Effects of genetic factors on high altitude training performance

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Abstract

High altitude is considered to be 1800-6000 meters. With the decrease of atmospheric pressure at this altitude, adequate oxygenation cannot be achieved in the tissues and hypoxia develops in the circulatory system. Athletes aim to provide superior performance by training in hypoxic conditions. Varying adaptations in hypobaric hypoxia environments by geographically separated populations represent well-trained specimens that may be relevant to endurance performance. While inhabitants of the Andes show higher levels of hemoglobin and saturation than Tibetans at similar altitude, Ethiopian climbers maintain oxygen delivery despite the hemoglobin levels and saturation typical in sea level ranges. It can also be predicted a significant relationship between the angiotensin converting enzyme (ACE) genotype, which affects metabolic efficiency and performance in hypoxic environments (high altitude). One of the genes that develop at high altitude and occur in response to hypoxia is the hypoxia inducible factor 1 alpha (HIF-1α) gene encoded by the hypoxia inducible factor (HIF-1A) gene. The vascular endothelial growth factor (VEGF-A) gene, which is another gene with angiogenetic factor produced in response to hypoxia, is revealed by the transcription of the HIF-1 alpha gene. Genetic heritage, environmental factors, and the character of exercise loads applied within the framework of lifestyle, neuromuscular development, balanced nutrition, and cultural differences that trigger athletic success may reveal individual changes or differences. Considering all these variables, monitoring and control of performance improvement and athletic achievement graph may become more predictable.

Keywords
acclimatisation, exercise, HIF-1α gene, high altitude, hypoxia
Introduction

Adaptation Physiology on the High Altitude

High altitude is defined as between 1800-6000 m, higher is considered as extreme altitudes. The density of the air decreases as one climbs above sea level. The air contains the same proportion of oxygen (20.93%) at sea level pressure and at higher altitudes, but the local pressure of oxygen (PO2) and atmospheric pressure decreases with elevation. In this case, the blood cannot be adequately oxygenated due to the reduced partial oxygen pressure, and the oxygen reaching all tissues in the body is restricted as a result of insufficient oxygen saturation in the circulation. Hypoxia is defined as O2 deficiency at the tissue surface (Cerit and Erdoğan, 2019). Human metabolism initiates hyperventilation (increasing the respiratory rate and frequency) as soon as it reaches high altitude and triggered erythropoietin (EPO) to produce extra red blood cells in order to compensate for the hypoxic environment in the tissues. This is due to the increase in the number of erythrocytes in the blood cells (Cerit, 2021). Respiratory alkalosis occurs as more carbon dioxide is excreted from the body as a result of increased respiratory frequency. This change makes the blood alkaline and disrupts the acid-base balance. The human organism adapts to the newly formed situation by releasing bicarbonate ions (HCO3-) from the kidneys in such situations that occur under different conditions such as high altitude (Cerit and Erdoğan, 2019). The bicarbonate ions released from the kidneys normalize the deteriorated acid-base balance. With the increase in the level of hyperventilation, sufficient O2 is supplied to the tissue with a positive acceleration in heart rate and cardiac output (stroke volume). Apart from the aforementioned adjustments, the amount of O2 transported to the tissue is tried to be increased by hormonal adaptations (such as the release of epinephrine and norepinephrine).

Although adaptation to high altitude studies started 143 years ago, it is still seen as one of the important topics today (Akpınar, 2018). High altitude concept rose to become popular in 1968, after the Olympic Games were held in Mexico City (altitude 2300 m). Through the games, it was observed by the press, that competitors from lower elevation countries were adversely affected by the low oxygen concentration in the air (Hamlin et al., 2013). Varying adaptations in hypobaric hypoxia environments by geographically separated populations represent well-trained specimens that may be relevant to aerobic performance (VO2max). While inhabitants of the Andes show higher levels of hemoglobin and saturation than Tibetans at similar altitude, Ethiopian climbers maintain oxygen delivery despite the hemoglobin levels and saturation typical in sea level ranges (Cerit and Erdoğan, 2018). There are many assumptions surrounding the roles of human physiological responses in the evolutionary development of the aforementioned adaptations at high altitudes and the hypoxic environment (the reaction of the body as a result of the decrease in the partial pressure of oxygen and the difficulty of breathing, resulting in difficulty in breathing). Given the origins of modern humans in East Africa (a higher, drier and cooler environment than the more distant ancestors could live), the altitude tolerance and possibly endurance performance of modern humans’ ancestral forms would have been well adapted, as the adaptation toughness performance shown to high altitude tolerance is very similar to its features. If the ancestral forms that developed in the mountainous regions of East Africa are indeed a high-altitude endurance feature, it can be thought that East Africans may have developed a better-regulated, high-capacity version, which is due to the assumption that they are more preferable for aerobic performance. Other populations may have developed low-adaptive and low-capacity versions through the selection of other skills during transition to different environments (such as Tibetan populations) (Moran et al., 2007).

Acclimatization and ACE Gene

The process of adapting the body to hypoxia that occurs under high altitude conditions is called acclimatization. While there may be many adaptive responses that can occur immediately at high altitude, some adaptations may take weeks, months, or even years, and the said changes gained are lost a few weeks after reaching sea level (Cerit and Erdoğan, 2019). Physiological adaptations that
occur at high altitudes can also be affected by many variations such as humidity, sun and atmospheric pressure (Strzala et al., 2011). The native speakers of the Quechua language, who adapt to high altitude living conditions by combining their genetic advantages with their lifestyle, can move quite comfortably under difficult conditions that many people cannot overcome. Considering the progress made in the last 20 years, a much more accurate picture of the genetic elements that affect aerobic performance phenotypes and training ability can be predicted over the next decade. However, it should be concluded, based on the available data, that the overall picture of genes involved in endurance performance as the targeted phenotype is not very sharp. Contrary to the idea that perhaps only a dozen genes or less are involved, the current understanding is that a high number of genes are involved in athletic performance improvement. Studies conducted on mountaineers and soldiers show that ACE improves physical performance by increasing oxygen and nutrients to muscle cells (Montgomery et al., 1997). ACE is a vasoconstrictor enzyme that regulates electrolyte balance and systemic blood pressure (Cerit et al., 2006). It is associated with cardiovascular, skeletal muscle function, rapid muscle contraction activity (with DD genotypes) and muscle efficiency (with II genotypes) in athletic performance development. II genotypes have a greater natural ability for endurance than sprinting (Cerit, 2018, 2020).

It can also be predicted a significant relationship between the ACE genotype, which affects metabolic efficiency and performance in hypoxic environments (high altitude). Professional British male climbers who climbed higher than 7000 meters without using additional oxygen, compared to control groups, showed a significant increase in I allele frequency. Similar findings were found in 139 climbers aiming for an 8000-meter ascent (Thompson et al., 2007). There is also a confirming epidemiological evidence among indigenous people who speak the Quechua language and those living above 3600 meters in a small region called Ladakh located in India and Tropic regions of America. On the other hand, the researchers did not observe any relationship between elevation and responses to EPO incitement in 63 athletes subjected to elevation of 2,200 meters of the

ACE genotype (Qadar et al., 2001; Gonzalez et al., 2006; Bigham et al., 2008; Puthucheary et al., 2011). It has been reported that some people who are not genetically compatible and who are at risk of living in high altitude conditions suffer from mountain sickness (headache, nausea, vomiting, weakness and loss of appetite) or altitude sickness due to the fact that they cannot meet the acclimatization conditions at altitude (Akpinar, 2018). Development of sports performance is under the influence of the lifestyle in which the genetic structure is inherited from our ancestors and the environmental conditions we live in. The maximum oxygen utilization capacity (approximately 66% VO$_2$max value) encoded in our genes through genetic inheritance is the main determinant of long-distance running performance. It is a known fact that running efficiency or running economy are as effective as the maximum oxygen usage capacity in increasing the competition performance graph of especially elite athletes (Cerit, 2020). The first change observed in athletes exposed to hypoxia is the decrease in VO$_2$max values, which is one of the determinants of aerobic endurance. The maximal oxygen uptake capacity decreases with increasing altitude. As a result of the researches, it has been observed that the VO$_2$max value decreases by 0.9% at every 100 m height after 1.100 m (Buzdağlı and Koz, 2019). The most evident adaptation observed in metabolism during long periods of high altitude is the increase in the oxygen carrying capacity of the blood or the number of erythrocytes (Cerit and Erdoğan, 2019). Oxygen, which is free in the air during breathing, is taken into the lungs by ventilation. Oxygen molecules taken into the lungs are transported to hemoglobin via capillaries. Hemoglobin and oxygen molecules bound to hemoglobin are transported to tissues through arteries in the body, and are transferred from the capillaries to the mitochondria, which is the energy center of the cell and is genetically transferred from the mother to her offspring. Oxygen molecules transferred to the mitochondria are used in the production of adenosine triphosphate (ATP) energy and contribute to the efficiency of the body's aerobic energy metabolism (Kurdak, 2012). However, the use of energy sources obtained from the anaerobic system under hypoxic conditions has priority (Barlas et al., 1994). When this energy production efficiency, which is required
for the body, is examined, it is observed that there is a positive relationship between the amount of hemoglobin in the body and the number of oxygens bound to hemoglobin.

**EPO Gene and Other High Altitude Associated Genes**

The formation and number of erythrocytes in the body can change with various factors. Hypoxia in the circulatory system that occurs at high altitude is one of them. When climbing to high altitude, the amount of pressure exerted by the atmosphere on the body decreases. The release of EPO is initiated by the renal synthesis process from the kidneys due to hypoxia that develops in the circulatory system after climbing to high altitude. The aforementioned hormone (erythropoietin) secretion triggers the production of red blood cells (erythrocytes) in the bone marrow. In order to eliminate the negative effects of hypoxia developing in the circulatory system at altitude, more erythrocytes are produced. Stem cells triggered by the EPO gene increase the number of erythrocytes by creating stress in the circulatory system where hypoxia develops (Kaya et al., 2020). Positive accelerations in erythrocyte and hemoglobin counts increase the oxygen carrying capacity of the blood, improving VO$_2$max and athletic performance development. Hemoglobin increase, which positively affects athletic performance, reaches the desired level in about 4-7 days when climbing to high altitude. In the researches on the subject, it has been stated that weekly hemoglobin increase is 1%, and the difference between sea level and 2500m altitude above sea level is 12%. For this reason, the minimum adaptation period (acclimatization) needed for the metabolism to move comfortably under high altitude conditions has been determined as 12 weeks (Cerit and Erdoğan, 2019).

One of the factors that determine individual athletic performance is the amount of circulating hemoglobin. The EPO gene increases the amount of hemoglobin and triggers aerobic capacity positively, providing high performance in long-term endurance efforts (Jelkmann et al., 1997). EPO gene enhancers, which are actively used in the field of nephrology today, are also used illegally in the sports world (Doğan et al., 2012). EPO gene triggers and enhancers (such as blood doping, EPO injections, hemoglobin-based oxygen carriers, cobalt chloride salts), which are in the gene doping category, have been banned by the World Anti-Doping Agency (WADA).

Erythropoietin is injected intramuscularly into the body with recombinant human erythropoietin (EPO injections). Although it is actively used in the field of nephrology today, it is quite inconvenient and risky to use in healthy individuals and athletes. Sudden and unconscious increase in blood density in the body can cause high prevalence of morbidity such as autoimmune diseases, hypertension, pulmonary embolism and thromboembolism. Many sports fans were disappointed when famous cyclist Lance Armstrong admitted that he had used EPO injections for years. While EPO tests were used for the first time in the Sydney Olympics in 2000, the urine samples of the athletes were examined and many athletes whose medals were taken away from them in branches such as rowing, wrestling, gymnastics and athletics were punished. In the same year, many athletes refused to take the doping test and withdrew from the Olympics (Tarakçıoğlu, 2013).

Blood doping, which is among the EPO gene supplements, occurs when the blood of athletes who train at high altitudes where hypoxic reactions can occur in the body, is stored under appropriate conditions and transfused to them or to another person whose blood type is suitable. If the transfusion process is applied to the person again, autologous blood transfusion is called as homologous blood transfusion if it is applied to another athlete with appropriate values. There are several complications in both autologous blood transfusions and homologous blood transfusions. Blood transfusion complications may be common in both procedures. Anaphylactic shock and similar serious complications may arise in cases such as hypertension that may occur during transfusion or when blood samples taken are not stored under appropriate conditions. In homologous blood transfusions, in addition to the complications mentioned, if there is a virus or any disease in the blood of athletes, it may be possible to transfer the virus or disease to the person to be transfused and to experience risky situations. In addition to these complication risks, increasing the number of blood
cells in a person unnaturally and suddenly may lead to diseases with high mortality and morbidity, such as stroke, thromboembolism, pulmonary embolism, and heart diseases (Kaya et al., 2020). 

(HIF-1α) a gene encoded by the hypoxia inducible factor (HIF-1A) gene get cultivated at elevated altitudes in order to response to hypoxia inducible factor 1 alpha (Ahmetov and Fedotovskaya, 2012). With this gene that accelerates glycolysis metabolism, it has been observed that the endurance capacity increases with the increase of oxidative reaction and aerobic performance. In addition, the risk of type 2 diabetes mellitus disease, which affects public health, decreases with the acceleration of glycolysis metabolism (Koku, 2015). In the energy category, the hypoxic stimulus response variant (rs11549465) of individuals with the HIF1A genotype is homozgyous normal, the energy metabolism variant heterozygous PPARG Coactivator 1 Alpha (PPARGC1A) (rs8192678) that recommends normal energy levels in athletic performance ability. Adrenoceptor Beta 1 (ADRB1), Nuclear Respiratory Factor 1 (NRF1), Apolipoprotein E (APOE) are the primary genes responsible with oxidative phosphorylation, mitochondrial genesis, metabolic regulation of lipoproteins, and oxygen intake (Cerit et al., 2020a).

The vascular endothelial growth factor (VEGF-A) gene, which is another gene with angiogenetic factor produced in response to hypoxia, is revealed by the transcription of the HIF-1 alpha gene (Tekin, 2008). In hypoxic conditions, an increase occurs in the oxygen concentration in the tissues together with the number of capillaries. Response to hypoxic conditions developed by angiogenesis supported by VEGF-A gene. Angiogenesis: It allows the formation of new capillaries in cases such as hypoxic and vascular damage that occurs in body tissues (Güran et al., 2004; Tepebaşi et al., 2016).

High Altitude Workouts

High altitude training is one of the most effective strategies for enhancing the performance of athletic capacity. Long-distance runners carry out long-term loads under oxygen-poor conditions to enhance their exercise efficiency through high altitude training (Zhang and Chen, 2018). High altitude training is an exercise form favoured by both the trainers and the athletes to prepare for and adapt at higher elevations and to prepare for competitions at sea level. High-altitude training forms are adaptive effects resulting from prolonged periods of hyperventilation, increase in heartbeat number, erythrocyte amount and hemoglobin concentration. Athletes do high altitude training to take advantage of these effects (Akpinar, 2018). High altitude training creates the potential to improve competitive performance. Increases the athlete's match-specific endurance. Increases restructuring after the match (Cerit, 2021). High altitude training is the most preferred training applications in endurance sports to increase aerobic endurance and movement economy. Different altitude and environmental conditions cause adaptive changes in sports organisms that can be defined as "natural doping". These metabolic changes occur in tissues at the cellular level without the need for drug intake (Strzala et al., 2011).

Training at high altitude gives a faster physiological response compared to sea level. The main reason for the change in question is that hypoxia puts the human body under stress and training practices in altitude. The ideal altitude for high altitude training is between 1800 m and 2300 m and the approximate length of stay is 2 to 4 weeks. Light-paced aerobic workouts at height increase the endurance performance level and contribute to the increase of the aerobic performance level exhibited at sea level. Height training forms can be classified in five ways: preparation, acclimatization, main training in a high environment, returning back to appropriate altitude in order to adapt, attendance in the objective race (Akpinar, 2009).

After many studies emphasizing the positive results of high-altitude training for the athlete, many athletes and sports clubs in various sports branches have included high altitude training in their training programs. However, high altitude training does not provide the same effect on every athlete. Differences such as the athlete's fitness level, age, health status and energy level affect this inefficiency (Wolski et al., 1996). The effectiveness of altitude training also depends on the athlete's personal background. For example, hemoglobin values above normal limits are a great advantage for altitude training (Cerit, 2021). The ideal high-altitude training was developed by Levine and Stray-Gundersen in 1992 with the idea of
living in high, training in low. It was stated that in perfect training, it is necessary to be included in the acclimatization process for successful effect and endurance capacity, but supportive training should also be done at sea level to increase the aerobic endurance. The researchers in question proved the validity of the idea of living at high and low training with the study they conducted in 1997 (Cerit and Erdoğan, 2019). Short-term and vigorous exercises (anaerobic) in the first days of high altitude can affect the performance negatively by disrupting the acid-base balance of the blood with an increase in blood lactate level. For this reason, aerobic loads should be preferred in the preparation phase of high-altitude training and then anaerobic exercises should be preferred. High altitude training can also provide positive effects from high-level athletes to non-elite athletes with low fitness or sedentary athletes. On the other hand, some studies have stated that high-level athletes do not show a more significant performance difference than their previous levels when returning to sea level after high altitude training. In addition, it has been observed that endurance athletes are more affected by gas changes in the hypoxic environment compared to untrained individuals. Under ideal conditions, the competition to be held when returning from high altitude to sea level should be held within a maximum of 2 weeks. The positive effects of high altitude continue for about 2-3 weeks after reaching sea level and then disappear (Akpinar, 2009).

In order to provide a more appropriate, time-efficient and cheaper way to train in oxygen-poor environments, a number of new technologies have been cultivated to apply live altitude training in artificial environments. Artificial high altitude training applications could be achieved by reducing the environmental pressure of stimuli such as hypobaric chambers or by implementing different methods such as nitrogen dilution (hypoxic chambers and rooms) and oxygen filtration (hypoxator machines) (Hamlin et al., 2013). The advantage of the artificial elevation is that it can easily be combined with training under normal conditions. The hypoxic forms of the training under natural and artificial altitude conditions are almost similar (Cerit, 2021).

High Altitude and Oxidative Stress

As a result of high-altitude training, the concentration of myoglobin that carries oxygen to the muscle cells and the number of mitochondria that are the source of energy increase and contribute positively to the oxygen demand and oxygen transport system of the muscles (Cerit and Erdoğan, 2019). However, it is accepted that training loads gradually increase the level of oxygen uptake and flow to the mitochondria and can cause oxidative stress after a certain intensity and duration. It has also been observed that not only aerobic loads, but also anaerobic training stimuli can cause oxidative damage. The increased load at high altitudes may increase the body's vulnerability to oxidative stress, leading to oxidative damage (Bakonyi and Radak, 2004). Numerous reactive oxygen species (ROS) that occur in metabolism during high altitude training can cause oxidative damage at the cellular basis. In a regular physiological state, 95% of the ROS in cells is manufactured from mitochondria. ROS is a by-product throughout the respiration process of mitochondria and could be passivate by antioxidant systems in the body. Mitochondria are not the only main sites where endogenous free radicals are manufactured yet are also the aim of free radical assault. While excessive ROS causes great damage to the mitochondria, it can also open the pores of the mitochondrial permeability pathway by reducing the membrane potential (Zhang and Chen, 2018). Hence, antioxidant supplementation seems to be a crucial and natural instrument for exercising by decreasing oxidative stress (Bakonyi and Radak, 2004). High-intensity loads applied at high altitudes have an independent effect on free radical formation and the resulting oxidative stress. However, no evidence has been found in the results of the studies conducted to date that the oxidative stress caused by altitude is harmful for normal training or recovery processes. A limited number of studies show that the harmful consequences of oxidative stress can occur whenever people are exposed to excessive altitudes for prolonged periods of time. Nevertheless, additional research is required to comply this indefinite outcome (Quindry et al., 2016; Cerit et al., 2020b).
Conclusion

High altitude training practices and movement styles that have been researched and developed for more than a century have gained momentum with the development of technology. The focus of high-altitude training, which is used today to increase aerobic (endurance) capacity with both artificial oxygen masks and different training methods, is that the body cannot have sufficient oxygenation due to atmospheric pressure. Aerobic endurance capacities of athletes can be increased by natural methods with high altitude training practices. During such high-altitude training practices, the individual characteristics and genetic predispositions of the athletes should be taken into account, optimal diet and necessary vitamin / mineral support should be provided. With acclimatization, athletes whose aerobic endurance capacity has increased can achieve noticeably positive success in competitions. HIF-1 alpha gene, which is the hypoxia inducing factor that comes into play with the decrease in oxygen concentration observed in hypoxic environments, performs acclimatization with the vascular endothelial growth factor VEGF and EPO genes. This situation has turned the direction of the research done especially on top level athletes to the methods that can be applied to trigger candidate genes associated with hypoxia (Cerit et al., 2006; Cerit, 2018; Cerit et al., 2020a). The genetic advantages of elite athletes allow them to perform at a high level. For the development of athletic performance at a high level, environmental factors, lifestyle and motivation, as well as the correct sequence of genetic variables make it easier to reach the peak (Bigham et al., 2008). In addition, genetic compatibility cannot always be associated with high performance. There are many factors that affect performance, the important thing is to ensure that all components contribute to the optimum level of performance. High altitude training can contribute positively to performance improvement, but it is obvious that the effects of genes on high altitude performance improvement can be influenced by individual differences and epigenetic factors.

Conflict of interest

Authors declare no conflict of interest.

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