REVIEW ARTICLE

A Brief Review on ACE I/D Gene Polymorphism and Blood Pressure Response to Exercise Training

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ABSTRACT

Exercise has been suggested as the best and the most affordable way for managing blood pressure. The insertion/deletion of angiotensin I-converting enzyme (ACE) I/D gene polymorphism had been reported to be linked with several diseases such as hypertension and diabetic nephropathy. Several studies showed that blood pressure response to exercise training for health management also vary among individuals with different genotypes of ACE I/D gene polymorphism. A study of 9 months of endurance exercise training at 75 to 85 % of VO2max showed that the decrease of resting blood pressure in I allele carriers was greater than D allele carriers. In contrast, other study discovered that adult women with D allele had greater reduction in resting blood pressure than those with I allele, following a 12-week combined aerobic and resistance exercise training. Despite the inconsistencies of some findings, it has remained unknown if the ACE I/D gene polymorphism would also influence blood pressure response to isometric handgrip training that had been found to be superior to the dynamic resistance exercise training in controlling and preventing high blood pressure. Thus, this article was to review the literature on ACE I/D gene polymorphism and blood pressure response to exercise training that could serve as the basis for future research to identify individuals who will lower resting blood pressure the most with exercise training program for health management.

Keywords: Genetics, Blood pressure, Handgrip exercise

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INTRODUCTION

Genetics is a branch of science that studies heredity and how an organism inherits, as well as transfers characteristics from one generation to the next (1). Human genetics, then, emphasizes on the variation that occurs in human beings (2). The fundamental component in genetics is known as gene, which is a region of deoxyribonucleic acid (DNA) that contains particular information for making a specific protein for building tissues of the organ formation (3).

Generally, genes that control human physical traits occur in pairs called alleles, which are alternative forms of genes located on loci (positions) on the same chromosome (4). For example, high or low, round or wrinkled, red or white. Each human inherits two alleles for respectively gene from each mother and father (5). Alleles can exist in the form of dominant and recessive, and if a gene is composed of a pair of dominant alleles or only one dominant allele is present, the characteristic from the dominant allele will appear over the characteristic carried by the recessive allele (6). However, the recessive allele is able to show its characteristic if paired with another recessive allele (7). Thus, this natural selection creates a scenario one particular gene may produce different phenotype (characteristic) outcomes (8). Moreover, the differences in allele may be significant to explain the variation in human physiology (e.g. muscle fibre) (9).

Genetics play a key role in almost every aspect of human physical performance and health. The effect of the genetic factor on human physical ability as well as health has been extensively studied over the past several decades (10, 11). Historically, the first strong proof for the involvement of genetic factor in human physical performance arose from a family study known as the HEalth, Risk factors, exercise Training And GEnetics (HERITAGE) Family Study (12). Since then, efforts have been made to recognize candidate genes to human physical performance. Through the first annual version
of human gene map for performance and health-related fitness, more than a few genes or markers linked to physical performance and the related phenotypes for health have been identified (13-17). The most updated version of this yearly publication revealed that there are 239 genes associated with human physical performance (18).

The angiotensin I-converting enzyme (ACE) gene, in particular, has attracted much attention for research that focused on hypertension due to its role in the renin-angiotensin system (RAS); a physiological system that regulates blood pressure (19-21). I allele of the ACE I/D gene polymorphism produces less ACE protein compared to the D allele of this polymorphism (22). The lower production of ACE protein decreases the conversion of ANG I to ANG II resulting in increased vasoconstriction that lead to decrease blood pressure (23, 24). On the contrary, a higher level of ACE (22), which resulted in higher level of ANG II will led to a greater vasoconstriction that causes increases in blood pressure (25). Given these different physiological characteristics, there is a possibility that possessions of different ACE I or D alleles may influence individual blood pressure response to exercise training.

The influences of the ACE I/D gene polymorphism on blood pressure in response to exercise training have been investigated in several studies, but no study has investigated the effect of isometric exercise training on blood pressure response among individuals with different genotypes of the ACE I/D gene polymorphism. The isometric exercise training that typically consisting of four sets of 2-minute handgrip (26, 27) or leg contractions (28) at 30 % to 50 % of maximal voluntary contraction (MVC) (29, 30) with 1 to 4 minutes of rest period between each contraction (26, 29) conducted three to five times per week for 4 to 10 weeks (31, 32) has been shown to be more effective than other modes of exercise training in producing hypotensive effects by about 10 mm Hg and 7 mm Hg in systolic blood pressure and diastolic blood pressure, respectively (33). The isometric exercise training has the potential to ensure long-term adherence in managing blood pressure as it is easy to perform, does not require a higher intensity of training and less exercise time (34).

Hence, the available literature on the effects of different exercise training on blood pressure, particularly to isometric exercise training, and the knowledge regarding ACE I/D gene polymorphism as the potential mechanism that may influence blood pressure response to exercise training will be discussed in this review.

**EXERCISE AND BLOOD PRESSURE**

Hypertension has become one of the significant threat causes for chronic diseases, such as heart attack and stroke (35). The National Health and Morbidity Survey 2011 described that 32.7% of adults aged 18 years old and above in Malaysia suffered from hypertension (36). Nonetheless, it is well established that hypertension can be controlled and prevented through lifestyle modifications, such as dieting and exercising (37). Exercise training helps to strengthen the heart where the heart will pump more blood with less effort, thus decreasing the force on arteries, which in turn lowers blood pressure (38). Nevertheless, the optimal exercise training program in preventing and controlling high blood pressure has remained unclear as the magnitude of the training-induced effects may vary across the different prescribed training regimen (39).

**ENDURANCE EXERCISE TRAINING AND BLOOD PRESSURE**

Endurance exercise, which comprises large muscle groups in vibrant activities such as running and swimming, has presented to lower resting blood pressure in both hypertensive and normotensive individuals (40-43). In fact, a recent meta-analysis study reported that moderate to high intensity endurance exercise training not more than 210 minutes per week for less than 24 weeks abridged the resting systolic and diastolic blood pressure by 3.5 and 2.5 mmHg, respectively, with the largest fall in blood pressure greater in hypertensive compared in normotensive individuals (44). This adaptation is supported by several acute studies have demonstrated that a similar magnitude of blood pressure reduction was observed for up to 22 hours after cessation of a set of moderate-intensity endurance exercise training (41, 45, 46). It was also shown that moderate-intensity endurance exercise training increases exercise capacity (47) and decreases heart rate during exercise by 11.3 b.min-1 in hypertensive patients (48).

Although endurance exercise training promotes beneficial effects on blood pressure regulation, it is most unfortunate that approximately 50% of adults among those engaged in aerobic exercise program discontinued within 3 to 6 months (33). Dropout from this exercise program had been reported due to several factors, such as lack of time and medical condition (e.g. obesity or arthritis) (33).

**RESISTANCE EXERCISE TRAINING AND BLOOD PRESSURE**

Resistance exercise training (or also known as strength training) refers to any type of exercise training with resistance (e.g. dumbbells and elastic band) against the force of muscular contraction (49). Resistance training, such as weightlifting, is generally designed to build muscle and increase strength (50). Resistance training has not previously been recommended for hypertensive patients that is mostly due to the report by MacDougall et al. (51) who revealed that systolic and diastolic blood pressure could reach values of 320 mmHg and 250
mmHg, respectively, during the double leg-press in normotensive individuals.

However, subsequent studies have clearly demonstrated that resistance training can lower resting blood pressure (29, 52, 53). Furthermore, several meta-analysis studies have consistently reported that both resting systolic and diastolic blood pressure could be reduced by 3 to 4 mmHg following resistance exercise training (54-56). Interestingly, no incident of clinical high blood pressure has ever been reported after the resistance exercise training (54). Nonetheless, contrary to the findings obtained from endurance exercise training, the amount of blood pressure reduction after resistance exercise training had been equivalent in hypertensive and normotensive individuals (55, 56). Taken together, these findings demonstrated that resistance exercise training could be incorporated into an exercise program for blood pressure management.

Of the different modes of resistance exercise training, a current meta-analysis study reported that the reduction in resting systolic blood pressure was larger after isometric resistance training (-10.9 mmHg) compared to dynamic resistance training (-1.8 mmHg) (44). A similar pattern of reduction was also observed for resting diastolic blood pressure (44).

**ISOMETRIC RESISTANCE EXERCISE TRAINING AND BLOOD PRESSURE**

Unlike dynamic resistance exercise that involves movement at the joints, the isometric resistance exercise does not require any movement of the affected joint and the muscle length will remain unchanged (57). Over several years, numerous studies have studied the role of isometric resistance exercise training in reducing blood pressure (26-30, 58-60). In fact, a current meta-analysis study reported that the reduction in resting blood pressure had been largest following isometric resistance exercise training (systolic: -10.9 mmHg, diastolic: -6.2 mmHg) compared to endurance (systolic: -3.5 mmHg, diastolic: -3.7 mmHg) and dynamic resistance exercise training (systolic: -1.8 mmHg, diastolic: -2.5 mmHg) (44).

Although the optimal protocol of the isometric resistance exercise training has not been established at present, the most common protocol of this exercise training composed of four sets of 2 minutes handgrip (26, 27) or leg contractions (28) at 30 to 50 % of maximal voluntary contraction (MVC) (29, 30) with 1 to 4 minutes of rest period between each contraction (26, 29) that are conducted 3 to 5 times per week for between 4 to 10 weeks (31, 32). Relative to exercise trained-muscle, hand grip isometric exercise training (29, 32) was found to reduce resting blood pressure more than leg isometric exercise training (61). In addition, with regard to exercise intensity, the isometric handgrip exercise training performed at 30% of MVC (58) elicited greater decline in resting blood pressure relative to a comparable exercise at 50% of MVC (59). On the other hand, as for training frequency, Badrov et al. (32) reported that the effect of the isometric exercise training in pulling down blood pressure had been independent of the volume of training as groups that have had trained 3 or 5 times per week produced a similar magnitude of reduction in blood pressure. Interestingly, the influence of isometric exercise training on blood pressure could be seen after only 4 to 5 weeks of training with long duration of training, such as 8 to 10 weeks, having shown to elicit larger reductions in blood pressure (62).

It has also been demonstrated that the effect of the isometric exercise training is more pronounced in individuals with hypertension than those individuals with normal blood pressure (34). In addition, several studies have shown that no harmful effect was detected when performing isometric exercises as no overload was discovered in the cardiovascular systems and the hemodynamic parameters immediately after the end of the first session of this type of exercise training (63-66). In comparison to aerobic exercise training, the isometric exercise training has the potential to ensure long-term adherence as it is easy to perform, does not require high level of physical exertion (or exercise intensity), and completed in less time (34). Therefore, based on the findings of the previous research, isometric exercise training could be a very effective training tool for hypertensive and normotensive individuals to control and prevent high blood pressure, respectively.

At present, the mechanisms by which isometric exercise training elicits reduction in blood pressure remained uncertain (34). Wiles et al. (67) proposed that the rise in blood pressure during isometric exercise will stimulate the baroreceptors, which are sensory afferent nerve endings found in the carotid sinus and the aortic arch. When blood pressure is raised, the baroreceptors are stretched and this cause a reflex-mediated upsurge in parasympathetic nerve activity, as well as a decrease in sympathetic nerve activity (67). Consequently, this leads to a decline in the heart rate, while the diameter of blood vessels increases and causes further drop in the blood pressure (67). Moreover, other studies have suggested that the reduction in blood pressure after isometric exercise training is connected to the repeated power of hydrogen (pH) changes due to muscle fatigue and lactate production that act as a metaboreceptor stimulus (68); augmentation in vasodilator substances, such as, nitric oxide (NO) (69); and reduction in peripheral vascular adaptations (70).

**HUMAN ANGIOTENSIN CONVERTING ENZYME (ACE) GENE**

Hypertension is known as a polygenic hereditary disease concurrently predisposed by a variety of nurture factors.
The genetic factor is likely to give approximately 30% of the inter-individual variability towards blood pressure (48). With that, several candidate genes involves in blood pressure regulation had been proposed and among these, the angiotensin converting enzyme (ACE) gene was initially believed to influence blood pressure response to exercise due to its role in the renin-angiotensin-aldosterone system (RAAS) (19-21). In humans, the ACE gene is situated on the long arm (q) of chromosome 17 (17q23.3), spans 21 kilo bases (kb) in length, and embraces of 26 exons and 25 introns. The ACE gene is responsible for producing the angiotensin converting enzyme (ACE), a main factor in the RAAS (71). The ACE converts angiotensin I to angiotensin II, which results in increasing blood pressure through a series of event such as renal sodium retention, vasoconstriction and release of norepinephrine. ACE also breakdowns bradykinin, a potent vasodilator that lowers blood pressure (72). Angiotensin II has also been shown to promote myocyte hypertrophy (73), proinflammatory cytokines (74) and activation of the sympathetic nervous system (75). Through its effects on bradykinin and angiotensin, the ACE plays an essential role in regulating arterial blood pressure (20). On this basis, one of the genetic variations that occurs in the ACE gene, which is known as ACE I/D gene polymorphism, which results in inappropriate high levels of ACE, have been associated with the development of hypertension and its complications (71).

**ACE I/D GENE POLYMORPHISM**

Among several polymorphisms in the ACE gene, the ACE I/D gene polymorphism (rs4646994) was found to have a strong linkage with the level of plasma ACE as it accounted for 47% of the total phenotypic variance of ACE activity (22). The ACE I/D gene polymorphism may result in three possible genotypes of II (with low ACE serum levels), ID (with intermediate ACE serum levels), and DD (with high ACE serum levels) (22). Individuals with II genotype were shown to demonstrate lower ACE concentrations, while the DD genotype were associated with elevated levels and activity of ACE, which consequently lead to surge in blood pressure by elevating the production of angiotensin II, which was transformed from angiotensin I, initiating the constriction of blood vessels and also the increasing the reabsorption of water and sodium by the kidneys as well as elevating blood volume and blood pressure (76, 77). One study demonstrated that, apart from the circulating levels of ACE, the DD carriers was found to had higher activity of ACE from the heart, and this phenomenon was related with a greater incidence of cardiovascular disorders (78). Besides to association with hypertension, the ACE gene polymorphisms autonomously modified age-related increases in pulse pressure with a significantly greater slope of age-pulse pressure and age-systolic blood pressure relationships for DD genotype rather than other genotypes (79). Given that the ACE I/D gene polymorphism has an important role in regulating blood pressure regulation, the degree to which individuals with high blood pressure could reduce their resting blood pressure with exercise training likely to vary among individuals with different genotypes of ACE I/D gene polymorphism.

**THE DISTRIBUTION OF ACE I/D GENE POLYMORPHISM ACROSS ETHNICITY**

The current literature has observed variation in the distribution of the ACE I/D gene polymorphism in different racial and ethnic groups. Among the racial groups, the highest frequency of I allele was reported in Black (Australian Aboriginal) population (0.97) (80), while the D allele was reported highest among the Caucasian population (0.77) (81). In addition, the distribution patterns of I and D alleles in the Black population were about 0.97 to 0.27 and 0.73 to 0.03, respectively. In Black population, the Australian Aboriginal population was reported to have the highest frequency of I allele as compared to other ethnic groups of Black population (80). Other than that, the D allele was reported to be the most prevalent among Nigerians (82) and Somalis (83). Meanwhile, the trend observed among Amerindians (84) was closely similar to those reported for Pima Indians (85), Coastal Papua New Guineans (86), Sothos (87), Mulatto (48), and Alaska Natives (87).

On the other hand, in the Caucasian populations, the frequencies of I and D alleles ranged from 0.78 to 0.23 and 0.77 to 0.22, respectively. Among the Caucasians, the highest frequencies of I and D alleles were noted for Mexican (84) and European (81) populations, respectively. Nonetheless, I allele was observed to be less prominent among European (81) and Caucasian populations from the Middle East, such as Egyptians (88) and Omanis (89). Moreover, the occurrence of I allele among Mexicans (84) was observed to have close similarities with the studies conducted by (90) in European population. Furthermore, the high frequency of D allele observed among Europeans (81) was fairly similar with those reported for Egyptians (88) and Omanis (89). The distribution trend of ACE I/D gene polymorphism in Australian samples (80, 91) was reportedly identical with studies among the Brazilian (48) and European (92) populations. In addition, results retrieved from several studies conducted in the same ethnic group, such as Turkish, were markedly similar to each other (93-96). Nevertheless, varying results have been reported from studies in European populations. While Cambien et al. (90) reported that the frequency of I allele was 0.73 in their cohort sample, I allele was found to be less frequent in other studies; 0.23 (81), 0.43 (97), and 0.51 (98).

Meanwhile, in the Asian population, the frequencies of I and D alleles ranged from 0.76 to 0.42 and 0.58 to 0.24, respectively. I allele was reported to be most prominent in the Javanese population (99), whilst the
highest frequency of $D$ allele was observed in the Kazakh sample (100). Besides, there were two studies conducted by Jayapalan et al. (101) and Yusof et al. (102) that looked into different ethnic groups in Malaysia. In study by Jayapalan et al. (101), they observed higher frequencies of $I$ and $D$ alleles among Malays and Indians, respectively. Meanwhile, Yusof et al. (102) observed both Malay and Chinese groups showed to have higher frequency of $I$ allele over the $D$ allele, whereas the $D$ allele appeared to be more prevalent than $I$ allele in Indian and Other Bumiputra groups. Although there was a slightly difference in the frequencies of $ACE\ I$ and $D$ alleles in Malaysian population observed in studies by Jayapalan et al. (101) and Yusof et al. (102), the similar trend of ethnic variation was observed.

The different pattern in the distributions of $ACE\ I/D$ gene polymorphism across different ethnicities were apparently consistent with the research findings on the effect of $ACE\ I/D$ gene polymorphism in the susceptibility to certain diseases (103-109). For instance, a study by Ng et al. (109) showed that the association between $ACE\ I/D$ gene polymorphism and diabetic nephropathy was more common in the Asian population than those from the Caucasian population. Based on the findings in the distributions of $ACE\ I/D$ gene polymorphism in general populations worldwide and the research findings on the effect of $ACE\ I/D$ gene polymorphism in disease susceptibility, there is a possibility that the effects of $ACE\ I/D$ gene polymorphism on human physical performance such as blood pressure response to exercise training may vary depending on the ethnic origin, which indicates that such findings previously reported for Caucasian population may not be relevant and could be different in Asian population. Nevertheless, whether the effects of $ACE\ I/D$ gene polymorphism on human physical performance vary between different ethnic groups has remained unclear at present due to insufficient comparative analyses across ethnicities in the current literature (11, 110). A recent meta-analysis showed that the effects of the $ACE\ I/D$ gene polymorphism on human physical performance have been mostly reported among Caucasian population and less reported in the Asian population (11).

**$ACE\ I/D$ GENE POLYMORPHISM AND EXERCISE TRAINING ON BLOOD PRESSURE**

The association between genetic polymorphism and human physical performance has been receiving much attention in the past decade. In fact, polymorphism of the $ACE$ gene became the first genetic element presented to impact significantly on human physical performance (1). Gayagay et al. (111) first demonstrated the additive effect on performance in elite Australian rowers having possessed the $II$ genotype compared to the controls. Similarly, Montgomery et al. (12) reported an 11-fold increase in duration of exercise after a 10-week physical training program among British army military recruits who possessed $II$ genotype, when compared to those with $DD$ genotype. Since then, $ACE$ gene has attracted much attention worldwide as a candidate gene related to sporting performance due to its role in the RAAS (3).

Few studies have investigated the influence of the $ACE\ I/D$ gene polymorphism on blood pressure response following to endurance exercise training. Hagberg et al. (112) demonstrated that with 9 months of endurance exercise training, the older overweight hypertensive men who possessed of either $II$ or $ID$ genotype had reduced both their resting systolic and diastolic blood pressure more than individuals with $ACE\ DD$ genotype (systolic: -10 vs. -5 mmHg; diastolic: -10 vs. -1 mmHg). Meanwhile, in a study that involved Japanese men with mild to moderate essential hypertension, mean arterial pressure were significantly decreased in individuals with $II$ and $ID$ genotypes, but not in those individuals with $DD$ genotype following 10 weeks of ergometer cycling training (113). The effects of $ACE\ I/D$ gene polymorphism on blood pressure responses following exercise were not limited to only endurance-type training. More recently, Montrezol et al. (114) found significant reductions in systolic and diastolic blood pressures in 24 hours period following 16 weeks of resistance training at 50% of 1-repetition max (RM) in those who presented with $II$ genotype, compared to other genotypes. Freire et al. (115) in their earlier study had showed that individuals having the $ACE\ D$ allele are predisposed to to exaggerate hemodynamic responses (i.e. systolic and diastolic blood pressure, heart rate and resting pulse pressure) to acute resistance exercise. Several mechanisms have been implicated in the reduction of blood pressure by $ACE$ polymorphisms, the most discussed being related to NO release post exercise, with $I$ allele carriers demonstrating higher NO bioavailability after a single bout of aerobic exercise compared to $DD$ genotype carriers (116, 117). In addition, exercise also elicits an increase in release of Angiotensin 1–7, as well as ACE2, which are vasodilators that leads to a greater NO production and resulting in a decline in systemic blood pressure (118).

While $ACE\ I/D$ polymorphisms have been related with beneficial blood pressure responses to exercise training, there have been some discrepancies between the outcomes of the association studies with the $ACE$ gene. Studies by Rankinen et al. (119), Montgomery et al. (120), and Dengel et al. (121) found that the $ACE\ I/D$ gene polymorphism did not influence blood pressure response to 20 weeks of endurance exercise training. Similarly, Mota et al. (122) reported that occurrence of chronic reduction of resting blood pressure seen with dynamic resistance exercise training for three months in older hypertensive women was not associated with $ACE\ I/D$ polymorphism. Kim (123) on the other hand, showed that adult women with $DD$ genotype had a greater reduction in diastolic blood pressure than those with $II$ and $ID$ genotypes after 12 weeks of mixed of aerobic and resistance exercise training. With regards to
acute resistance exercise, de Souza et al. (124) reported no significant differences on systolic and diastolic blood pressure (SBP and DBP), as well as mean arterial pressure (MAP) following three sets at 60% of 1-RM in women exhibiting polymorphism II, ID and DD, as well as no effect of ACE polymorphism.

The inconsistency amongst the findings from the published studies on the ACE gene indicates the requirement to consider the types of subjects involved, ethnicities, methods and duration of blood pressure measurement, and exercise intensities among others. It has been suggested to consider reporting effect size for biological variables with clinical relevance such as blood pressure, especially under circumstances where predictable statistics reveals no differences (124). Isometric handgrip training has been reported to be more efficient in lowering resting blood pressure compared to other different modes of exercise training (44), however, the mechanism by which isometric handgrip training triggered reduction in resting blood pressure remains unknown. Given that the ACE I/D gene polymorphism influenced blood pressure response to endurance and resistance training, there is a possibility that the ACE I/D gene polymorphism might also influence blood pressure response to isometric exercise training.

CONCLUSION

The general findings covering all related studies available in the literature endure to support the assumption that both endurance and resistance-type exercise training reductions blood pressure in the large majority of patients with hypertension. The discovery that ACE gene insertion/deletion (I/D) polymorphisms are implicated in cardiovascular disorders has ushered in a new period of exploration of the ACE gene as a potential marker for a functional polymorphism in blood pressure responses following exercise. Previous evidence revealed a possible association of ACE I/D genotype with beneficial outcomes in blood pressure in response to endurance and resistance exercises in healthy and hypertensive individuals, however minimal data available also indicate no influence by the ACE gene polymorphism. Thus the findings remain inconclusive and needs to be interpreted with caution as the complexity of phenotypes also includes the probability of multiple connections between genes, or genes and environmental factors.

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