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ORIGINAL ARTICLE

Time course responses of serum GH, insulin, IGF-1, IGFBP1, and IGFBP3 concentrations after heavy resistance exercise in trained and untrained men

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Abstract To investigate the effect of heavy resistance exercise on IGF-1 system, 19 healthy trained men and 15 healthy untrained men volunteered to participate in this study. The subjects were randomly divided into experimental and control groups. Subjects of experimental groups were forced to perform a heavy resistance exercise with the intensity of 70–80% of 1RM in selected movements. The blood samples were taken from all subjects four times; before (T1), immediately after (T2), 5 (T3), and 8 (T4) hours after exercise. Analysis of data showed that a session of heavy resistance exercise induced significant increase in GH at T2 ($P < 0.05$) and a significant decrease in insulin at T4 ($P < 0.05$) and a significant decrease in IGFBP3 at T4 ($P < 0.05$) in trained group. In untrained group, no significant change in any of the variables was observed. However, the procedure of response in variables was almost similar in two experimental groups. Although, the exercise did not appreciably affect IGF-1 levels, it decreased in all groups at length of time after exercise. In addition, the exercise did not have any notable effect on IGFBP1 levels over time. In conclusion, the findings of this study indicate that the intense resistance exercise can lead to changes in blood concentrations of IGF-1 system components which are observable in blood circulation over time and the amounts of changes depend on subjects' fitness levels and exercise variables.

Keywords GH · Insulin · IGF-1 · IGFBP1 · IGFBP3 · Heavy resistance exercise

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Introduction

Insulin-like growth factor 1 (IGF-1) is the most important member of Somatomedin family that plays a major role in somatic growth and cellular proliferation, differentiation, metabolism, and survival [1]. IGF-1 has been the subjects of many researches, mostly because of its pivotal roles in metabolic processes and growth [2]. Effect of exercise on IGF-1 system is one aspect that has been investigated by many researchers [3–6]. Though, few studies showed concern in studying the response of IGF-1 system to resistance exercise [7, 8]. Bermon et al. [7] examined the impact of a single session of resistance exercise on the levels of IGF-1 in elderly subjects, and found an increase in IGF-1 concentrations after exercise with no significant change in insulin-like growth factor binding protein-3 (IGFBP3) levels. Indeed 8 weeks training period on the same study population caused a sustained release of IGF-1 in the aging subjects regardless of their training status. It has been stated by many studies that alteration of IGF-1 components levels is the result of performing both exercise and training session [3, 4, 7, 9]. However this idea, especially in concept of resistance exercise and training, has been challenged by some investigators [8, 10]. In this regard, Nindl et al. [8] performed a 13 h monitoring of individual components of the IGF-I system, including total and free IGF-I, IGFBP-2 and -3, and the acid-labile subunit

(ALS), in ten young men after a high-volume, multi-set exercise session and found that heavy resistance exercise might rather change the partitioning of IGF-I among its family of binding proteins instead of changing the absolute amount of IGF-I. It is not clear yet whether resistance exercises, as a single stimulus, is able to considerably affect the IGF-1 system, and also whether resistance training can make a long-term adjustment in levels of IGF-1 system. Studying the time course of changes in different components of IGF-1 in response to exercise by few researchers has given us valuable information [3, 4, 6, 11, 12] including identification of recovery period, adaptation mode, direction and the possible shapes of answers and changes in this system. This study aimed at evaluating the time-course responses of serum GH, insulin, IGF-1, IGFBP1, and IGFBP3 concentrations after heavy resistance exercise in trained and untrained men. Since IGF1 is an anabolic hormone, it is reasonable to expect more response in acute and chronic resistance exercise in comparison to other exercises. Considering this assumption resistance exercise protocol was chosen for this research.

Methodology

Study design

Among volunteers, who were informed by flyers, 34 young male students of Tarbiat Moallem University were selected. The information regarding life style, past medical history, and physical activity of the volunteers were obtained by a questionnaire. Only the male subjects with an age range between 20 and 30 years were included in the study [13]. The exclusion criteria were defined as: smoking (current or previous), cardiovascular, metabolic, and musculoskeletal disorders, and taking any medication and supplements. Based on the training status of the participants, they were divided into two groups. The trained group was composed of physical education students who were on a regular resistance training program for at least 2 h, three times per week over the last 10 months. Untrained group was non physical education students without any regular exercise programs for the last 10 months. Based on this classification, trained and untrained groups consisted of 15 and 19 students, respectively. Approval was obtained from the Ethics Committee of Endocrinology and Metabolism Research Center of Tehran University of Medical Science. All the participants signed a written consent form. The study was designed as an interventional study in which the data was obtained both at baseline (pre-test) and at several time points after the intervention (post-test).

At the day of test, the students arrived at the physical activity room before 7.30 a.m and stayed till 7 p.m. After serving breakfast body weight and height were measured. Body mass index was calculated by dividing body weight (kg)/height (meters squared). The first blood sample was drawn before starting the training program (pre-test). Afterward, the individuals of each trained and untrained groups were randomly divided to experimental and control groups. Therefore, the trained group was divided to experimental trained group (E1, $N = 10$) and control trained group (C1, $N = 9$). The untrained group also was divided into experimental untrained group (E2, $N = 8$) and control untrained group (C2, $N = 7$).

Exercise protocol

Resistance exercise was contained of work with weights of 70–80% maximum strength for selected movements (in this order: chest press, stretch wire, front leg with device, and back leg with device) in that every move was performed in four consecutive sets and repeated to the extent of disability in repetition. 70–80% of One Repetition Maximum (1RM) was calculated by the 1RM% estimate table, from the number frequency of one selected weights in one time to the extent of disability to repeat it, if the number of repetitions do not exceed 10–12 times [8, 14]. Total activity time was approximately 60 min for each subject. It was ideal to perform routine resistance exercise protocol for all subjects, however, since doing these heavy movements by untrained group was impractical we changed the protocol as follows: recovery time between sets was 2 min and between exercises was 4 min.

Data collection

At the day of the test, all the subjects consumed similar meal as breakfast (at 7:30–8:00 a.m). Two hours after breakfast (at 10:00 a.m) first sampling (pre-test) was performed for all the participants (T1). In both E1 and E2 groups, heavy resistance exercises were performed for 3 h while the C1 and C2 were in sitting or standing position without any additional exercise like movements. The second blood sampling was immediately after completion of the exercise session (T2). It should be noted that because we could not engage all the subjects of E1 and E2 groups simultaneously in exercise test, and also because the order of movements performance by the subjects should be equal, we had to test the subjects two by two. Since, the training session was long and the time interval could affect the results of the study, subjects were arranged in resistance exercise in the same manner that they had been first participated, and then were treated by the same order in all stages of sampling. After the second sampling (T2), the launch was served and then the five (17:00 p.m) and eight (20:00 p.m) hours post exercise sampling (T3 and T4

respectively) were performed. All research variables including GH, insulin, IGF1, IGFBP1, and IGFBP3 were measured in all four samples.

Research variables

Insulin (Co. DRG), Growth Hormon (GH), total IGF-1, IGFBP1, and IGFBP3 (all from Co. Mediagnost) were measured by ELISA. Coefficients of variations for variables (CV) for all the variables were less than 6.7%.

Statistical analysis

The statistical tests were performed using the SPSS statistical package version 16 (Chicago, IL, USA). To test data distribution for each variable, Kolmogrov–Smirnov test was used. The nonparametric test was used for non-*normal distributed data*. To evaluate the between groups differences of each variable at base line and after training session ANOVA test was used. Bonferroni test was applied in case of detecting significant effect. For non-normal distributed variables, the Friedman test was used to compare over time changes and in case of being significant, Wilcoxon test, as post hoc test, was used. For comparing between groups variables the Kruskal–Wallis test was used and in case of significancy, Mann–Whitney as post hoc test was used. Significant level was considered at $P \leq 0.05$ level.

Results

Base line

The baseline clinical and metabolic markers of four groups are presented in Table 1. The four groups had similar BMI however the mean age of C2 individuals were significantly higher compared to other three groups. Analysis of biochemical parameter at base line revealed any significant difference in serum concentrations of pre-exercise variables between trained and untrained groups.

GH

As shown in Fig. 1a and Table 2, in group E1, GH values started to increase after initiating the exercise and reached to its highest and significant levels at T2 ($P \leq 0.05$) and then returned to basal levels at T3 and stayed stable till last measurement (T4). In all other three groups, the GH levels stayed almost without changes over all the time points measured in this study, however, the changes in GH levels were more prominent in E2 group compared to other two groups (C1 and C2), thought this change was still in a non-significant manner ($P = 0.061$). Between groups analysis using the Mann–Whitney test showed only a marked difference in GH levels at T2 between C2 and E1 ($P = 0.02$).

Insulin

Analysis with ANOVA showed that in E1 group insulin levels declined with moderate slope after exercise and stayed at levels lower than the baseline during all times points. The difference was statistically significant at T4 compare with T1. In E2 group, insulin levels was reduced in a non-significant manner after exercise at T2, and then returned to basic values and remained in the same levels over time. The same pattern was observed for C1 and C2 groups. Between groups analysis of insulin concentrations, using post hoc Bonferroni test, showed a marked difference at T3 and T4 between E1, E2, and C2 groups (Fig. 1b).

IGF1

In all four groups contributed in this study, serum concentration of IGF1 started to decrease over time and this decrease was continued over the measure time point (T2, T3, and T4). In E1, C1, and C2 groups, this decline in IGF1 reached significant values at T3 and T4, while for E2 the significancy was attained only at T4 time point. For all these four groups the final measurement of IGF1 levels was lower than base line (Fig. 1c).

Table 1 Characteristics of study subjects in four groups

Variable	Group				*P*	*F*
	Exp. trained (E1)	Con. trained (C1)	Exp. untrained (E2)	Con. untrained (C2)		
Age (years)	22.40 ± 1.84	22.00 ± 0.87	21.75 ± 0.89	24.57 ± 1.62	6.36	0.002*
Height (cm)	179.58 ± 5.14	177.11 ± 7.66	173.63 ± 4.56	174.47 ± 5.96	1.81	0.166
Weight (kg)	75.00 ± 6.80	71.78 ± 9.00	70.38 ± 10.40	70.57 ± 10.63	0.50	0.685
Body mass index (BMI)	23.23 ± 1.50	22.80 ± 1.74	23.29 ± 2.71	23.26 ± 3.71	0.08	0.971

* C2 group differences with groups E1, C1, and E2

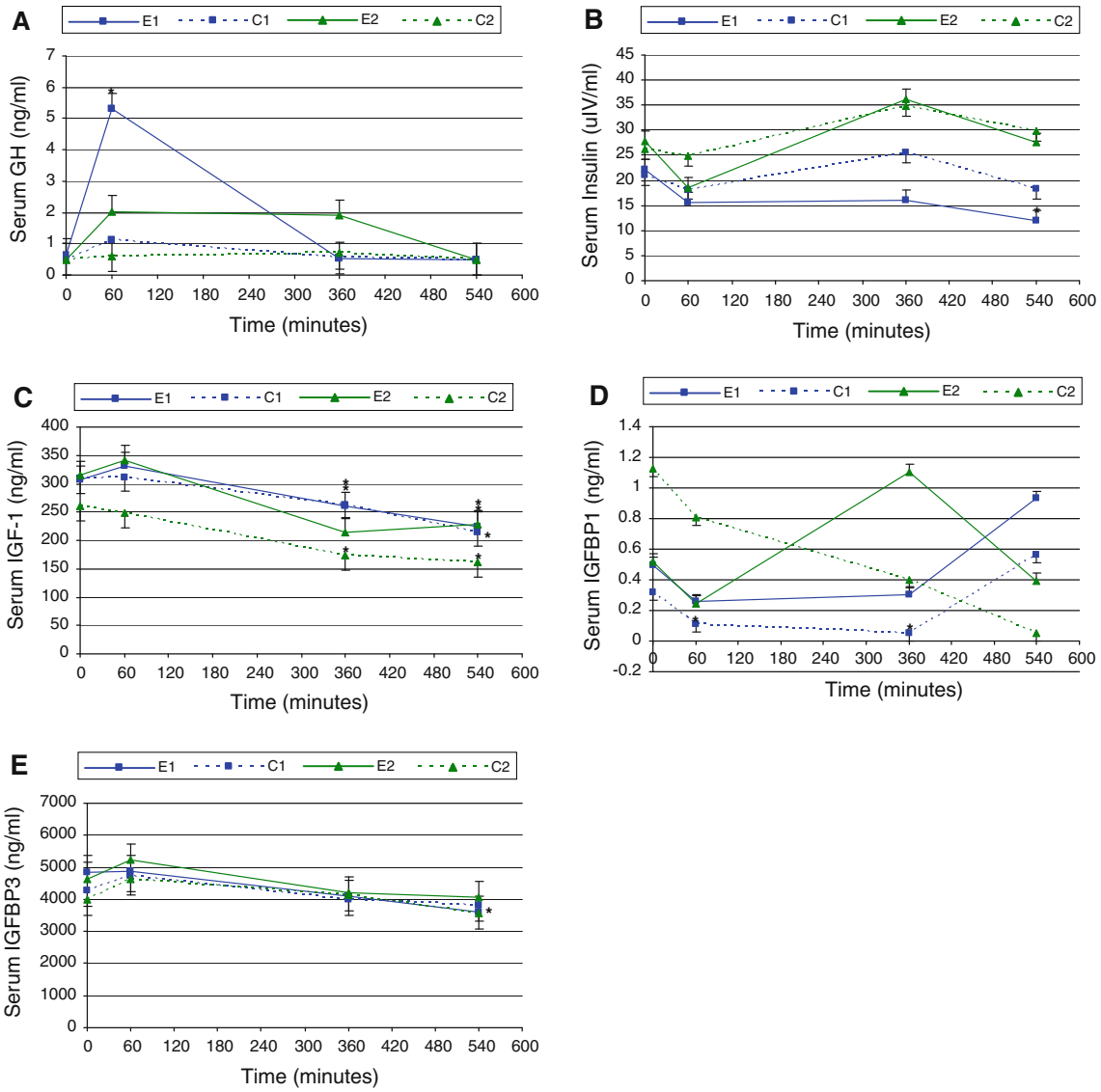

Fig. 1 Trends of changes in GH (**a**), insulin (**b**), IGF-1 (**c**), IGFBP1 (**d**), and IGFBP3 (**e**), in consequence of heavy resistance exercise at different times. *Significant differences with respect to time T1, $P \leq 0.05$

IGFBP1

The C2 individuals had higher levels of IGFBP1. After initiation of exercise, levels of IGFBP1 started to decrease in all four groups. In C2, this decrease was continued until the end of the time pints. In E1 and C1 groups, the IGFBP1 stayed stable until T3 and then a sudden rise was observed in serum levels of this cytokine in these groups. In E2, the levels of IGFBP1 first was raised and then at T3 a sudden diminution of IGFBP1 levels was observed in this group (Fig. 1d).

At any time points, no significant difference in IGFBP1 levels was observed between studied groups.

Discussion

GH

In this interventional study, we observed that performing a single session of heavy resistance exercise for 60 min with the 70–80% of 1RM, could cause an increase in blood concentrations of GH immediately after exercise, though this elevation of GH levels was only significant in trained group. Similar results have been reported by other investigators [3, 6, 10, 15]. Viewing the significant elevation of GH levels, compared to baseline, only in trained groups, can be explained by the fact that trained individuals have

Table 2 GH, IGF1, IGFBP1, IGFBP3, and insulin values in four groups in consequence of heavy resistance exercise at different times

Group	Time				*P*	Explanation
	T1	T2	T3	T4		
GH						
E1	0.65 ± 0.47	5.32 ± 6.67	0.54 ± 0.16	0.50 ± **0.001**	0.002*	Between T1 &T2
C1	0.50 ± **0.001**	1.21 ± 1.00	0.56 ± 0.18	0.50 ± **0.001**	0.112	–
E2	0.50 ± **0.001**	1.87 ± 3.47	1.74 ± 2.20	0.50 ± **0.001**	0.061	–
C2	0.50 ± **0.001**	0.61 ± 0.30	0.70 ± 0.53	0.50 ± **0.001**	0.392	–
IGFBP1						
E1	0.50 ± 0.91	0.26 ± 0.34	0.31 ± 0.77	0.93 ± 1.95	0.773	–
C1	0.32 ± 0.33	0.11 ± 0.18	0.05 ± **0.001**	0.56 ± 1.02	0.039*	Between T1 with T2 & T3
E2	0.52 ± 1.09	0.24 ± 0.55	1.11 ± 1.49	0.39 ± 0.97	0.205	–
C2	1.12 ± 1.86	0.81 ± 1.59	0.40 ± 0.92	0.05 ± **0.001**	0.145	–

Group	Time				*F*	*P*	Explanation
	T1	T2	T3	T4			
Insulin							
E1	20.99 ± 7.71	15.71 ± 4.03	15.98 ± 4.13	11.96 ± 3.67	8.66	0.001*	Between T1 with T2, T3 & T4
C1	22.13 ± 11.23	17.94 ± 7.91	25.44 ± 6.47	18.27 ± 5.32	6.09	0.003*	No significance than T1
E2	27.90 ± 16.67	18.51 ± 13.34	36.11 ± 27.53	27.48 ± 16.21	3.40	0.040*	No significance than T1
C2	26.30 ± 11.20	24.15 ± 8.08	34.71 ± 17.68	29.77 ± 16.60	1.11	0.366	–
IGF-1							
E1	306.80 ± 73.93	331.10 ± 79.61	260.10 ± 80.73	224.50 ± 85.27	34.68	0.001*	Between T1 with T3 & T4
C1	308.33 ± 73.11	311.89 ± 56.18	263.33 ± 41.03	214.56 ± 74.90	14.62	0.001*	Between T1 with T3 & T4
E2	314.25 ± 92.24	341.88 ± 89.63	214.88 ± 65.45	227.50 ± 100.33	10.97	0.001*	Between T1 & T4
C2	259.71 ± 55.77	247.57 ± 66.12	173.43 ± 59.63	160.86 ± 73.36	40.28	0.001*	Between T1 with T3 & T4
IGFBP3							
E1	4860.90 ± 882.92	4869.90 ± 728.33	4096.70 ± 722.02	3614.10 ± 519.03	11.66	0.001*	Between T1 & T4
C1	4294.11 ± 568.48	4732.11 ± 416.40	3999.89 ± 686.04	3815.00 ± 640.37	4.42	0.013*	No significance than T1
E2	4648.13 ± 748.42	5241.63 ± 428.49	4200.88 ± 566.38	4050.88 ± 610.30	6.29	0.003*	Between T2 with T3 & T4
C2	3967.71 ± 1437.84	4631.00 ± 749.76	4144.14 ± 950.47	3562.86 ± 705.56	2.35	0.107	–

* Significance: $P < 0.05$ considered to be significant

greater GH response compared to untrained individuals, when they were exposed to resistance exercise. It has been proposed that reaching threshold intensity, manifested by the peak of exercise intensity, is more powerful determinant of GH secretion magnitude than just intensity of the exercise [3, 16]. In our study, the relative intensity of resistance exercise was similar in two groups, however, due to the nature of the trained group, they were able to move heavier weights. Therefore, the mean peak of exercise intensity was higher in this group compared to untrained individuals, which may explain, at least partially, the significant elevation of GH levels in this group and not in untrained group compare to their baseline levels. It is also important to notice that pulsatile nature of GH secretion in response to various irritants makes it very difficult to accurately predict the proper time of GH secretion [1]. It is possible that the time pattern of loss and escalation of GH levels would be different among individuals with different fitness levels and that peak of changes to be detected in the untrained group does not follow the same time pattern as trained group. Ehrnborg et al. [3] showed that the peak of GH release is delayed to 15 min after starting the exercise. By accepting the assumption that the peak of GH release is occurred between 15 and 30 min of the exercise and with regard to protocol of our study which contained relatively long period of exercise, it is plausible that an increase of GH half-life as a consequence of GH adaptation to exercise training in this group has been occurred. The possibility of creating changes in GHBP levels, a protein which binds to GH and augments its half-life in blood, after exercise

training has been proposed by some researches [15, 17]. These factors were not measured in our study and further researches are required to clarify this hypothesis.

Insulin

Another finding of this study was a diminution of insulin levels following resistance exercise which has also been reported by previous studies [5, 15, 16]. Sensitivity of glucose transport process increases in response to insulin and IGF-1 after exercise [18]. Increased insulin sensitivity in muscle mutually with decrease in Insulin concentrations holds in balance at the beginning of exercise. This balance most probably will prevent the exercise-induced hypoglycemia [19]. Decreased serum insulin levels reflect the increase in the anabolic actions of Insulin in processes such as glucose transfer, glycogen production, and activation of glycogen synthesis and amino acids transfer [20]. Insulin primarily increases the capacity glucose transport by stimulating the glucose transport into skeletal muscle, through the transfer of GLUT-4 from an intracellular site to sarcolemma [21]. In skeletal muscle, glucose transport capacity can also be stimulated by IGF-1 [22]. In fact in long-term, training could improve the function of components engaged in the glucose transfer process, by creating modifications in IGF-1 system. Insulin-like effects of IGF-1 consist of a direct stimulating action on glucose uptake by muscle (the major role) and augmentation of glucose transition [1]. One consequence of such changes needs reduction of insulin to keep the glucose homeostasis properly. Taking together, all these observations point to the fact that exercise in trained individuals could improve the insulin sensitivity with subsequent decrease in demand for insulin to maintain the glucose homeostasis [5, 23].

IGF1

In regards to IGF-1, we did not reach significant levels of difference following resistance exercise, in both trained and untrained groups compare to their baseline levels of IGF-1. The observations from previous studies are controversial. In some studies, a transient elevation of IGF-1 at the beginning of exercise was noticed [4, 16]. In this study, however, we can not rule out the possibility of detecting an increase in IGF-1 levels soon after exercise initiation, because of the lack of early sampling and also because of long duration of our resistance exercise protocol.

Nindl et al. [8] explained that effects of resistance exercise on circulating IGF-1 system may not have been detected by any changes in IGF-1 values, because IGF-1 can be distributed among its binding proteins family. This could, in our study, explain the absence of a significant increase in serum concentrations of IGF-1 after resistance exercise. On the other hand, an increase in clearance rate of IGF-1, because of an increase in permeability of glomerular filtration and saturation of proximal tubular resorption of filtered proteins, could also count for lack of elevation of serum IGF-1 after resistance exercise in our study [24]. Measuring the urinary IGF-1 could provide us with a valid documentation in this manner. IGF-1 is locally produced and acts in an autocrine/paracrine pattern [25]. In muscle, IGF-1 binds to type I receptor and insulin type I hybrid receptor and increase the glucose uptake by muscle [1]. However, increase in IGF-1 is not associated with security mechanisms of maintaining the glucose homeostasis, particularly in untrained individuals. This event potentially could result in hypoglycemia after exercise. Therefore, lack of increase in IGF-1 levels after exercise could interpret as a compensatory mechanism for preventing the post exercise hypoglycemia.

IGFBP

In this study, no significant change was observed in IGFBP1 levels following a session of heavy resistance exercise. IGFBP1 is thought to be the main regulator of IGF-1 bioavailability in short periods, which itself is regulated by several factors including insulin, glucocorticoid, GH, and factors having cAMP-agonistic effects [26]. Changes in other circulating IGFBPs levels may also be involved in changes of IGFs access during training and exercise [8, 9]. This component of IGF-1 system is mostly influenced by metabolic disturbances altering energy flow or balance [27] and prolonged activities in terms of several hours or days are needed for the IGFBP1 response manifestations [5, 23, 27, 28]. However, some investigators reported the changes in concentrations of this protein in response to short-time exercise [15, 19, 29]. It is presumed that other factors than low concentrations of plasma glucose would be engaged in maintaining the glucose homeostasis in regards to IGFBP1 response to exercise [19].

Lavoie et al. [29] showed that maintaining normal levels of blood glucose through intravenous injection of glucose did not prevent the increase in IGFBP1 levels during a single prolonged cession of exercise in rats. Based on a strong negative correlation between liver glycogen and plasma IGFBP1 levels, they proposed that increase in IGFBP1 levels during exercise is related to the decrease in liver glycogen content. This hypothesis explains why despite maintaining blood glucose levels and no changing in insulin levels, IGFBP1 levels is increased during prolonged exercise and also why long-term exercise protocols would better reveal the IGFBP1 response than short-term protocols. Our observation regarding no changes in IGFBP1 could be explained by the short mode of our exercise protocol that does not provide enough time for

diminution of liver glycogen storage with subsequent increase in serum IGFBP1.

In our study, serum IGFBP3 concentrations started to decrease over time in a way that at the end of the study (T4) it reached a significant level. This carrier protein has long half-life [1, 2], which may count for detecting the significant levels of difference at the time points close to the end of the study, and is known as the key regulator of IGF-1 availability. It is believed that this protein compel the inhibitory effects on cell growth [1, 24].

In line with our observations, Bermon et al. [7] investigated the IGFBP3 response to a session of resistance exercise. They found no significant changes in concentrations of IGFBP3 in both athletic and rest groups. However in their study, the IGF-1 system response was monitored every 6 h which could be considered as a relatively long period that let the IGFBP3 responses to be lightened up. This study showed that detection of post-resistance exercise IGFBP3 proteolysis process requires time monitoring more than 7 h.

Nindl et al. [8] detected an augmentation of IGFBP3 in responses to heavy resistance exercise at the first hour after initiation of exercise. They postulated that exercise (typically resistance) is able to regulate the acute production and immediate secretion of IGFBP3 independent of the changes in IGF-1, probably because of the flow of metabolic residues and substrates. Nevertheless, it is possible that the physiological operators of IGFBP3 act independently and differently from the GH and IGF-1 during exercise [4].

Conclusions

As a result, heavy exercise (acute and typically resistance) leads to responses of IGF-1 system components which can be measured and observed as changes in serum concentrations, but this response depending on the fitness level can be varied for both direction and size among different individuals. In addition, the intensity of exercise is a determinant factor for stimulating part to part response of this system and its magnitude. Worth mentioning that sometimes for viewing noticeable changes of some components of this system (e.g., IGFBP1) is compulsory the exercise be long enough (it might be named as a time threshold) to stimulate the physiological response. Responses of various components of IGF-1 system to exercise might be associated with time separation, so that the response of one component comes into view with time delay than other component. For this purpose, it is crucial that the consecutive observations to be carried out over time to prevent from losing the response of a component (time course study) in which the possible changes not to be overlooked. Otherwise, to study IGF-1 system, it is better to concentrate on a particular part of it and set the sampling based on its probable behavior.

Conflict of interest None.

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