

## **Independency of acute regulation of IGF-1 system components to growth hormone and insulin in response to resistance exercise**

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### **Abstract**

**Background:** The aim of this study was to determine possible relationship between changes induced by exercise in serum concentrations of growth hormone and insulin with IGF-1 system components over time in trained and untrained individuals.

**Methods:** Nineteen healthy men among physical education students as trained group and 15 healthy men among non-physical education students as untrained group voluntarily participated in this study. The subjects randomly were divided into experimental (trained and untrained) and control (trained and untrained) groups. Blood samples were obtained just before; and at immediately, four and seven hours after the end of exercise. Serum concentrations of GH, Insulin, total IGF-1, IGFBP1 and IGFBP3 were determined.

**Results:** No significant difference was observed in the pre-exercise concentrations of variables between the trained and untrained individuals. However, a strong and positive correlation between areas under curves of variations in IGF-1 and IGFBP3 was identified in the experimental trained group ( $r=0.872$  and  $p=0.001$ ); and also, there was correlation between areas under curves of variations in Insulin with IGF-1 ( $r=0.752$  and  $p=0.05$ ) and in IGF-1 with IGFBP3 ( $r=0.922$  and  $p=0.003$ ) in the control untrained group, but no statistically significant relationship was observed in the control trained and experimental untrained groups.

**Conclusion:** Overall, there was no relationship between acute changes in levels of IGF-1 components with GH and insulin after resistance exercise and the role of each component of the system in mutual regulation of the other components may be more important than nonmember factors of the system during exercise and the following recovery period.

**Keywords:** GH, Insulin, IGF-1, IGFBP1, IGFBP3, Resistance exercise

## Introduction

IGF system is a collection of the closely related peptides and proteins which plays the pivotal role in the growth and metabolism. IGF-1 as the most important member of this family applies strong growth effects on muscular and bony tissues (1). This peptide also mediates insulin like actions, especially in muscle tissue and it circulates in plasma in form of combination with one of its six binding proteins (2). Studies show that diurnal fluctuations of GH may regulate serum levels of circulating IGF-1 (3). On the other hand, it is revealed that insulin levels can also affect IGFBP1 levels and thus, involves in the regulation of accessible IGF-1 rate for tissues (4).

Many studies have examined IGF-1 system behavior from different aspects (5, 6, 7). The acute effects of exercise on serum concentrations of IGF-1 system components and its chronic adaptations with training have been studied in the field of exercise physiology (8-12). However, the relationship between components of this system and other hormones in response to exercise has been less considered.

Researches indicate that there is a feedback-regulatory relationship between GH and IGF-1 system whereby, GH secretion increases hepatic production of IGF-1. In addition to special effects, IGF-1 mediates some GH actions, especially in muscle and bone tissues and levels of circulating IGF-1 interrupts GH secretion as a negative feedback (3). Despite this, recent studies in the field of exercise and training emphasize on independency of acute regulation of IGF-1 to GH following exercise (13). Kraemer et al. demonstrated that different factors in acidic and alkali state of blood can differently regulate responses of GH and IGF-1 to exercise (12). This means that the IGF-1 reaction to exercise may be adjusted independent of GH. However, it is not still clear whether IGF-1 system response to exercise is really independent of GH or GH can also stimulate hepatic production of IGF-1 under these conditions (9).

About insulin, researches repeatedly have shown that there is a reverse relation between insulin and IGFBP1 levels (14). Although, Anthony et al. showed that hepatic production of IGFBP1 during exercise can be independent of insulin (15). Given this, it seems that further

investigations require clarifying the relationships between IGF-1 system components with other hormones. In this manner, present study was trying to fill part of the space of this area.

## Methods

### Subjects

Subjects in this study were voluntarily selected between non-athlete students of Tarbiat Moallem University and physical education students of the same University and 15 non-athletic men students as untrained group and 19 athletic men students as trained group participated in research. Then, general information about the effort procedure and study steps was given to the subjects and written consent was obtained. Subsequently, the subjects of each groups (trained and untrained) were randomly assigned to experimental and control groups based on height and thus, four groups were constituted. All stages of the research were approved by ethics committee of Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences (according to Helsinki Declaration and instructions of the Ministry of Health and Medical Education). Characteristics of subjects are presented in Table 1.

### Exercise Protocol

Resistance exercise was contained of work with weights of 70-80% maximum strength for selected movements (chest press, stretch wire, front leg with device, back leg with device) that each activity was performed in four consecutive sets and repeated to the extent of disability in repetition. Seventy to eighty percent of One Repetition Maximum (1RM) was calculated by the 1RM% estimate table, from the frequency number of one selected weights in one time to the extent of disability to repeat it, if the number of repetitions not to be more than 10-12 times (10, 16). Total activity time in average was 120 minutes for each subject.

Present project which had interventional nature was performed in semi-experimental design with pretest and post test at several times in the two experimental groups and two control groups. The day of the test, two hours after consuming the same meal i. e. breakfast,

the first sampling (pre-test) of all subjects was done (at 10:00 am). Then, the subjects in experimental groups (trained and untrained) performed the resistance exercise. Next, samples were taken at immediately, four and seven hours after completion of the exercise session. Data related to the first sampling were considered to compare pre-exercise values of variables between trained and untrained individuals. It must be noted that the protocol of interventions for experiment and control groups, including the time and type of meal, the frequency and time of blood sampling, except for the experienced intervention that was only taken in the experiment groups, were the same.

Variables that were measured in laboratory analysis were consisted of GH and Insulin as predictive variables and total IGF-1, IGFBP1 and IGFBP3 as criterion variables. Insulin (Co. DRG), Growth Hormone (GH), total IGF-1, IGFBP1, and IGFBP3 (all from Co. Mediagnost), were measured via ELISA method. Coefficients of variations for variables (CV) were reported in laboratory as follows (intra assay-inter assay); growth hormone: 3.9-4.2, insulin: 3.1-4.8, IGF-1: 5.9-6.5, IGFBP1: 6.1-6.7 and IGFBP3: 3.4-6.0.

### Statistical Analysis

The data were analyzed by software SPSS 13.00. Kolmogorov-Smirnov test showed that the distribution of data on insulin, total IGF-1 and IGFBP3 are normal and for other variables are abnormal. T-test for Insulin, total IGF-1 and IGFBP3, and Mann-Whitney test for GH and IGFBP1 were used to compare pre-exercise values of variables between the two groups. For correlation analysis, the area under curve (AUC) of each variable was calculated

individually for subjects. In the next step, the scores related to the obtained areas under curve for the variables were analyzed with Pearson correlation. Significant level was considered at  $p \leq 0.05$ .

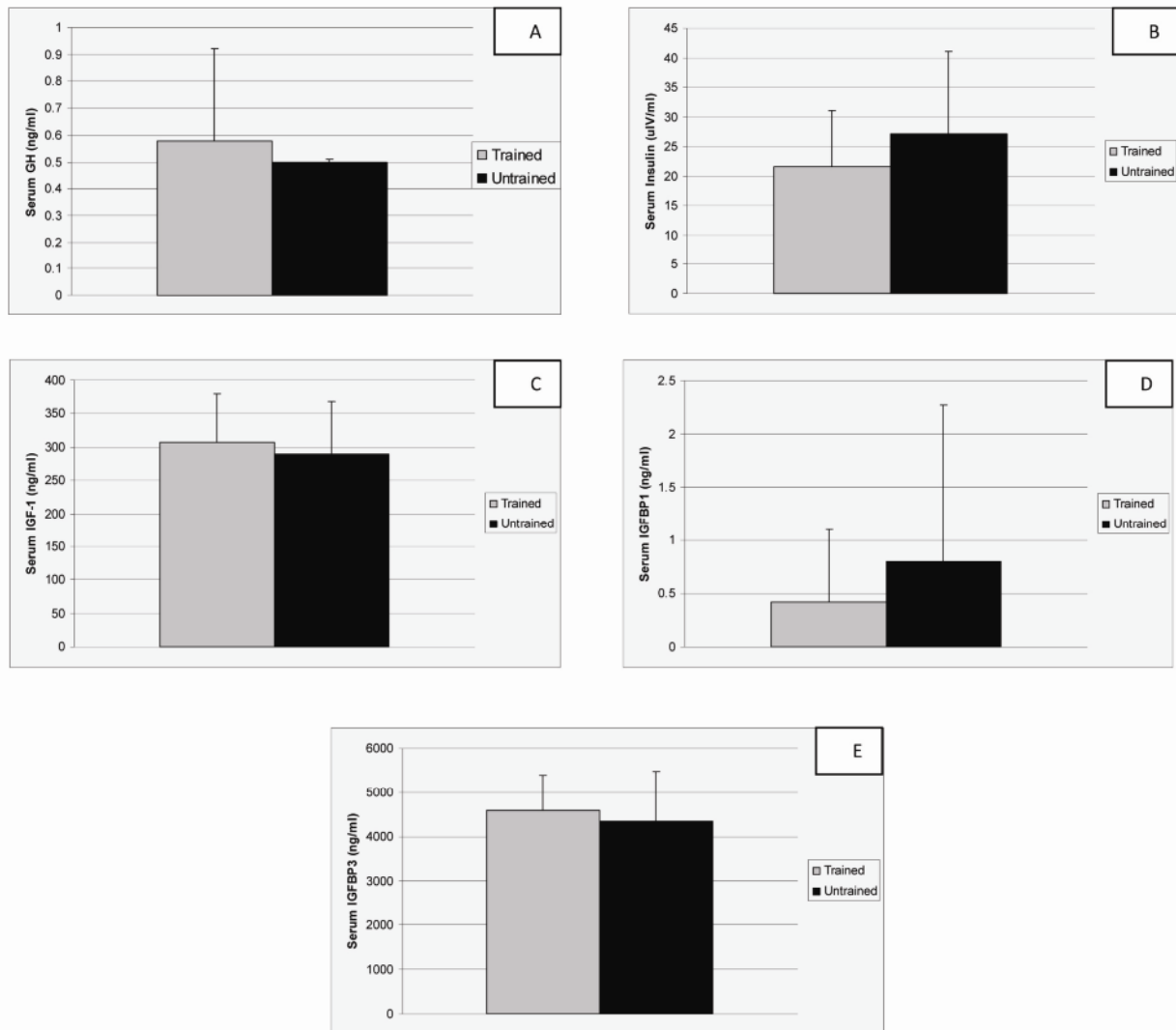
### Results

Neither T-test nor Mann-Whitney test revealed any significant difference in serum concentrations of pre-exercise variables between the two groups (Figure. 1, A to E). The scores related to the areas under curves of IGF-1 and IGFBP3 correlated in the experimental trained group ( $r=0.872$  and  $p=0.001$ ). No statistically significant relationship existed among variables in the control trained and experimental untrained groups. In the control untrained group, the scores related to the areas under curves of IGF-1 with IGFBP3 ( $r=0.922$  and  $p=0.003$ ) and insulin ( $r=0.752$  and  $p=0.05$ ) correlated. Also, the areas under curves of IGFBP3 intended to show a correlation with insulin ( $r=0.699$  and  $p=0.08$ ). In addition, when data concerning to the two experimental groups was piled up for each variable and this action was performed as well in case of the two control groups, among the scores related to the areas under curves of IGFBP1 with IGF-1 ( $r=-0.544$  and  $p=0.03$ ) and IGFBP3 ( $r=-0.518$  and  $p=0.04$ ) the correlation was revealed in the composed control group. When investigating the main data (and not the score related to the area under curves), we found that the same last correlations with slight difference exists for IGF-1 ( $r=-0.411$  and  $p=0.02$ ) and IGFBP3 ( $r=-0.524$  and  $P=0.001$ ) with IGFBP1 in the pre-exercise values.

Table (1): Anthropometric characteristics of trained and untrained subjects

Variable	Group		P
	Trained	Untrained	
Age (years)	22.21±1.44	23.07±1.91	0.145
Height (cm)	178.41±6.39	174.02±5.08	0.037*
Weight (kilogram)	73.47±7.86	70.47±10.13	0.337
Body mass index (BMI)	23.03±1.59	23.27±3.09	0.781

\* Statistically significant differences



**Figure 1. Graphs of pre-exercise values in GH (A), Insulin (B), IGF-1 (c), IGFBP1 (d) and IGFBP3 (e) in trained and untrained individuals**

## Discussion

In this study, we did not observe statistically significant relationship between changes in GH levels over time with changes in IGF-1 levels after resistance exercise. GH may play a role in regulation of circulating IGF-1, so that it is assumed that exercise stimulates GH release and GH causes tissue production of IGF-1 and increasing of plasma IGF-1 (17). On the other hand, at least a 12-hours delay is necessary for which GH lead to significant increase in the hepatic production of IGF-1 (18). Therefore, increased concentrations of circulating IGF-1 which have been reported after exercise can be independent of the liver mechanisms induced by GH. To date, conventional theory for the IGF-1 secretion is that the factor does not follow a standard

endocrine releasing in response to increase of endogenous GH (12). The importance of our findings about GH hides in the fact that present data on IGF-1 system supports the belief from lack of an acute endocrine regulatory relationship between GH and IGF-1 and IGFBP3 following an acute intensive exercise stress, because the changes in GH over time had no correlation with the relative changes in IGF-1. In previous studies, it was tried to target this problem by using a strenuous exercise protocol which required consumption of an alkaline solution of bicarbonate by subjects. This solution should have weakened GH response in subjects, but despite this, it failed to elucidate IGF-1 and IGFBP3 responses after performing high intensive exercise (12). Also, following a sub

maximal exercise, the GH concentrations did not change, but anyway, serum IGF-1 levels increased after exercise (13). These findings display lack of GH effect on IGF-1 system following acute exercise.

Given these evidences, it seems that acute physiological operating signals of GH and IGF-1 system might be different (12). Physiological operating signals for exercise-induced increasing in serum IGF-1 and IGFBP3 may be sensitive to lactate changes, whereas acidic and alkaline status aspects of blood (e.g., hydrogen) are associated with increase in GH concentrations after exercise; or various variables within the acidic and alkaline status of blood might differently mediate GH and IGF-1 responses to intensive exercise (12). While study on the doping phenomenon clearly shows that the use of exogenous GH lead to considerable increase almost in all IGF-1 system components (9, 19), there is no reason to believe that endogenous GH cannot induce such changes in IGF-1 system. However, how acute changes in GH may affect IGF-1 system during a more prolonged recovery period after intense exercise (e.g. more than 12h), remain unknown.

In this study, the temporal changes in plasma insulin levels revealed no correlation with the temporal changes in plasma IGFBP1 values. Although plasma insulin concentrations could partly predict circulating IGFBP1 levels after exercise, but it cannot demonstrate that the relationship would be as an acute regulatory role after exercise. Mechanisms of acute secretion regulation and immediate expression of IGFBP1 gene may be independent of insulin (15, 20). Despite the general belief that reduction in insulin levels during physical activity increases the hepatic IGFBP1 expression, Anthony et al. suggested on mice that even by returning blood glucose and insulin levels to normal values with consuming a meal after exercise, serum IGFBP1 concentrations will consistently remain high. They concluded that IGFBP1 response to an exercise session is independent of insulin, glucose and amino acids accessibility (15). Our results also show that insulin levels can not predict IGFBP1 levels in response to exercise even in a relatively long period of time. In addition, Lavoie et al. demonstrated that IGFBP1 expression rate during exercise may

depend on liver glycogen content. In this study, by injecting glucose during exercise, it was tried to be kept the blood glucose levels in normal range. This action largely improved loss of insulin concentrations, but it affected only a little on the increased IGFBP1 response, while comparing hepatic glycogen values with IGFBP1 concentrations revealed that hepatic glycogen content is strong predictor of IGFBP1 response during the exercise (20). However, it is still too early to conclude what determines the IGFBP1 response to exercise is the hepatic glycogen content. In the present study, when the data of control group was merged, a reverse relationship was clarified between IGFBP1 with IGF-1 and IGFBP3. IGF-1 reduction during the long activities might be a supporting feedback for the increase which is observed in IGFBP1 concentrations. This issue was not displayed by our findings, but Nindl et al. found that levels of free and total IGF-1 and IGFBP3 reduce intensively following a short period of increase in daily physical activity and decrease of calorie intake while IGFBP1 levels enhanced to 256% (21). On the other hand, exercises can typically augment the IGFBP proteases activity which is present in the blood circulation (22). This could potentially reduce IGFBP3 affinity to IGF-1 which in turn can cause to increase the rate of IGF-1 that circulates as free form in plasma (8, 11, 16). Increase of free IGF-1 may stimulate production of IGFBP1 by the liver. Thus, IGFBP1 increases to receive extra values of free IGF-1. Despite all, this theory in which physiological operators of IGF-1 system components may be difference during exercise or similar signals differently operates various components of IGF-1 system; still remains in force and further research require making clear the details of this issue.

Other interesting finding of this study was that periods of the training (typically resistance) probably do not alter function of GH/IGF-1 axis, because the IGFBP3 which is known as reflection of spontaneous secretion of growth hormone had no significant difference between the two groups (trained and untrained). Therefore, our results approve that strength training with any duration cannot modify basic concentrations of IGF-1. Of course, this finding cannot be generalized to aerobic training which seems the program duration may be a determinant factor or to sedentary

individuals that training causes prominent physiological changes in them. Also, some parts of our findings are in contrary to the report of Koziris et al. in which they observed increase in free and total IGF-1 and IGFBP3 after 4 months training in swimming team members of men and women (11). Such contradictions are abundant in the findings of different researchers and they are not easily explained. Perhaps the type of foods, the number of meals, the volume and quality of food and the use of nutritional supplements can be a possible suspect for reason of discordant observations. A proper diet may lead to a proportionate energy flow and balance which can assist to improve the process of developing training adaptations (23); the opposite of this theory is also reliable (21, 24).

In case of different effects of exercise on various groups, knowledge of phenotypic differences and anthropometric characteristics between individuals could help to understand these contradictions, and at first glance, it may seem that training method explains divergent and different responses observed after exercise training. Interestingly, the research literature about the effects of chronic training on concentrations of circulating IGF-1 is conflicting; some studies exhibit positive effects (11, 14, 25); whereas others do not demonstrate any effect (8, 26).

Findings of the researches which investigate IGF-1 response to chronic training would be in connection with this view that both of training intensity and duration will determine final levels of IGF-1 (25). Probably, the primary training status of individuals and also relative physiological stress applied during training influence the response (14). Thresholds of training intensity and duration might require being an appropriate stimulus for creating change in individuals with different fitness levels. It seems that if training intensity be high enough, the change in IGFBP3 and its proteolysis occur in both trained and untrained subjects (25). On the other hand, among many other factors that regulate IGF-1 concentrations, the changes induced by training in body composition may also play a role (24). Skeletal muscle shows high concentrations of IGF-1 receptors and it is sensitive to anabolic effects of the growth

factor (1, 2). Therefore, the relationship between IGF-1 and lean body mass may partly reflect optimized anabolic effects of GH-IGF-1 status induced by training. Though, this optimization was not seen here in concentrations of circulating IGF-1, we suppose that lack of a significant increase in basal concentrations of IGF-1 in the trained group, does not reject the possibility of such an improvement in GH-IGF-1 status, because as before, it has been reported a differentiation and separation of training effects on circulating concentrations of GH and IGF-1 (14). Severe dependency of IGF-1 on energy balance might make complex and ambiguous the relationship between exercise training and IGF-1 (21, 24). Some researchers showed that the calorie cost induced by increased daily physical activity for 7 days led to reduction in IGF-1 concentrations which its extent was similar in both of energy balance and also along with energy deficit during experimental period (25). However, improvement in the GH-IGF-1 status was not confirmed by the results of this study.

Evaluation of the resting concentrations of anabolic and catabolic hormones may provide a vision regarding to the physiological mechanisms involved in high levels of muscular function and subsequent mechanisms. By the same token, we observed no significant difference in pre-exercise serum concentrations of GH between trained and untrained groups. This issue was not something out of mind because serum GH concentrations typically during traditional strength training do not alter despite increase in adaptation compatibility for changing and transforming of tissue in response induced by acute exercise after resistance exercise (10). Our data supports previous researches which show a lack of change in resting concentrations of GH.

It was mentioned that chronic adaptations of IGF-1 after resistance training may be mediated partly by manipulating the volume and intensity of training. On the other side, IGF-1 concentrations are regulated by GH secretion. Although, immediate expression mechanism of IGF-1 activated by GH is not clear, super family of GH stimulate IGF-1 secretion by the liver and other tissues. Though, no change in the resting GH was

observed in this study, unmeasured changes might be occurred in GH pulsatility (e.g. secretion at night or during the day which was

not measured in this study) or other forms of GH with a different molecular mass (27).

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