Effect of different muscle contraction mode on the expression of Myostatin, IGF-1, and PGC-1 alpha family members in human Vastus Lateralis muscle

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Abstract
Muscle contraction stimulates a transient change of myogenic factors, partly related to the mode of contractions. Here, we assessed the response of IGF-1Ea, IGF-1Eb, IGF-1Ec, PGC1α-1, PGC1α-4, and myostatin to the eccentric Vs. the concentric contraction in human skeletal muscle. Ten healthy males were performed an acute eccentric and concentric exercise bout (n = 5 per group). For each contraction type, participants performed 12 sets of 10 repetitions knee extension by the dominant leg. Baseline and post-exercise muscle biopsy were taken 4 weeks before and immediately after experimental sessions from Vastus Lateralis muscle. Genes expression was measured by real-time PCR technique. There was a significant increase in PGC1α-1, PGC1α-4, IGF-1Ea and, IGF-1Eb mRNA after concentric contraction (p ≤ 0.05), while the PGC1α-4 and IGF-1Ec significantly increased after eccentric contraction (p ≤ 0.05). It is intriguing to highlight that; no significant differences between groups were evident for changes in any variables following exercise bouts (p ≥ 0.05). Our results found that concentric and eccentric contractions presented different responses in PGC1α-1, IGF-1Ea, IGF-1Eb, and IGF-1Ec mRNA. However, a similar significant increase in mRNA content was observed in PGC1α-4. Further, no apparent differences could be found between the response of genes to eccentric and concentric contraction.

Keywords Eccentric contraction · Concentric contraction · Gene expression · PGC-1 alpha · IGF-1 · Myostatin

Abbreviations
CON  Concentric  PGC-1 alpha  Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
ECC  Eccentric  RE  Resistance exercise
GAPDH  Glyceraldehyde 3-phosphate dehydrogenase  RT-PCR  Real-time polymerase chain reaction
HIIT  High-intensity interval training
IGF-1  Insulin-like growth factor-1
MGF  Mechano growth factor
mRNA  Messenger ribonucleic acid
MVIA  Maximal voluntary isometric actions

Introduction
Skeletal muscle synthesized and released myokines, which act as auto-, para- and endocrine mediators [1]. Myokines could affect non-muscle tissue and make crosstalk among muscles and other tissues. Moreover, skeletal muscle possesses high plasticity; therefore, it can undergo functional and morphological changes in response to different physical activity or disease conditions [2]. Acute and chronic muscle contraction elicit muscle cell adaptation, affecting metabolic and contractile characteristics of muscle [3]. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator, was initially detected in brown fat, and it regulates the several genes that influence the metabolism [4]. Previous researchers found that PGC-1α might have a significant effect on the signaling
process of exercise-stimulated muscle. In this regard, it has been shown that PGC-1α facilitate beneficial adaptations such as mitochondrial protein expression, oxidative stress, and angiogenesis process following acute and chronic exercise training at the skeletal muscle [1, 5]. New isoforms of PGC-1α, including PGC-1α1 to PGC-1α4 resulting from the modified PGC-1α gene, have been recently identified [6]. Among them, PGC-1α1 and PGC-1α4 involved in oxidative alterations and both hypertrophy and muscle strength, respectively [7]. In both Vitro and Vivo conditions, PGC-1α4 stimulates muscle hypertrophy, and animals with overexpression of PGC-1α4 showed resistance to the effects of post-cancer muscle loss [6]. However, Lundberg et al. found that PGC-1α4 is not associated with muscle hypertrophy after resistance training for 5 weeks [8], and no change reported in PGC1α-4 expression following a resistance training bout [9]. Although, a correlation between PGC-1α1 and hypertrophy or muscle strength are yet reported [10]. One study represented that PGC-1α1 could protects skeletal muscle from atrophy through FOXO3 transcription factor [10]. As well as, PGC-1α1 expression and mitochondrial protein synthesis increased 6 h after the strength training [11].

Previous researchers found that PGC-1α activity might increase insulin-like growth factor 1 (IGF-1) expression in both human and animal muscles [6, 12]. IGF-1 has a significant role in anabolic signaling, such as growth, differentiation, and regeneration in the muscle tissue [6]. Family members of IGF-1, IGF-1Ea, IGF-1Eb, and IGF-1Ec contribute to muscle remodeling and muscle hypertrophy [13]. Injection of IGF-1Ea, the predominant IGF-1 isoform, into mice muscle, prevented from loss muscle of age-related or sarcopenia [14]. IGF-1Ec, which well-known as a mechanical growth factor (MGF), stimulates proliferation and activation of satellite cells [15], as well as increasing the level of MGF mRNA through exercise attenuated muscle atrophy in rats [16]. IGF-1Ea and MGF genes are up-regulated in young males after a single strength exercise bout [17]. However, the gene expression of both isoforms did not change in the elderly [18]. The information about IGF-1Eb is limited, although the increase in IGF-1Eb corresponded to the peak of post-exercise myogenic changes in young men [19].

Previously, the significant association among IGF-1, PGC-1α4 with myostatin has been detected [6, 9, 12]. In this regard, total PGC-1α mRNA increased following a resistance exercise bout, where myostatin mRNA expression has been decreased [12]. Moreover, eliminating the myostatin gene in young adults was related to increased PGC-1α4 mRNA after a resistance training program [6]. Myostatin knockout in mice has been associated with a 2–3 fold increase in the size of myofibrils [20]. It has been shown that myostatin decreases in response to a variety of loads, including a short period of swimming training [21], prolonged cycling, treadmill running [22], and isometric resistance training [23] after atrophy caused by the removal of limb load. However, some studies have reported no change or increase in myostatin. In this regard, no effect on myostatin has been shown after 1 week of eccentric resistance in young women [24]. Nevertheless, myostatin mRNA has been mostly decreased after eccentric, concentric, and isometric contraction, especially after eccentric exercise [25]. Further, no difference has been reported on the expression of myostatin according to eccentric contraction velocity in human skeletal muscle [26]. Therefore, there is a discrepancy in myostatin level following exercise.

On the other hand, muscle contraction is involved in two isometric and isotonic types. During an isometric contraction, the muscle fibers remain fixed against an external force, while the dynamic contractions are divided into concentric and eccentric contractions [27]. It has been suggested that eccentric contraction stimulates more adaptations than a concentric contraction. However, when concentric and eccentric exercises are matched for either maximum load or work, the increase in muscle size is similar [28]. Besides, eccentric contractions require less motor unit activation and consume less oxygen and energy for a given muscle force than concentric contraction [29]. From all the above, it can be concluded that the signaling pathways of these two contractions are likely to result in structural, physiological, and molecular differences in skeletal muscle. Hence, our research aimed to investigate the different myogenic markers in young human skeletal muscle after an acute eccentric and concentric exercise bout. We hypothesized that the mode of contraction might have a significant role in PGC-1α, IGF-1 isoforms, and myostatin.

**Procedures**

**Subjects**

Ten healthy males called to participate in the research, which was confirmed by the ethical committee of Tehran University (Ethic No: IR.UT.SPORT.REC.1397.029), Tehran. They were divided into two groups including eccentric (N = 5, Weight = 72.1 ± 9.61 kg, BMI = 24.26 ± 1.97 kg/m², Age = 25.15 ± 2.68 years) and concentric (N = 5, Weight = 71.5 ± 8.16 kg, BMI = 23.45 ± 2.26 kg/m², Age = 26.76 ± 3.45 years). All subjects were healthy and untrained within 6 months before the research. In order to minimize the gender effect on gene expression, only men were used in this study. All subjects were given both written and oral explanations about procedures and then informed consent.
Maximal voluntary isometric contraction

Seven days before beginning the exercise program, all subjects were attended in the laboratory to determine maximal voluntary isometric contraction with the isokinetic dynamometer system (Biodex USA isokinetic dynamometer) through a knee extensor exercise. It should be noted that all subject was given a familiarization and brief warm-up before testing. Moreover, the rate of perceived exertion questionnaire (RPE) has been explained.

Exercise protocols

In experimental sessions, the procedures were reviewed again for the subjects to understand how the exercises were performed. After a warm-up with the isokinetic system consisted of 2 sets of 5 repetitions, and rest time between each set was 30 s. The subjects then performed one of two different protocols with the dominant leg. At the end of each set, the perception of pressure was determined using the RPE 20-point scale. When the subject declared the number 20, the verbal encouragement was continued for another two sets, and when the subject was unable to perform the protocol thoroughly, the exercise was stopped. Eccentric and concentric knee extension contraction has been completed at 60°/sec by maximum force capacity. To match the workload, the designated torques were the same in both eccentric and concentric protocols. Contractions included 12 sets with ten reps for the dominant leg, with 30 s of rest between each set.

Muscle biopsy

The Bergstrom percutaneous needle technique took the Vastus Lateralis muscle biopsies for all subjects between 11 and 12 a.m. in Tehran University of Medical Sciences. Before each biopsy, local anesthesia was used to the fascia superficial and skin with lidocaine. The samples were cleaned from blood and connective tissue, then frozen immediately in liquid nitrogen and stored at −80 °C until gene expression analysis. Baseline and post-exercise muscle biopsy were taken 4 weeks before and immediately after eccentric and concentric contraction.

Gene expression analysis

Total RNA was extracted through the muscle samples using a kiazol solution (Cinnacolon, Iran), based on the guidance of the manufacturer, and to ensure contamination without genomic DNA, it was exposed to DNase (DNase I Ferments). The quality of extracted RNAs was evaluated with the spectrophotometric device (DPI-1, Kiagen). RNA was reverse-transcribed with the Strand cDNA synthesis kit (Oligo dt MWG-Biotech, Germany) based on the guidance of the manufacturer. Each PCR reaction was carried out using the TaqMan Universal PCR master mix (Applied Biosystems) and SYBR green technology in the ABI PRISM sequence detection system (Applied Biosystems). Samples were run using at least three samples in triplicate for 40 cycles by using standard real-time PCR cycling conditions—the sequences of Primer used in the present study presented in Table 1. The expression of GAPDH confirmed that PCR conditions were optimized. Melting diagrams were performed to check the accuracy of PCR reactions. They were evaluated for each gene individually and at each reaction time and negative control diagrams to check for contamination in each reaction. The Relative expression of PGC1α, IGF-1, and myostatin mRNA normalized by GAPDH mRNA, which is utilized as an endogenous control, and data has been analyzed by the standard ΔΔCt method.

Statistical analysis

Statistical analysis was conducted using SPSS software (version 21; IBM, Chicago, IL) and reported as mean ± SD. An independent t-test was used to identify the statistical differences between groups at baseline. The normality of the data was considered using the Shapiro–Wilk test with Levine test used to determine equal variances, and log transformations (log10) were performed where normal distribution was violated. Two-way ANOVA (group × time) was used to analyze data. Where significant differences were detected in the main effect of time, paired t-tests were performed to determine the origin of such effects. Partial eta squared ($\eta_p^2$) were used to calculate the effect sizes for ANOVA. A level of $P < 0.05$ was considered statistically significant.

| Table 1 | Primer sequences for real-time PCR measurement |
|---------|-----------------------------------------------|
| Gene    | Forward/Reverse | Primer (5′ → 3′) |
| PGC1α-1 | F               | G\_TT\_A\_G\_G\_G\_A\_A\_G\_A\_T\_A\_T\_A\_T\_G\_T\_G\_G\_G\_T |
|         | R               | T\_G\_T\_G\_T\_G\_T\_G\_T\_T\_G\_T\_A\_G |
| PGC1α-4 | F               | C\_A\_A\_G\_C\_A\_A\_G\_A\_G\_A\_G\_G\_A\_G |
|         | R               | C\_G\_A\_A\_G\_T\_G\_T\_A\_A\_G\_T\_G\_T\_A\_G |
| IGF-1Ea | F               | G\_T\_G\_G\_G\_A\_C\_G\_A\_G\_G\_G\_C\_T\_T\_T\_T\_T\_T |
|         | R               | C\_T\_G\_T\_T\_C\_T\_G\_A\_C\_T\_T\_T\_C\_T\_C\_T\_A\_C |
| IGF-1Eb | F               | G\_G\_A\_A\_G\_G\_A\_G\_A\_G\_G\_A\_G\_G\_A\_G |
|         | R               | T\_T\_T\_A\_G\_G\_C\_A\_G\_A\_A\_T\_G\_T\_T\_G |
| IGF-1Ec | F               | G\_A\_A\_G\_G\_G\_G\_A\_G\_G\_A\_G\_G\_A\_G |
|         | R               | A\_C\_A\_A\_A\_G\_A\_C\_A\_C\_T\_G\_A\_G\_T\_G |
| Myostatin| F                | T\_G\_A\_A\_G\_T\_T\_G\_A\_G\_G\_A\_G\_T\_G |
|         | R               | G\_T\_G\_T\_A\_G\_T\_A\_G\_T\_A\_G\_G\_A\_G |
| GAPDH   | F               | G\_C\_A\_G\_G\_A\_T\_G\_T\_T\_C\_T\_G |
|         | R               | C\_T\_T\_G\_T\_A\_T\_G\_A\_G\_A\_G\_G\_A\_G |

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Result

The results of PGC-1α1 and PGC-1α4 mRNA levels in the eccentric and concentric groups are shown in Fig. 1. The results of two-way ANOVA showed a significant main effect of time (F (1.8) = 0.845, P = 0.039, ηp² = 0.123), but no interaction between time and groups (F (1.8) = 1.211, P = 0.313, ηp² = 0.168) was seen on PGC-1α1 mRNA expression. In the concentric group, intragroup data analysis showed a significant increase in post-exercise time compared to baseline in PGC-1α1 mRNA expression (P < 0.05).

Moreover, a significant main effect of time (F (1.8) = 30.371, P = 0.001, ηp² = 0.835) was detected on PGC-1α4 mRNA expression level. Further, there was no significant interaction between time and groups (F (1.8) = 0.002, P = 0.969, ηp² = 0.000) on PGC-1α4 mRNA expression level. A significant increase in PGC-1α4 mRNA expression level was seen on post-exercise time compared to baseline in both groups (P < 0.05).

IGF-1 isoforms and myostatin expression levels in ECC and CON groups are represented in Fig. 2. A significant main effect of time (F (1.8) = 6.383, P = 0.045, ηp² = 0.515), but not interaction between time and groups (F (1.8) = 3.587, P = 0.107, ηp² = 0.374) was detected on IGF-1Ea expression level using two-way ANOVA analysis. IGF-1Ea expression level significantly increased in the CON group (P < 0.05) but not in ECC. Moreover, the results showed a significant main effect of time (F (1.8) = 0.920, P = 0.037, ηp² = 0.133), but not interaction between time and groups (F (1.8) = 0.098, P = 0.765, ηp² = 0.016) on IGF-1Eb mRNA level.

In the concentric group, intragroup data analysis showed a significant increase in post-exercise time compared to baseline in IGF-1Eb1α1 mRNA expression (P < 0.05).

The results of two-way ANOVA showed a significant main effect of time (F (1.8) = 0.720, P = 0.049, ηp² = 0.107), but not interaction between time and groups (F (1.8) = 1.034, P = 0.348, ηp² = 0.147) on IGF-1Ec expression level. IGF-1Ec expression level were significantly higher on follow-up than that the baseline value in the ECC group (P < 0.05). Further, there was no significant main effect of time (F (1.8) = 4.497, P = 0.078, ηp² = 0.428) and interaction between time and groups (F (1.8) = 1.978, P = 0.209, ηp² = 0.248) on myostatin expression level.

Discussion

Muscle contraction is generally considered in two types: eccentric, which involves lengthening of the sarcomere, and concentric, which requires a shortage of sarcomere length. Here we evaluated the response of PGC1α-1, PGC1α-4, IGF-1Ea, IGF-1Eb, IGF-1Ec, and myostatin mRNA in Vastus Lateralis muscle after acute eccentric and concentric contraction. The result showed that the PGC-1α4mRNA significantly increased after concentric and eccentric contraction. In contrast, PGC-1α1 showed a significant increase only in the concentric group.

Previous studies investigated the response of PGC-1α mRNA to acute resistance exercise [30]. Ruas et al. similarly noted that the PGC-1α4 is preferentially improved following resistance exercise in animal and human muscle [6]. Moreover, it has shown that PGC-1α4 increased at 2 h [31], 3 h [30], and 6 h [31] after resistance exercise. In one
study, acute electrostimulation of muscle cells elevated PGC-1α mRNA levels, which returned to the basal levels after 10 and 24 h [32]. It seems that PGC-1α isoforms are regulated by exercise and may facilitate beneficial adaptations such as mitochondrial biogenesis, fiber type composition, prevent muscle atrophy, and required for increment in myotube size. In this regard, PGC-1α4 transgenic mice have an increase in muscle force production proportional to the increase in muscle mass, indicating forced PGC-1α4 expression in muscle results in functional hypertrophy [6].

Additionally, some studies have shown that the response of PGC1α isoforms is strongly dependent on exercise intensity [31]. It has been found that a combination of resistance exercise with high intensity interval training (HIIT) developed greater PGC-1α4 compared to only resistance exercise [31]. However, Dieli-Conwright et al. have found no substantial differences in PGC-1α mRNA after eccentric contraction [9]. Moreover, aerobic resistance exercise increased PGC-1α mRNA in train and untrained subjects [33], whereas PGC-1α4 was not preferentially induced by resistance exercise in trained and untrained muscles [8]. In this regard, it seems some factors such as exercise protocol, characteristics of subjects, and exercise type could influence the response of PGC-1α isoforms.

Moreover, previous studies have shown a significant lower of PGC-1α resting level in old rats compared to young rats [34]. However, following 40 min contractile activity, PGC-1α promoter activity increased in aged muscle [3]. Besides, it has been shown that performing exercise by deficient glycogen availability in muscle attenuates PGC-1α signaling [35]. Thus, the presence of glycogen availability in muscle could disrupt exercise-induced cell signaling processes. Thus, it seems that factors like glycogen availability, gender, and age of subjects, despite exercise type associated with the change of PGC-1α isoforms after exercise training [9]. Further, although acute muscle contraction, despite type, changes the expression of PGC-1α mRNA isoforms, this observation highlights the need for more investigations to understand better the role of PGC-1α isoforms in exercise-induced skeletal muscle adaptation.

Furthermore, the results showed a significant improvement in the expression of IGF-1Ea and IGF-1Eb after concentric contractions. By contrast, in the eccentric group, only IGF-1Ec demonstrated a significant increase. Our findings are supported by previous studies, which investigated the acute response of IGF-1 isoforms to resistance exercise. The increase of IGF-1Ea after muscle contraction in the present study is similar to results in young men in previous studies, where an increase of IGF-1Ea was found following eccentric
resistance exercise at 6 h, 48 h, and 72 h after exercise [19]. However, in some other studies, IGF-1Ea mRNA content decreased by approximately 44% after 1 and 6 h after exercise [36] or remained unchanged in younger or older males until 24–48 h after exercise [37].

Moreover, it seems that the response of IGF-1Ea after exercise depends on individual training status. Most studies on non-trained subjects found no change in post-exercise IGF-1Ea mRNA expression [38, 39]. In contrast, some researchers have reported increased IGF-1Ea mRNA in untrained individuals at various points of time after exercise [19, 38, 40]. Therefore, despite differences in biopsy time points, the different results may have related to the difference of chronic versus acute response to exercise, intensity, or type of exercise. Information about IGF-1Eb is limited. A previous study has discovered that mRNA expression of IGF-1Eb is not significantly different following the eccentric contraction in postmenopausal women [9]. In another study, IGF-1Eb expression was up-regulated 72 h after damaging exercise and remained elevated at 120 h post-exercise, suggesting that IGF-1Eb may have specific roles following muscle injury [19]. Moreover, the examination of aged transgenic mice revealed that the local expression of IGF-1Eb was protective against age-related loss of muscle mass and force [41]. It has been previously demonstrated that muscle overexpression of IGF-1Ea and IGF-1Eb were able to promote anabolic effects on muscle [42].

Evidence suggests that IGF-1Ec mRNA expression increases 2–2.5 h after exercise [40, 43] in young subjects, while older subjects show no change at either time point [43, 44]. Therefore, age appears to influence the expression of IGF-1Ec. Further, some studies did not report changes in expression of IGF-1Ec mRNA at 3, 4, and 6 h after exercise [19, 40]. Ahtiainen et al. have shown that IGF-1Ec mRNA increased at 48 h after exercise, and expression trends increased at 72 and 120 h after exercise [39]. As IGF-1Ec is involved in the early stages of satellite cell activation [45], change in IGF-1Ec expression following an acute bout of muscle contraction may reflect an ability of the skeletal muscle to activate and proliferate satellite cells. Moreover, IGF-1Ec expression has been reported to have a high degree of variability in expression following various contraction protocols in humans [19], which may be attributed to the differences in the intensity of the exercise stimulates and the post-exercise time course examined.

Furthermore, the results indicated that there were no significant differences in up-regulates and down-regulates of myostatin mRNA in the concentric and eccentric group, respectively. Negative controlling muscle mass is the primary function of myostatin. Hence, knockout myostatin transgenic mice showed improvement of muscle hypertrophy [46]. It seems that muscle contraction could modulate the acute gene expression of myostatin in skeletal muscle tissue. In this regard, acute resistance exercise has been indicating to attenuate myostatin expression in young adults 4 h [47] and 24 h after exercise [44].

Furthermore, in animals model, it has been indicated that eccentric contraction has more effective than concentric and isometric contractions in attenuating myostatin in skeletal muscle [25]. It seems that the down-regulation of mRNA expression in myostatin is the dominant response between two and 24 h after resistance exercise [48]. However, evidence suggests that the expression of myostatin mRNA returned to baseline on 48–72 h of acute resistance training [49]. Further, in transgenic mice, increasing PGC-1α expression results in a decrease of myostatin mRNA expression around 60% [6]. Moreover, another study showed higher PGC-1α expression after resistance exercise compared to the combination of aerobic and resistance exercise, which also showed a trend towards a more considerable suppression of myostatin [30]. In young men, the PGC-1α gene was up-regulated significantly in both concentric and eccentric exercises, while myostatin was down-regulated only in the eccentric group. By considering the role of myostatin on muscle growth, these findings can confirm previous findings that eccentric exercise is superior to hypertrophy over other types of contraction [50].

There were some possible limitations in this research, which should be considered in the next researches. The more muscle biopsies are suggested at various interval times post-exercise. For future research, this possibility can be discussed thought increasing the number of muscle biopsy samples at different points of time after exercise. Protein expression should be investigated using either immunohistochemistry or western blotting.

Conclusion

The present study indicated that acute concentric exercise significantly increased the PGC-1α1 and PGC-1α4 mRNA in the Vastus Lateralis muscle. Furthermore, myogenic IGF-1Ec was found to increase substantially in response to eccentric contraction, while IGF-1Ea and IGF-1Eb improved after concentric contraction. Myostatin expression attenuated in the eccentric group compared to an increase in the concentric group, however the results showed no significant differences. These finding provide insight into the molecular-level muscle adaptive response correlated with muscle strength and muscle mass occurring with regular resistance training.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were by the ethical standards of the ethical committee of Tehran University (Ethic No: IR.UT.SPORT.REC.1397.029) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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