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**THE IMPACT OF ALTITUDE ON GROWTH HORMONE, INSULIN, CORTISOL,
AND INSULIN GROWTH FACTOR**

**YOUNESS HEMMATY ARDALI¹, SETORKI M^{2*}, DOUDI M³, AKRAM RAZAVI¹,
ROQAYEH ALIYARI AMIRABADI⁴**

1: Department of Physical Education and Science Sport, Izeh Branch, Islamic Azad University, Izeh, Iran

2: Department of Biology, Izeh Branch, Islamic Azad University, Izeh, Iran

3: Department of Microbiology, Falavarjan Branch, Islamic Azad University, Isfahan, Iran

4: M. Sc. in Biostatistics, Department School of Public Health Sciences, Shahroud University of Medical Science Shahroud, Iran

***Corresponding Author: E Mail: doctor.setorgi@gmail.com**

ABSTRACT

The purpose of this study was to compare growth hormone (GH), insulin, cortisol, and insulin growth factor (IGF) in high altitudes and their persistence after returning from the altitude.

In the present study, 12 subjects with the history of physical activity and mean age of 22.6 ± 150 were selected. Blood samples were taken two times from the subjects in order to compare the changes of GH, insulin, cortisol, and IGF. First blood sample was taken at the start of altitude (1830 meters) and the second sampling was performed 72 hours after reaching the altitude of 4000 meters.

The results showed that the cortisol and insulin hormone levels after 72 hours of staying in the altitude of 4000 meters significantly increased compared to the 1830 meters. GH also increased, but this increase was not significant. IGF levels decreased, but were not significant.

A number of endocrine and neuroendocrine pathways are activated in response to hypoxic stress, while other pathways are inhibited. An optimal adaptation to stressful environment depends on the balance between activity and resistance.

Keywords: Growth hormone (GH), Insulin growth factor (IGF), Cortisol, Altitude

INTRODUCTION

Exposure to altitude and adaptability is considered by most sports scientists. Acute effects of reduced oxygen tension depend on individual reaction. A number of systems, such as the cardiovascular systems, endocrine, and lungs, when exposed to height, react to hypoxia (collaborative response). These systems rarely react separately, but sometimes, instead of interacting with each other, they provide an individual response in order to collaborate in this environment [1].

Acute and chronic exposure to high altitude induces different physiological changes, including inhibition or activation of hormonal systems. High altitude causes various physiological changes, both when returning to sea level and when in acute conditions for a long period of time, such as regulation of hormonal secretion. The reports on the acute effects of exposure to hypoxia on sex hormones, prolactin, and growth hormone (GH) are often contradictory [2-4].

Altitude is determined through hypoxia, reduced temperature, and atmospheric pressure. Many researchers are concerned with the physiological responses to hypoxia,

because they have a strong influence on metabolism. Exposure to hypoxia at altitude causes changes in glucose homeostasis associated with increased concentrations of glucose and insulin in the first few days. Altitudes higher than 4500 meters cause discomfort and can, therefore, be inappropriate for the improvement of insulin sensitivity [5].

Brooks et al. showed that in high altitude insulin concentrations strongly increase [5] and this increase persists until one week after [6], and after 15-21 days insulin concentration level drops to that at sea level [5, 6]. Insulin secretion increases to compensate for resistance. Therefore, the concentration of insulin in the blood also increased. Brooks and Roberts showed that there is an increase in the amount of insulin activity in skeletal muscles during the transition from sea level to heights [5, 7]. Sawhney *et al.*, studied the effect of hypoxia on circulating insulin levels of euglycemic men at sea level (SL, 220 m) during their stay at high altitude (3500 m, SJ), and in high altitude natives (HAN) [8]. A significant increase in insulin secretion was

observed during their stay at a high altitude (3500 m, SJ). This increase in insulin secretion was significantly higher in sojourners (SJ) than HAN. Thus, the circadian rhythm of insulin, during exposure to height, showed changes.

Insulin-like growth factors (IGFs: insulin growth factor), including IGF-I and IGF-II, are a family of polypeptide growth factors that are related to proinsulin regarding construction [9]. IGF1 mediates many of the growth-promoting effects on the GHs during life after birth [10, 11]. On the other hand, in this study the level of cortisol hormone was also examined when placed at height. In some studies, an increase in plasma cortisol concentrations in response to acute hypoxia has been reported [12, 13]. The purpose of this study was to compare the GH, insulin, cortisol, and IGF in altitude and their persistence after returning from the altitude.

METHODS AND MATERIALS

This study was performed on male students of Ardal Branch, Islamic Azad University, Iran. Thus, 12 individuals with a history of sport and physical activity, with a mean age of 22.6 ± 1.50 were chosen through purposive and convenient sampling as study subjects. Blood sampling was performed 2 times periodically at specified time intervals; the first was performed at the height of 1830 meters (the

start of moving towards the height), and the second sampling, 72 hours after remaining in an altitude of 4000 meters.

The study environment was a part of Zagros Mountains called Zard-Kuh. During the study period, all participants took advantage of the same diet and exercised 2 times a day. These activities started by warming up, followed by 1.5 hours of recreational volleyball, and finished by cooling down. To estimate the intensity of their activity, light exercise was performed at 50% to 60% VO_2 max (maximum heart rate, MHR). A CASIO GPS altimeter instrument (Tokyo, Japan) was used to determine the desired height. A 5 cc syringe with needle number 22 was used to take a 5 cc blood sample from the vein of the right arm. Then, the samples were centrifuged for 15 minutes (3000RPM/Minute), and serum was separated. Parameters of GH, insulin, cortisol, and IGF1 were measured using biochemical kits (co sigma) and Elisa methods.

Statistical Analysis

In this study, the test t-paired, for comparison of averages, at a significance level of 0/05 was used, and ultimately be based on power analysis was evaluated

RESULTS

Based on paired t-test, the mean cortisol and insulin hormone levels in the two

measurement stages (first and second blood sampling) were significantly different ($P < 0.05$). However, the mean growth hormone

and IGF1 level in the two blood sampling stages had no significant difference ($P > 0.10$) (Figures 1-4).

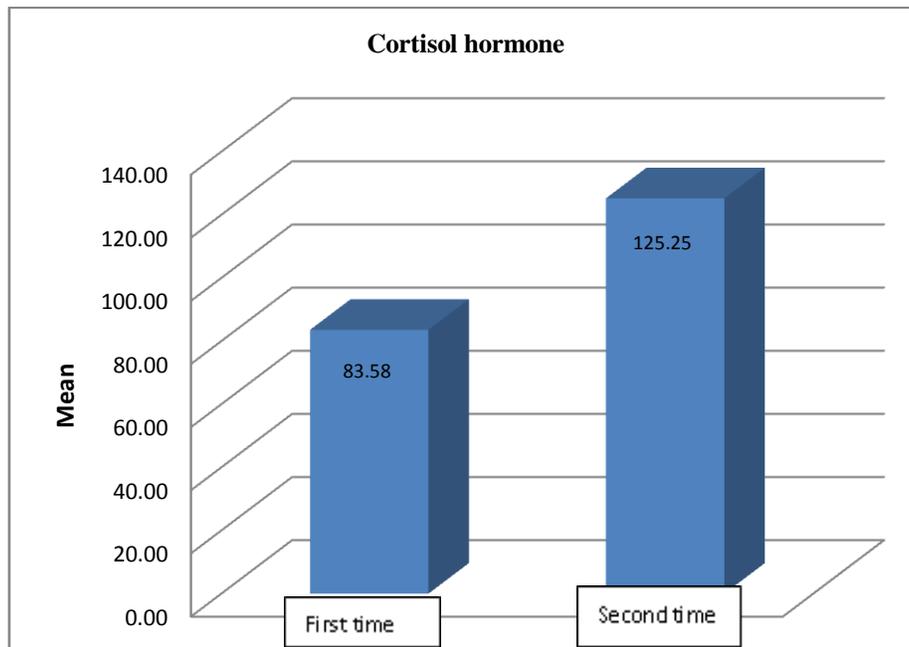


Figure 1: Changes in cortisol (ng/l) Hormone of the Subjects at Different Times: First Time (1830 Meters) and Second Time (4000 Meters)

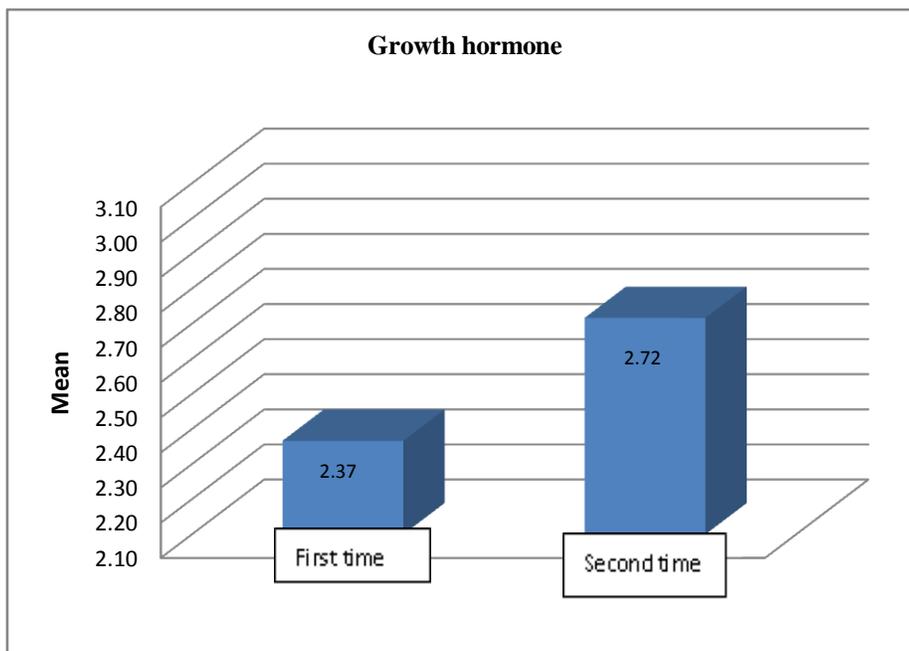


Figure 2: Changes in Growth Hormone (ng/l) of the Subjects at Different Times: First Time (1830 meters) and Second Time (4000 Meters)

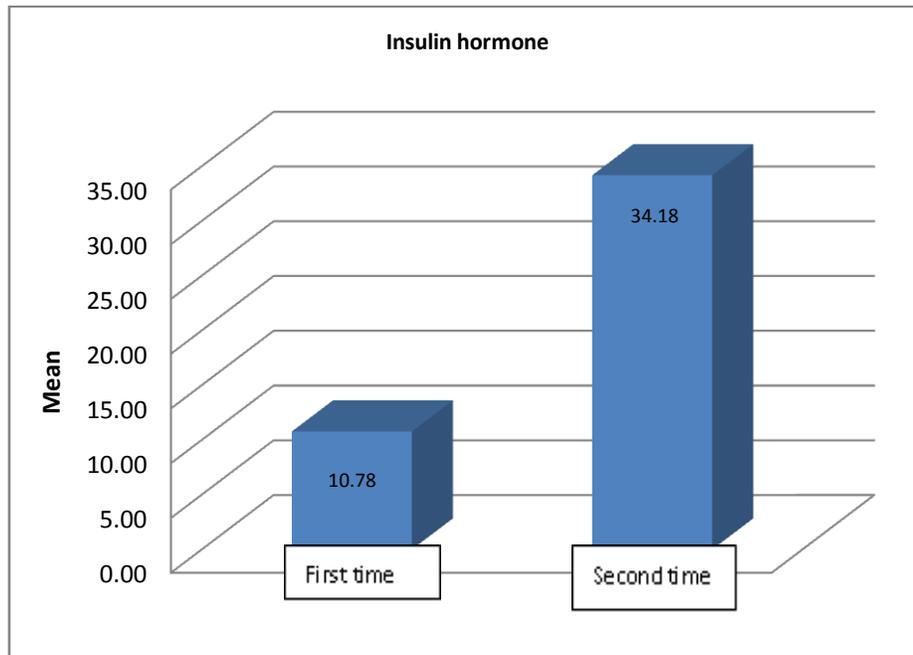


Figure 3: Changes in Insuline Hormone (ng/l) of the Subjects at Different Times: First Time (1830 Meters) and Second Time (4000 Meters)

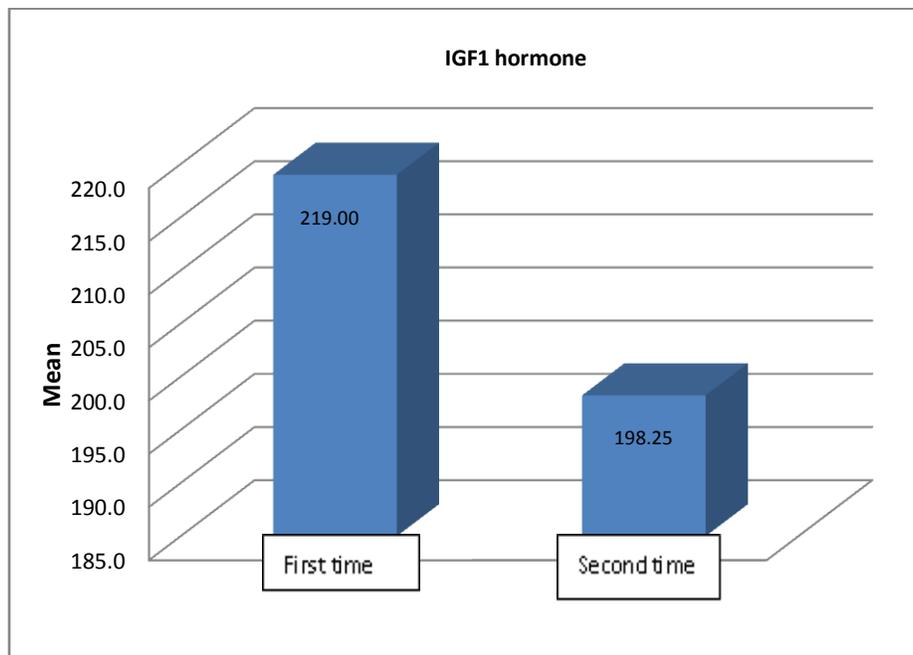


Figure 4: Changes in IGF1(ng/l) (Insuline Growth Factor 1) Hormone of the Subjects at Different Times: First Time (1830 meters) and Second Time (4000 Meters)

DISCUSSION

The results showed that the cortisol and insulin hormone levels after 72 hours of staying at 4000 meters increased significantly compared to an altitude of 1830 meters. The growth hormone also increased, but this increase was not significant. Moreover, IGF levels decreased, but this decrease was not significant. A number of endocrine and neuroendocrine pathways are activated in response to hypoxic stress, while other pathways are inhibited. For example, cortisol release is activated, but aldosterone release is inhibited by hypoxia (although these two hormones were secreted from adjacent areas of the same organ). An evident resistance, which occurs with a particular stimulation, limits the effects of activated pathways. These down-regulation processes neutralize the activity of a number of phenomena that lead to an increase in stress hormones (cortisol and catecholamine) in response to hypoxia. Thus, in general, an optimal adaptation to stressful environment depends on the balance between activity and resistance [14].

Given the central role of GH in the regulation of substrate metabolism and anabolism, the Growth hormone-growth hormone releasing hormone (GH-GHRH) axis, under conditions of increased physical stress, should be taken into consideration. Growth hormone secretion

is controlled by GHRH and its effects are opposed by somatostatin and various GH-releasing peptides (GH secretagogues) [15, 16]. GH binds to its specific protein (Growth hormone-binding protein, GHBP) in plasma and applies its effects both directly and through the production of growth-like factor 1 (IGF1).

In addition to the absolute levels of IGF1 regulated by growth hormone, the amount of unbound IGF (such as available IGF1) depends on their interaction with proteins bound to IGF (IGFBP). In addition, changes in these bounded proteins play an important role in the available IGF fine-tuning [17, 18]. Studies have shown that the amount of growth hormone and its response to GHRH increased in high altitudes or increased exercise under hypoxic conditions [19-21]. Anand et al. reported a significant increase in growth hormone levels. This observation could be due to their high number of subjects, long time exposure to altitude, or environmental stress. Because exercise, chronic hypoxia, and stress are all causes of growth hormone increase [22]. GHRH pulses are important factors in stimulating the release of growth hormone in normal conditions. The cause of changes in growth hormone level at high altitudes is not known. However, this hormone can play a role in modifying the

metabolism in order to meet the increased needs, both in short and long term exposure to height [23].

Lactic acid has been proposed to stimulate the release of growth hormone during exercise [24]. Hypoglycemia can also induce growth hormone secretion [25]. Increased plasma glucose levels are observed when growth hormone levels are increased. Growth hormones are important for normal thyroid hormone secretion; therefore, hypothyroidism is associated with a deficiency of this hormone [26]. The range of the growth hormone response to exercise depends on the exercise and fitness. Furthermore, the exposure to acute hypoxia (2325 m), inhibits the response of growth hormone and IGF1 to submaximal physical exercise in untrained individuals (not trained) [27].

Ramirez et al. studied the effect of high altitude on dynamic secretion of pituitary gland-hypothalamus in men. Results of this study showed that the growth hormone responses to GHRH in men who are at high altitude increased compare to men at sea level. Moreover, the amount of IGF1 in the presence of normal levels of IGFBP3 significantly increased[20].Jens Jorn Larsen et al. studied the effect of altitude hypoxia on glucose homeostasis in men and found that glucagon and growth hormone concentrations

remained unchanged, while the concentration of glucose, C-peptide, and cortisol increased (after 48 hours) [28].

The study by Jean-Paul Richalet *et al.* concerning the effects of high altitude hypoxia on the hormonal response to hypothalamic factors showed that cortisol increased, but no change was observed in growth hormone and IGF1 levels [29].

CONCLUSION

The results of the present study show that the cortisol and insulin hormone levels after 72 hours staying at 4000 meters increased significantly compared to an altitude of 1830 meters. The current study differs from previous research and so far no research has been conducted in accordance with these conditions. Most of the researches have been conducted for long periods at altitudes of 1800-3000 meters, or at difficult conditions for long durations of time, such as Mount Everest. Both conditions are hard, expensive, and impossible, because remaining in high altitudes necessitates high costs, and as the duration of the study is extended the probability of sample loss increases. However, if we are seeking use altitude and hypoxic conditions efficiently, the duration of the study should be shortened so that more people can be present at heights.

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