes and metabolic syndrome.

Keywords: Type 2 diabetes, Insulin resistance, Myostatin gene expression, Soleus muscle, Resistance training

Introduction

Diabetes mellitus (DM) is a common endocrine disease; in which, concentration of the blood sugar is higher than the normal one. This disease is divided into two major types. Type 1 diabetes or insulin-dependent diabetes mellitus (IDDM) is characterized by degradation of beta cells in Langerhans islets of the pancreas and decreased insulin secretion. Type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM) is characterized by insulin resistance due to genetic and multiple acquired factors such as obesity and immobility (1). Diabetic myopathy refers to clinical conditions; through which, the muscle size and strength/endurance are decreased (2). Muscular atrophy is one of the uncontrolled diabetes indices and is created due to increased proteolysis and decreased protein synthesis. Thereby, ability of the injured musculoskeletal muscles for recovery decreases. Studies have shown increased proteolysis, decreased protein synthesis and muscle atrophy in laboratory models of type 2 diabetes (3, 4). Size and strength of the muscles not only provide ability of daily activities, but also are essential in metabolic activities, including glucose homeostasis. Moreover, size and density of the muscles can slow down the side effects of diabetes (5).

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Myostatin is a new member of the large family of transforming growth factor β (TGF-β). Expression of this gene negatively regulates growth of the skeletal muscles (6). When muscular atrophy or dystrophy occurs, increases in this hormone is seen and when muscle overload occurs after atrophy, decreases in the hormone is observed (7). After synthesis in skeletal muscles, myostatin is secreted into the blood circulation. By binding to serine/**trunnion** kinase activin II IIB on surface of the muscle cells, the hormone stimulates expression of P21 (inhibitor of cell cycle cyclins) (8), decrease of myogenic regulatory factors (including myogenin) (9) and ultimately decrease of proliferation and differentiation of satellite cells in adult myofibres (8). It has been demonstrated that myostatin prevents differentiation and proliferation of myoblast in skeletal muscles and adjusts the synthesis of muscle proteins via Akt/mTOR pathway (10, 11). Studies have shown that complete removal of myostatin in rats results in increased skeletal muscle masses by two to three times due to the increased size of myofibrils (8). Furthermore, myostatin functions are not limited to inhibiting muscle growth. Myostatin not only plays a role in muscle growth, but also affects insulin resistance [12]. The contrast between myostatin and insulin signaling was first seen in rats with increased myostatin expression. This increase was shown to be associated with immunity against obesity due to nutrition as well as insulin resistance (13). These findings were supported by findings on increased expression of mRNA, myostatin protein, obesity and insulin resistance in human samples (11, 14). Moreover, short-term use of external myostatin induced insulin resistance in myostatin-free rats (15).

Reduces in mobility and daily exercises can increase likelihood of diabetes and other metabolic disorders (16). Therefore, exercising is suggested to prevent complications and control diabetes (17). Resistance training has been shown to increase muscle mass, strength and performance in diabetics. Furthermore, resistance training can increase insulin function in musculoskeletal systems (17, 18). Skeletal muscle is a dynamic tissue which adapts in response to various physiological stimuli, such as short and long-term sports activities. Following these adaptations, functional capacity and physical performance of the individuals are improved (19). Various studies have investigated effects of various types of physical training on myostatin. Studies have shown that myostatin decreases in response to various applied loads, including short-term training courses (20), long-term ledalling on ergometers, running on treadmills (7) and isometric resistance training after muscle atrophies (21). However, studies have reported no changes or increases in myostatin. For example, Jensky et al. (2010) showed that seven sessions of extreme extrinsic resistance training with one leg and introversion one as open chain knee isokinetic movements included no effects on myostatin mRNA levels in young women (22). In contrast, Negaresh et al. (2019) investigated effects of whole-body resistance training in healthy elderly people and patients with sarcopenia and showed that resistance training decreased myostatin in both groups (23). Willoughby (2004) demonstrated that heavy resistance training in healthy individuals for 12 weeks was associated to increased expression of mRNA and myostatin protein (24). However, decreases in myostatin expression due to training is controversial. In the current study, increased expression of myostatin was seen in rats after 31 min of extroversion activity (25). In contrast, Hittel et al. (2010) reported decreases in muscle and plasma myostatins after 5 months of aerobic training in middle-aged people. Bassi et al. (2015) investigated effects of swimming aerobic exercises on muscle myostatin expression in two major metabolic disorders (obesity and diabetes) and concluded that diabetes was associated to increased precursor and myostatin proteins, aerobic exercises could change expression of the muscle myostatin in diabetic rats and myostatin was involved in energy homeostasis (26).

In general, as few limited types of studies have been carried out on effects of training and physical activities on myostatin in diabetics due to the effect of myostatin on insulin resistance in diabetics. Based on the leteratures, no studies have been carried out on the effects of resistance training on myostatin gene expression in muscles and insulin resistance in diabetic rats. Therefore, the aim of this study was to investigate effects of resistance training on myostatin gene expression in muscles and insulin resistance index in type 2 diabetic rats.

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Materials and Methods

Animals: This study was an experimental study with post-test design and experimental and control groups using laboratory methods (Ethics Code: IR.SSRC.REC.1397.007). In this study, 14 Wistar male rats weighing 200–250 g and aging 8–10 weeks were provided by Baqiyatallah University of Medical Sciences, Tehran, Iran. Rat foods were purchased from animal feed companies as pallets and the rats had access to water and foods *ad libidum*. During the study, animals were hosted in fully controlled animal cages (five rats per cage) with dimensions of 1.6 × 2.2 m and controlled light (12**:**12 h light**:**dark cycle, light started at 6 am and dark at 6 pm**)**, temperature (22 ±3 °C) and humidity (nearly 45%) conditions. After one week of acquaintance, animals were divided into two major groups of experiment and control gropups.

Diabetes induction: To induce type 2 diabetes, a solution of nicotinamide was injected intraperitoneally at doses of 110 mg kg^{-1} after one night of fasting. After 15 min, the newly prepared STZ solution in citrate buffer (pH 4.5) was injected intraperitoneally at doses of 60 mg kg^{-1} (1). One week after diabetes induction, the fasting blood glucose (FBS) was assessed and rats with glucose levels of 150–400 mg dL^{-1} were considered as type 2 diabetics.

Resistance training protocol: Training included eight weeks with five weekly sessions. Resistance training in each session was repeated 10 times with 90 s rest periods between repeats. Training included ascending from a 26-step 1-m ladder with a vertical gradient of 85%. Resistance was achieved using attaching a weight to the base of rat tails. The experiments started a week after getting familiar to use of ladder with the resistance weight weighing 30% of the rat body weight. Resistance reached 100% of body weight within eighth weeks (27).

Biopsy: All rats were anesthetized 48 h after the last training session using intraperitoneal injection of ketamine (50 mg kg^{-1}) and xylazine (4 mg kg^{-1}). Then, a qualified specialists performed surgery to extract rat soleus muscles. After surgery, extracted tissues were washed using PBS solution, placed in liquid nitrogen immediately and stored at -80 °C until use.

RNA extraction: To extract RNA from homogenized tissues, 1 ml of YTzol was added to 100 mg of the muscle tissues, mixed well and incubated at room temperature for 15 min. Then, 400 µl of cold chloroform were added to the sample and mixed for 15 s. The mixture was centrifuged at 4 °C at 12,000 rpm for 15 min. This solution, containing RNA, was transferred to a strile microtube and 500 µl of ethanol were added to the micotube and stored at -20 °C for 24 h. After storage, solution was centrifuged at 12000 rpm for 15 min at 4 °C. The supernatant was carefully removed and 1 ml of cold pure ethanol was added to the RNA precipitate and centrifuged at 7,500 rpm for 5 min at 4 °C with. Then, supernatant was carefully removed and the RNA precipitate was diluted with 100 µl of illusion buffer. Concentration and 260/280 absorbance ratio of the samples were assessed using spectrophotometer. The absorption ratio for all samples included 1.6–1.8. Samples were stored at -80 °C funtil use. After extracting high purity and concentration RNA, cDNA synthesis was carried out according to the manufacturer's instructions. First, RNA, primer and water were mixed together and incubated at 65 °C for 5 min. Solution was set on ice for 2 min and then mixed with mixing enzyme and mixing reaction and incubated at three consecutive steps as follows: 1) 25 °C for 10 min; 2) 42 °C for 30 min; and 3) 85 °C for 5 min. The synthesized cDNA was stored at -80 °C until further use. A quantitative RT-PCR method was used to calculated mRNA expression. Each PCR reaction was carried out using chromogenic device and SYBR Green according to the manufacturer's instruction. Thermal cycling consisted of 40 cycles; each cycle included 94 °C for 20 s, 58–60 °C for 30 s and 72 °C for 30 s. Melting chart was used to check accuracy of the PCR reactions for each gene. Sequences of the primers are shown in Table 1.

Table 1. Primer sequences used in this study

Gene	Amplicon size	Gene reference		Primer sequence
Myostatin	159 bp	NM_001191052.1	F	5´-CTACCACGGAAACAATCATTA-3´
			R	5´-AGCAACATTTGGGCTTTCCAT-3´

Glucose concentration was assessed using glucose oxidase colorimetric enzyme and glucose kit (Pars Azmoon, Iran). Coefficients of variation in internal and external tests of glucose included 1.74 and 1.19%, respectively. Sensitivity of the test included 5 mg dl^{-1}. Serum insulin was assessed using ELISA kit (Demeditec, Germany). The internal and external group coefficients of variation and sensitivity of insulin assessment included 2.6 and 2.88% and 1.76 IU, respectively. The Shapiro-Wilk test was used to verify normality of the data. After verifying normality of the data distribution, independent t-test was used to analyze data and compare between the groups. Pearson's correlation coefficient test with a significance level of $P<0.05$ was used to show relationships between the variables. Statistical calculations were carried out using SPSS Software v.16 (IBM Analytics, USA).

Results

A comparison of the mean weights of rats before and after eight weeks of resistance training is presented in Table 2.

It is noteworthy that no significant differences were seen between weights of the rats in diabetic control group and the resistance training group in pre-test stage (P = 0.490). In contrast, weights of the rats in post-test stage was significantly higher in control group, compared to that in resistance training group (P = 0.422). Comparisons of the means and standard deviations as well as independent t-tests of the resistance training effects on myostatin gene expression and levels of glucose, insulin and insulin resistance in the study groups is presented in Table 3.

Table 2. Rat weights before and after eight weeks of training (SD ±mean)

Index	Time / Group	Control diabetes group (n = 7)	Resistance training diabetes group (n = 7)
Weight (g)	Pre-test	230.43± 2.8	3.86± 231.71
	Post-test	265.14± 8.17	261.71± 7.22

Table 3. Comparison of the variables based on the independent t-test

Index / Group	Control daiebtes gorup	Resistance training diabetes gorup	P-value	Effect size
Myostatin (ng/mg protein)	1.01 ±0.09	0.37±0.58	&0.013	0.644
Glucose (mg/dL)	9.79±326.01	9.15±230.86	&0.001	0.983
Insulin (μU/dL)	0.69±6.54	0.52±5.41	&0.005	0.702
Insulin resistance	0.55±5.26	0.38±3.09	&0.001	0.926

&Significant differences in the groups at $P < 0.05$

Based on the findings from Table 3, the mean expression of myostatin protein gene of rat soleus muscle in the diabetic resistance training group was significantly lower than that in control group (P=0.013). Glucose, insulin and insulin resistance levels in diabetic resistance training group were significantly lower than those in control group (P values of 0.001, 0.005 and 0.001, respectively). Table 4 shows relationships between the mean of myostatin gene expression and levels of the variables. Based on the findings, a significantly positive relationship was seen between the mean of myostatin gene expression and the blood glucose level (P = 0.012, r = 0.539) as well as the expression of myostatin gene and the insulin resistance (P = 0.015, r = 0.525). However, no significant relationship was seen between the mean myostatin gene expression and the insulin level (P = 0.07, r = 0.402).

Table 4. Results of the Pearson's correlation coefficient test of the variables

		Myostatin
Glucose	r	0.539
	P	*0.012
Insulin	r	0.525
	P	*0.015
Insulin resistance	r	0.402
	P	0.070

*Significant relationship at $P < 0.05$

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Discussion

Myostatin is a candidate to control atrophy and loss of the muscle mass, which prevents activity of the satellite cells and therefore decreases muscle mass (28, 29). Under activation conditions, myostatin is linked to an activin receptor of type IIB, which results in activation of P21 proteins (inhibitors of cell cycle cyclins) and Smad (molecules inducing intracellular messages to downstream flows). In fact, P21 inhibits proliferation of cellular cells and Smad3 prevents transcription of myogenic regulatory factors such as myosin, which plays a key role in eradication of cellular cells. Therefore, the major purpose of myostatin messaging is to suppress proliferation and differentiation of the cellular cells and eventually inhibit muscle growth (8, 9). A few studies have investigated the changes in gene expression and myostatin protein levels in muscles of diabetics during training. Similarily, Hitle et al. (2010) reported decreases in myostatin protein of muscle and plasma in diabetics due to the aerobic exercises (12). Dutra et al. (2012) showed that swimming exercise training decreased expression of myostatin and activin I and IIB, while increased expression of follistatin in the twin muscle and adipose tissue in diabetic rats with streptozocin (30). Ruth et al. (2003) reported a 37% decrease in myostatin mRNA in vastus lateralis muscles of dominant legs in young and old men and women within 48–72 h after nine weeks of intense resistance training (31). Moreover, Willoughby (2004) demonstrated that heavy resistance training in young healthy participants was accompanied by increased expression of mRNA and myostatin protein over 12 weeks. However, expression of myostatin mRNA after 12 weeks of resistance training did not made significant changes (24). In contrast, Gensky et al. (2010) showed that seven sessions of intense extroversion resistance training with one leg and introversion as open chain knee isokinetic movements included no effects on myostatin mRNA in young women (22). A possible reason for the controversy in results of the studies can linked to the training programs, including rest times, repetition numbers, exercise intensity and status or time of biopsy (48–72 h instead of 0.25–4 h after exercise). Holmie et al. (2007) demonstrated that myostatin mRNA levels did not show significant changes in 1-h training after 21 weeks of flexion and knee extension, while a significant decrease was seen within 48 h after training (32). Age of the participants is one of the effective mechanisms for decreasing expression of myostatin; therefore, levels of myostatin increase in elder people (33). An animal study has shown that resistance training decreases myostatin in quadriceps femoris muscles of young rats, but not old rats (34).

Based on the recent studies, myostatin plays a key role in regulating metabolism as well as muscle mass (6). In the present study, a significantly positive relationship was seen between the expression of myostatin gene and the insulin resistance in diabetic rats, and decreased expression of myostatin gene was associated to improved insulin resistance. These findings were similar to findings from other studies that reported high levels of myostatin in diabetic (35, 36), obese (11, 37) and elder (23) patients (associated with metabolic-cardiovascular risk factors such as insulin resistance). Hitle et al. (2010) reported that both muscle and plasma myostatins decreased by aerobic exercises and this decrease was linked to improvement of insulin resistance in diabetic participants. Therefore, a possible reason for insulin resistance in inactive people was attributed to increased myostatin (12). Some researchers believe that the role of myostatin in regulating metabolism is directly applied. For example, myostatin has been shown to inhibit activation of the Akt key enzyme in glucose metabolism (38); myostatin inhibition leads to increased transcription factor of PPAR-γ (peroxisome proliferator-activated receptor-γ), adiponectin and improved insulin resistance (39); and increased expression of myostatin results in decreased adiponectin and increased resistin and leptin in culture media (38). Myostatin treatment has been shown to decrease glucose removal in cells (40) and decreased myostatin to increase glucose removal in human cells (41). However, myostatin may play a role in indirect glucose removal through the expression of tumor necrosis factor alpha (TNFα), since TNFα is in contrast with the effects of insulin and glucose removals (42). Decreased myostatin in rats with genetic mutations increases glucose tolerance, protects against insulin resistance caused by high-fat foods, and decreases TNFα level and its expression in muscles and adipose tissues (15). In contrast, increased expression of myostatin is associated to

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increased TNFα level in rats fed on high-fat foods that results in further insulin resistance (15). Findings of the present study indicated a significantly positive relationship between the myostatin and the blood glucose and insulin resistance. Some researchers believe that the effect of myostatin on metabolism is indirect. They explain that elimination of myostatin is accompanied by increased muscle masses, which lead to further metabolic substrate extractions [43]. Therefore, it has been suggested that useful effects of myostatin removal or inhibition are used to metabolic indices such as improvement in insulin resistance and dyslipidemia (38, 44).

Conclusion

In conclusion, results of this study indicate that resistance training results in decreased myostatin expression and can lead to improved insulin resistance in type 2 diabetic rats. However it was not shown in this study that decreased effects of myostatin (due to resistance training) on improved insulin resistance in diabetic rats were direct or indirect, it was indicated that myostatin targeting is a new therapeutic option for the treatment of metabolic disorders such as obesity, diabetes and metabolic syndrome.

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