Original Article

Evaluation of ACE gene I/D polymorphism in Iranian elite athletes

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Abstract

Background: Angiotensin converting enzyme (ACE) is an important gene, which is associated with the successful physical activity. The ACE gene has a major polymorphism (I/D) in intron 16 that determines its plasma and tissue levels. In this study, we aimed to determine whether there is an association between this polymorphism and sports performance in our studied population including elite athletes of different sports disciplines. We investigated allele frequency and genotype distribution of the ACE gene in 156 Iranian elite athletes compared to 163 healthy individuals. We also investigated this allele frequency between elite athletes in three functional groups of endurance, power, and mixed sports performances.

Materials and Methods: DNA was extracted from peripheral blood, and polymerase chain reaction (PCR) method was performed on intron 16 of the ACE gene. The ACE genotype was determined for each subject. Statistical analysis was performed by SPSS 15, and results were analyzed by Chi-Square test.

Results: There was a significant difference in genotype distribution and allele frequency of the ACE gene in athletes and control group ($P = 0.05$, $P = 0.03$, respectively). There was also a significant difference in allele frequency of the ACE gene in 3 groups of athletes with different sports disciplines ($P = 0.045$). Proportion of the ACE gene D allele was greater in elite endurance athletes (37 high-distance cyclists) than two other groups.

Conclusions: Findings of the present study demonstrated that there is an association between the ACE gene I/D polymorphism and sports performance in Iranian elite athletes.

Key Words: Angiotensin converting enzyme, athletes, polymorphism, sports performance

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INTRODUCTION

The successful sports performance is influenced by many factors such as training, diet, environment, genetics, as well as other factors. Genetic information can determine the body shape and has a large effect over strength, lung capacity, flexibility, endurance, size, and fiber composition of muscles and is also

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important in anaerobic threshold.[1,2] Genetic factors influence maximal oxygen uptake (Vo2 max), which is related to capability of cardio-respiratory system to take and distribute oxygen in the body during exercise. Endurance sports, performed in long distances, require the best condition of aerobic or cardio-respiratory performance, while short-distance sprint and power performances are considered anaerobic activities, which are dependent on muscular speed.[2]

A number of genes have been identified that are important in athletic performance. One of these genes is angiotensin converting enzyme (ACE). This gene is 21 kb long and is located on chromosome 17q23, consisting of 26 exons and 25 introns.[3] Product of this gene is ACE enzyme that catalyzes the conversion of inactive angiotensin I into the active form angiotensin II, which is the main product of the renin–angiotensin system (RAS).[4] ACE enzyme also increases degradation of bradykinin, which is a growth inhibitor.[5]

Angiotensin II has an important role in stimulating aldosterone and causes reabsorption of more sodium and water in kidneys and increases both the amount of fluid in the blood and blood pressure.[6] Angiotensin II stimulates some cytokines and growth factors and, therefore, causes cell growth and proliferation.[7] Angiotensin II also has a trophic effect on the heart muscle cells,[8] and is a potent vasoconstrictor.[9]

Increase in the amount of ACE enzyme causes increase in the angiotensin II hormone. Rigat *et al*. demonstrated that a polymorphism in intron 16 of ACE gene can genetically control the plasma levels of ACE enzyme.[10] This polymorphism consists of an insertion (I) or deletion (D) of a 287-bp fragment in Alu-like sequence in intron 16. Individuals with the homozygous deletion allele (DD) have increased ACE levels in plasma and tissue, about twice as much as those who are homozygous for the insertion allele (II),[9,10] Individuals with the ID genotype have intermediate levels of ACE in plasma and tissue.

It is believed that ACE genotype affects the muscle strength in elite athletes[11,12] and has an important role in the morphology of cardiovascular system and the left ventricular hypertrophy in long-distance runners.[13]

Many of the previous studies demonstrated that excess of the ACE gene I allele is associated with some aspects of endurance performance. This was observed in studies, which were performed on Polish and Australian national elite rowers,[12,14] and Japanese runners.[15] Some other studies, investigating the ACE gene I/D polymorphism in power-oriented athletes, reported the association of the D allele with more power-oriented performances. This result was demonstrated in short-distance swimmers[16-18] and short-distance runners (sprinters).[16] There are also some studies that have failed to recognize any association in the ACE gene I/D polymorphism and athletic performance.[19,20]

In addition to the mentioned studies, many other studies have been performed in different countries to investigate the frequency of ACE genotype in elite athletes with endurance, power, or mixed disciplines. Results which were obtained from these studies confirmed or declined the previous findings. This difference might be because of genetic differences in diverse ethnic groups.[21]

The aim of this study is evaluation of the frequency of the ACE gene II, ID, and DD genotypes in a group of Iranian elite athletes, the control population, and also between the professional athletes in three functional groups of endurance, power, and mixed sports performances. By this approach, we would determine whether there is an association between this polymorphism and sports performance, which can be considered as a true genetic marker, in our athletic population, in order to direct athletes to suitable sports activities.

MATERIALS AND METHODS

Subjects and controls

In this study, a group of 156 Iranian male elite athletes aged from 18 to 40 years old were selected. All the athletes involved in national and international level sporting championships. Elite athletes were classified according to their sports fields in three sub-groups including mixed performance, endurance performance, and power or sprint performance.

Mixed group (n = 32) included three sport fields of basketball, volleyball, and taekwondo. Athletes who were professional in cycling were classified in endurance group (n = 37), and athletes who were professional in weightlifting and track and field were classified in power or sprint group (n = 87).

Control group consisted of 163 individuals who were native Iranian and matched with athletes in gender and age (male, 18-40 years old). The control group had not engaged in any regular sports activities. All the contributors were from healthy population, without cardiovascular or any major diseases.

Peripheral blood was obtained from all the athletes and the control group.

Molecular analysis

Genomic DNA was extracted from the peripheral blood by DNG™ plus DNA extraction kit, produced by Cinnagen Company, Iran.

Intron 16 of the ACE gene was amplified according to an article by Rigat *et al*.[22] PCR reaction was performed in a total volume of 25 µl of PCR buffer solution containing 0.2 mM of each dNTP, 5 pmol of each primer (sense oligo, 5' CTGGAGACCACTCCCATCCTTTCT 3' and antisense oligo, 5' GATGTGGCCATCACATTCGTCAGA 3'), 1.5 mM of $MgCl_2$, 0.5 U of *Taq* DNA polymerase, and 2.5 µl of 10x buffer. The PCR reaction was carried using the following cycling program: Initial denaturation at 95°C for 5 minutes followed by 35 cycles of denaturation at 95°C for 45 seconds, annealing at 67°C for 45 seconds, extension at 72°C for 1 minute, and a final extension at 72°C for 10 minutes.

5 µl of the PCR products then were loaded on 1.5% agaros gel and were observed. According to the length of the PCR products, we determined the type of the allele (I/D) and genotype of each sample [Figure 1].

Statistical analysis

Statistical analyses of data were performed using SPSS version 15.

Allele frequencies were estimated using the gene counting method. Genotype distribution of the ACE gene and allele frequency between athletes and controls and also among three groups of the athletes were compared by Chi-Square test. *P* values 0.05 or less were considered statistically significant.

RESULTS

The results of Chi-Square test demonstrated that there was a significant difference in allele frequency of the ACE gene in athletes and control group.

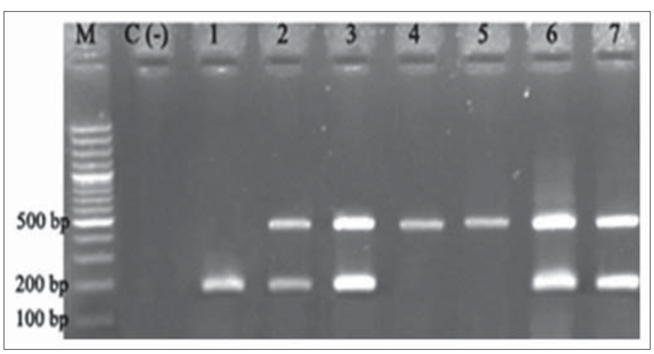

Figure 1: Representative of an agaros gel electrophoresis of PCR products of ACE gene. Lane 1; DD genotype (190 bp), lanes 2, 3, 6, 7; ID genotype (190, 490 bp) and lanes 4, 5; II genotype (490 bp). M is DNA weight marker

Frequency of the ACE gene I allele in athletes is significantly more than controls ($P = 0.03$). In addition, genotype distribution in athletes and control group was significantly different ($P = 0.05$). The results of distribution and proportion of the ACE gene alleles and genotypes in athletes and controls are presented in Table 1.

According to the statistical analysis, frequency of the ACE gene I allele (53.13%) was higher than the ACE gene D allele in mixed-oriented athletes. Distribution of the ACE gene I and D alleles in power-oriented athletes was equal (50%). In endurance-oriented athletes, there was a clear increase in proportion of the ACE gene D allele (63.51%) compared to the I allele. Statistical analysis demonstrated a significant difference in distribution of the ACE gene I and D alleles in three groups of athletes (*P* value = 0.045), but genotype distribution in athletes didn't show significant difference (*P* value = 0.11). Results of ACE allele frequency and genotype distribution in three groups of athletes are presented in Table 2.

DISCUSSION

In this study, we analyzed the ACE gene I/D polymorphism in three groups of athletes with different sports disciplines in comparison with a control group from not athletic healthy population. In our studied population, there was a significant difference in genotype distribution and allele frequency of the ACE

Table 1: The distribution and proportion of ACE alleles and genotypes in athletes and controls (*N*; number of subjects studied). By Chi-Square test, athletes had a significantly excess of having the I allele (*P*=0.03) or the II genotype (*P*=0.05), compared with controls

Group	ACE allele (%)		ACE genotype (%)		
	I	D	II	ID	DD
Athletes (*N*=156)	148 (47.44)	164 (52.56)	36 (23.08)	76 (48.72)	44 (28.20)
Controls (*N*=163)	127 (38.96)	199 (61.04)	27 (16.55)	73 (44.80)	63 (38.65)

ACE: Angiotensin converting enzyme

Table 2: ACE genotype distribution and allele frequencies in three groups of the athletes (*N*; number of subjects studied). Chi-Square test demonstrated a significant difference in distribution of the ACE gene I and D alleles in three groups of athletes (*P*=0.045)

Sports activity	ACE allele		ACE genotype		
	I	D	II	ID	DD
Mixed (*N*=32)	34 (53.13)	30 (46.87)	9 (28.13)	16 (50)	7 (21.87)
Endurance sports (*N*=37)	27 (36.49)	47 (63.51)	6 (16.22)	15 (40.54)	16 (43.24)
Power sports (*N*=87)	87 (50)	87 (50)	21 (24.14)	45 (51.72)	21 (24.14)

ACE: Angiotensin converting enzyme

gene between athletes and control group. In addition, there was a significant difference in frequency of the ACE gene I and D alleles in three groups of elite athletes.

ACE gene product, which is one of the important key components in RAS system, has a direct effect on generation of Angiotensine II.[4] Increase in the amount of ACE leads to increase level of Angiotensine II, which is followed by increase in aldosterone. ACE also decreased half-life of bradykinin, which is a growth-inhibitor.[23,24] Due to the key role of the ACE gene in regulation of both cardiac and vascular physiology, it is a candidate gene to be involved in athletic performance.[14]

By comparing the frequency of I/D polymorphism in athletes and that of the non-athletic population, we observed the excess of the ACE gene I allele in athletes. In a study by Ginevičienė *et al*., frequency of the ACE gene I allele was significantly higher in athletes compared to controls.[25] In another study, Amir *et al*. reported that frequency of D allele in athletes, who were marathon runners, was higher than control group.[21] There are also some studies that didn't identify any association with ACE polymorphism in athletes and control group.[16,19,20,26] It is believed that ethnic and geographic heterogeneities can be involved in such results.[21]

In the present study, we classified athletes in three groups by their sporting disciplines. Amongst three groups of athletes, we observed higher frequency of the ACE gene I allele in mixed performance athletes (53.13%) than that of two other groups of athletes. The frequencies were 36.49% and 50% in endurance-oriented and power-oriented athletes, respectively.

There are many studies that provide evidence about positive role of the ACE gene D allele in power-oriented and sprint performances.[27] Excess of this allele has been observed in short-distance runners and swimmers.[16-18,28] In our studied population, we observed equal frequency of the I and D alleles of the ACE gene amongst power or sprint group. In a study by Papadimitriou *et al*., it was reported that the ACE DD genotype could weakly influence sprint performance in elite Greek track and field athletes.[29] In another study, Moran *et al*. reported that the ACE gene I allele is more associated with strength-oriented performance than endurance.[30]

There are many studies that have reported an association between the ACE gene I allele with enhanced endurance performance in elite athletes. Although there are conflicting reports about it, excess of this allele is observed in long-distance runners, swimmers, rowers, and mountaineers.[14,16,31-33] The ACE gene I allele can serve as a genetic marker that might be associated with great athletic performance. Such association is probably due to its involvement in mechanisms related to a healthier cardiovascular system, improved aerobic capacity[20] or enhanced muscle efficiency.[14,27]

There is also some contradictory evidence in this field. For example, although Hruskovicová *et al*. reported an increased frequency of the ACE gene II genotype amongst successful marathon runners as endurance athletes,[26] Amir *et al*. reported that the ACE DD genotype is associated with excellent athletic performance amongst elite marathon runners.[21] It has been suggested that these highly different results may rise from genetic heterogeneity in different ethnic groups.[21] The most important finding of the present study was the significant higher frequency of the ACE gene D allele in elite endurance athletes. This group consisted of 37 male elite athletes who were professional in long-distance cycling. The ACE D allele is associated with high levels of angiotensin II via higher ACE activity.[34] This allele has a significant role in the left ventricular growth and increase in quadriceps muscle strength in response to physical training.[35,36] It also has a role in rising VO2 max levels, which indicate an improved oxidative capacity.[37] Comparing top-level Spanish professional cyclists with controls and elite Spanish runners, Lucía *et al*. demonstrated that the proportion of the ACE gene DD genotype was higher in cyclists than in the other two groups. In that study, the II genotype was higher in runners.[38] It is possible that cycling is a combination of endurance and strength exercise.[39] There are some other studies demonstrating that the ACE D allele can improve elite endurance performance. In a study by Tobina *et al*. on elite Japanese endurance runners, frequency of the ACE II and DD genotypes were not significantly different in athletes. Elite Japanese runners with the DD genotype had the best performance.[40] In another study on elite runners, the ACE gene DD genotype was significantly higher in endurance athletes (elite marathon runners) than in power athletes (sprinters).[21] In another study, Dékány *et al*. reported that frequency of the ACE gene D allele was significantly higher in elite endurance athletes compared to unsuccessful athletes.[41] Similar results were also observed in other studies that were performed on Lithuanian professional athletes[42] and on non-elite Caucasian Turkish athletes.[43] According to the mentioned studies, it is suggested that there is a relationship between the ACE gene D allele and excellent endurance performance.[21,40,41]

Our findings in the present study confirmed the association between the ACE gene I/D polymorphism and athletic performance in Iranian elite athletes. Prevalence of the ACE gene D allele among the elite endurance athletes enhanced the probability of its role in excellent endurance performance.

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