ASSOCIATION OF ACE GENE I/D POLYMORPHISM WITH HYPERTENSION AND PHYSICAL ACTIVITY LEVEL IN ADOLESCENTS: A SYSTEMATIC REVIEW

ASSOCIAÇÃO DO POLIMORFISMO I/D DO GENE DA ECA COM HIPERTENSÃO E NÍVEL DE ATIVIDADE FÍSICA EM ADOLESCENTES: UMA REVISÃO SISTEMÁTICA

DOI: 10.56083/RCV4N1-216
Recebimento do original: 28/12/2023
Aceitação para publicação: 29/01/2024

Nivaldo de Jesus Silva Soares Junior
Doctor in Biotechnology
Institution: Universidade Federal do Maranhão (UFMA)
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805
E-mail: soares.nivaldo@ufma.br

Carlos Alberto Alves Dias-Filho
Doctor in Biotechnology
Institution: Afya Faculdade de Ciências Médicas de Santa Inês
Address: Travessa do Bambu, 205, Centro, CEP: 65300-073
E-mail: carlosaadias@hotmail.com

Andressa Coelho Ferreira
Master in Adult and Child Health
Institution: Universidade Federal do Maranhão (UFMA)
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805
E-mail: andressa.cfer21@gmail.com

Carlos José Moraes Dias
Doctor in Biotechnology
Institution: Universidade Federal do Maranhão (UFMA)
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805
E-mail: carlosdias.ef@gmail.com
Mayara Moraes Machado Soares  
Specialist in Maternal and Child Health  
Institution: da Universidade Federal do Maranhão (UFMA)  
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805  
E-mail: mayaramaxadofono@gmail.com

Vinícius Santos Mendes  
Graduating in Medicine  
Institution: Universidade Federal do Maranhão (UFMA)  
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805  
E-mail: vinicius.mendes12@gmail.com

Flávia Castelo Branco Vidal  
Doctor in Human and Experimental Biology  
Institution: Universidade Federal do Maranhão (UFMA)  
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805  
E-mail: flavia.vidal@ufma.br

Cristiano Teixeira Mostarda  
Doctor of Science  
Institution: Universidade Federal do Maranhão (UFMA)  
Address: Av. dos Portugueses, s/n, Bacanga, São Luís - MA, CEP: 65080-805  
E-mail: cristiano.mostarda@gmail.com

ABSTRACT: Hypertension (AH) is a worldwide public health problem that involves several risk factors such as genetic inheritance and a sedentary lifestyle, leading to several other complications. Although more adults are increasing, the prevalence has increased among adolescents. In this sense, the study aims to make a systematic review of the ACE I/D polymorphism and its relationship with the prevalence of hypertension and adolescents' physical activity level. A search was performed in the literature of PubMed and Scielo databases. The investigation was limited to articles written in the english language in the last ten years. Articles published between 2012 and 2022 were included. Among the 17,126 articles identified in the systematic review of the literature, when applying the exclusion criteria, 12 were selected for complete reading, finishing with seven articles chosen for the review. Although there are few studies with this theme, we observed that studies have advanced that demonstrate the DD genotype of ACE I/D polymorphism as the most significant predictor of AH and still seeking a greater consensus on the influence of physical activity in this process.

KEYWORDS: ACE I/D Polymorphism, Physical Activity, Hypertension.

RESUMO: A hipertensão é um problema de saúde pública mundial que envolve vários fatores de risco, como herança genética e sedentarismo, levando a várias outras complicações. Embora mais adultos estejam aumentando, a prevalência aumentou entre os adolescentes. Nesse sentido,
1. Introduction

Systemic Arterial Hypertension (SAH) is a chronic degenerative disease characterized by being a worldwide and multi-factorial public health problem, where its main characteristic is the high and sustained levels of blood pressure (BP) [1, 2].

With this characterization of high blood pressure levels, when the presence of SAH and other risk factors begin to have a negative influence on the body, it is possible to infer that the impact on cardiovascular health will be more significant the sooner this scenario is pronounced, and this leads us to the fact that cardiovascular diseases are becoming increasingly prevalent in childhood and adolescence [3].

Thus, even though this pathology in adolescence is still in a smaller number, as previously stated, its precursors have been increasingly seen in young people. This increasing prevalence in adolescents has been related to...
several risk factors such as obesity, sleep disorders, sedentary lifestyle, and inadequate diet, leading to a lifestyle that contributes to this early appearance that is harmful to health, resulting in changes in BP[4-6].

Among these risk factors, obesity and a sedentary lifestyle directly relate to reducing regular physical activity time by this population. Studies have shown the influence of this regular practice on the improvement of lifestyle, sleep quality, reduction of body mass index (BMI), and consequently, blood pressure levels of individuals, especially adolescents [7, 8].

The concern becomes even more significant when we consider the genetic factor in the genesis of this SAH in adolescents. The influence of heredity is generally known. Studies prove that if this adolescent is the child of hypertensive parents, the probability of this adolescent becoming this pathology is also much higher than the child of normotensive parents [9, 10]. Thus, studies indicate the complexity of SAH and the factors that compose it, emphasizing that specific genes make it possible to explain approximately 50% of BP variation in individuals with a family history of hypertension [11].

The literature shows that even without being diagnosed with SAH, this genetic factor already reflects parameters such as the Autonomic Nervous System (ANS). Thus, this change is already shown early when analyzing these adolescents' Heart Rate Variability (HRV). Changes are also more prominent in sedentary individuals than active individuals [12].

Therefore, in genetics, it is necessary to observe the importance of the production and expression of regulatory components found in the endocrine system, such as the renin-angiotensin-aldosterone system (RAAS), being predominant in SAH. This association is related to higher production of angiotensinogen (AGT), angiotensin-converting enzyme (ACE), and angiotensin II type-1 receptor (AGTR1), causing an increased risk of SAH.
ACE, therefore, plays an essential regulatory function of BP and electrolyte balance, converting Angiotensin I (Ang I) into Angiotensin II (Ang II), the hormone responsible for vasoconstriction [13].

In this respect, it is essential to highlight those genetic parameters that can alter the production of ACE so that individuals who have the D allele (polymorphic) of the ACE I/D polymorphism have high serum and cardiac concentrations of ACE, unlike allele I (wild) [14]. Note that the gene polymorphism is a genetic variant that can alter cardiovascular physiological function [15] in individuals with a higher amount of DD angiotensin. This disorder can lead to changes in various mechanisms, such as autonomic dysfunction and electrolyte and endothelial imbalance, contributing to hypertension and other cardiovascular diseases [14].

Given this fact, they are identifying the presence of ACE I/D polymorphism as early as possible. The influence of regular physical activity as determinants in the onset of SAH or even in the attenuation of various symptoms is vital. However, few studies have studied this relationship in the adolescent population.

Thus, this review article aims to analyze what the literature brings about these analyses.

2. Methods

2.1 Systematic Review Strategies

The systematic review was carried out to demonstrate the results of the studies found that had some relation with the theme. For the eligible scientific articles, the search in the literature was performed in the Pubmed and Scielo databases. The research was limited to articles written in English in the last ten years, i.e., articles published between January 2002 and
January 2023. We use the following descriptors to search: ACE I/D polymorphism; Hypertension; Physical activity.

The studies included in this review were selected based on the inclusion and exclusion criteria evidenced in Figure 1.

Figure 1: Flow diagram of research strategy and study selection

![Flow diagram of research strategy and study selection]

Source: Own authorship
2.2 Study Selection Criteria

We examined the titles and abstracts of all the articles found in the bibliographic research to include all studies investigating the specific theme of the correlation between ACE polymorphism, level of physical activity, and risk of developing SAH. So that for better characterization of the included studies, main tests, and the results found in each, the data were organized and presented in table form.

3. Results

Seventeen thousand one hundred twenty-six studies were identified through a systematic review of the literature that excluded several articles not related to the subject. Seven studies were selected to make this study, which is characterized in table 1. The main results of the studies included in this review are shown in table 2.

Table 1- Study characteristics and patients

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study type</th>
<th>Sample</th>
<th>Age (Years old)</th>
<th>Study objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETKEVICIENE, et al. (2014)</td>
<td>Cohort study</td>
<td>Adolescents and adults (n=507)</td>
<td>12</td>
<td>Examine the independent effects of physical, behavioral, and genetic factors identified in childhood and middle age for the prediction of hypertension in adults.</td>
</tr>
<tr>
<td>FUENTES, et al. (2002)</td>
<td>Longitudinal cohort study</td>
<td>455</td>
<td>25 - 64</td>
<td>To evaluate the association of ACE I/D polymorphism with moderate-intensity self-reported leisure time physical activity (MILTPA), BP and history of hypertension</td>
</tr>
<tr>
<td>Source</td>
<td>Study Type</td>
<td>Participants</td>
<td>Age (Range)</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>KIM, Kijin. (2009)</td>
<td>Cohort study</td>
<td>105 women</td>
<td>38 ± 1</td>
<td>To analyze the association of ACE I/D polymorphism with obesity, cardiovascular risk, and insulin resistance; and the effect of physical exercise on these parameters according to the ACE polymorphism gene.</td>
</tr>
<tr>
<td>MÄESTU et al. (2013)</td>
<td>Cohort study</td>
<td>261 boys</td>
<td>12,04 ± 0,77</td>
<td>Investigate associations between ACE I/D polymorphism and different physical activity levels in healthy boys at the beginning of puberty.</td>
</tr>
<tr>
<td>ROLTSCH et al. (2005)</td>
<td>Cohort study</td>
<td>77 women</td>
<td>18 – 35</td>
<td>To evaluate the relationships of the ACE genotype with cardiovascular parameters during submaximal and maximum exercise in sedentary and trained young women.</td>
</tr>
<tr>
<td>WINNICK I et al. (2004)</td>
<td>Cohort study</td>
<td>355</td>
<td>18 – 45</td>
<td>Investigate the association between ACE I/D polymorphism and physical activity level.</td>
</tr>
</tbody>
</table>

Source: Own authorship
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Materials and Methods</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETKEVICIEN E et al. (2014)</td>
<td>BP, BMI, 24-hour recall.</td>
<td>- The significant predictors of hypertension in adult men were SBP and DBP in childhood, BMI gain from childhood to adulthood, and high alcohol consumption. - In women, the genetic risk score and DBP in childhood and BMI gain were significant predictors of hypertension in adulthood.</td>
</tr>
<tr>
<td>FUENTES et al. (2002)</td>
<td>The socioeconomic questionnaire, health status, lifestyle; blood test; BMI; BP. Serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides and DNA.</td>
<td>- The main predictors of BP were male gender, age, BMI, and arterial pulse. - ACE and MILTPA (moderate-intensity leisure-time physical activity) were associated with SAH; - No association between ACE and physical fitness; - No association between ACE and BP or SAH.</td>
</tr>
<tr>
<td>KIM, Kijin. (2009)</td>
<td>Anthropometric measurements (BMI); BP; Lipidogram; Exercise (12 weeks); carotid measurement. DNA; Glucose, Total Cholesterol, Insulin, Fibrinogen, Leptin.</td>
<td>- Tendency to the association of ACE with SAH but not obesity. - Indicative of higher cardiovascular risk for DD subjects - Attenuated response to an exercise intervention on the thickness of the Intima media thickness of the carotid artery in DD individuals.</td>
</tr>
<tr>
<td>MAEST et al. (2013)</td>
<td>Anthropometric measurements; Cardiovascular evaluation; Level of physical activity. DNA</td>
<td>ACE I/D polymorphism is associated with different physical activity levels in healthy boys.</td>
</tr>
<tr>
<td>ROLTSCH et al. (2005)</td>
<td>Anthropometric measurements. DNA</td>
<td>ACE I/D Polymorphism is not associated with normal levels of BP, submaximal or maximum physical exercise, and cardiovascular hemodynamics in young women.</td>
</tr>
<tr>
<td>WINNI CKI et al.</td>
<td>Clinical evaluation; Anthropometric measurements; 24-hour BP. DNA</td>
<td>ACE I/D polymorphism may be a specific genetic factor associated with physical activity levels in borderline and mild hypertensive individuals.</td>
</tr>
<tr>
<td>WONG et al. (2012)</td>
<td>Anthropometric measurements; IPAQ DNA</td>
<td>- ACE I/D polymorphism is significantly associated with the self-reported level of physical activity in normotensive Chinese and Singaporeans. - Individuals with DD or ID genotypes were more likely to report an insufficient or low level of physical activity than those with genotypes II.</td>
</tr>
</tbody>
</table>

Source: Own authorship
4. Discussion

SAH is the multi-factorial clinical condition characterized by sustained elevation of BP levels, both Systolic Blood Pressure (SBP) and diastolic blood pressure (DBP), where it is often associated with metabolic disorders, functional and/or structural alterations of target organs, being aggravated by the presence of other risk factors, such as dyslipidemia, abdominal obesity, glucose intolerance, and Diabetes Mellitus (DM) [16, 17].

SAH is also asymptomatic in adolescents, where early diagnosis and treatment in childhood are essential. Left untreated, SAH has serious health consequences at this stage, including organ damage since childhood and increased risk of cardiovascular disease, stroke, kidney disease, and the proper development of hypertension in adulthood [18].

The study by Petkeviciene (2014), who studied a population for 35 years, showed that SBP and DBP during childhood were associated with body weight, higher in overweight people. This study showed that over 35 years, the prevalence of SAH increased when related to the high increase in BMI [19].

And this study by Petkeviciene et al. corroborates with several others that indicate the increased prevalence of SAH in obese children, as well as data from the National Health and Nutrition Examination Survey conducted between 1963 and 2002, clearly presenting this relationship between BP increase in children proportionally to the rise in childhood obesity [20].

Petkeviciene et al. also showed that physical activity did not influence the results, as there was no difference in the level of physical activity in hypertensive and non-hypertensive patients. It is worth mentioning that walking was the most performed activity in both groups.

Concerning the genetic component, a relationship with women was observed. Similar to the study by O'Donnell (1998), which also has genetic
influence related to sex, but in the latter, the negative impact was more in males than in females [21].

In Fuentes' study, the population studied was middle-aged, and no relationship was found between ACE I/D polymorphism with BP or even SAH. And physical activity shows an inversely proportional relationship with BP and SAH, going against the literature [22].

Kim (2009) sought to analyze the association of ACE I/D polymorphism with obesity and did not find this relationship. Still, he did not find a strong relationship between ACE gene polymorphism and BP. The author has found a solid tendency to associate ACE with SAH. He indicated a higher cardiovascular risk for DD homozygous individuals, the study by Avila-Vanzzini (2015), with more significant influence in men than on women [23, 24].

In Kim's study, physical exercise was used as an intervention. The effect on carotid artery thickness was analyzed, demonstrating an increase in thickness in DD individuals even after the intervention, indicating an attenuated action of exercise due to DD polymorphism.

Mäestu (2013) investigated the association between ACE I/D polymorphism and different physical activity levels. It was observed that the level of physical activity was higher in homozygous DD children than in II. There was no relationship between ACE gene polymorphism and physical activity and SAH [25]. And this result also goes in line with studies that show the presence of at least one ACE D allele about the significantly better functional performance after exposure to greater physical activity interventions than the presence of allele I [26].

Despite these results, other studies have not observed significant differences in the relationship between the level of physical activity when relating to ACE I/D polymorphism [27]. So further studies still need to be conducted to demonstrate the mechanism by which ACE influences physical
activity. There is still no consensus on whether insertion polymorphism (I) or deletion polymorphism (D) would affect cardiometabolic parameters and aerobic capacity.

Roltsch, who evaluated the relationship between ACE and cardiovascular parameters during exercise, observed the non-association between these variables. Unlike the Mäestu study, the maximum VO2 was higher in the trained population, regardless of genotype. Roltsch observed that the trained women of all ACE genotypes had less fat percentage than the sedentary group, without showing a relationship between the level of physical activity and genotype. With cardiovascular variables, in maximal exercise, ACE polymorphism was not related to the blood pressure levels of the population evaluated, which differed in the submaximal physical exercise. The DBP of homozygous women II presented lower than DD [28].

Winnick's study (2004) sought to investigate the association between ACE I/D polymorphism and the level of physical activity. However, in the hypertensive population, it concluded that there might be this association in borderline and mild hypertensive individuals. The active individuals had mostly the sedentary ACE genotype II [29]. It differs from the studies mentioned above, but the population is also different because they are hypertensive.

Wong's (2012) study, which also sought to determine the association between ACE I/D polymorphism and physical activity levels, observed that there was an association in which individuals with DD and ID genotypes reported lower levels of physical activity when compared to individuals II, which is in line with Winnick's study, even though they were different populations because, in Wong's study, the population was normotensive [30].

We observed when confronting these studies that within the genetic variables related to SAH, we have the ACE I/D polymorphism, which can
influence the expression and production of regulatory components present in the endocrine system. Such as the renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the pathogenesis of essential hypertension [31].

Given this, the literature shows that this polymorphism can increase the chances of developing SAH [6, 32]. Being an essential genetic variant for the alteration of cardiovascular physiological function [15]. In individuals who have a higher amount of DD angiotensin, which can lead to changes in various mechanisms, such as autonomic dysfunction and endothelial function, contributing to arterial hypertension [33] and other cardiovascular diseases [14].

These data are in agreement with studies such as Park et al. (2009) and Guney et al. (2013), which analyzed the genotype of the polymorphism of the ACE gene with SAH in adolescents between 16 and 17 years of age, observed that the D allele has a higher amount of ACE at the cardiac level in hypertensive adolescents [14, 34].

This specific population of adolescents has required increasing study interest in SAH. Mainly due to prevalence has increased in the last decade to the influence of several factors such as lifestyle and the genetic component itself (MATOSSIAN, 2018), such as the polymorphism of ACE gene, which we find scarce in this relationship with this population.

When we talk about the lifestyle of the adolescent population, we talk about sedentary behavior that was already increasing and that with the pandemic of SARS-CoV2 increased considerably, generating equal concern about this risk factor for SAH and the genetic influence in this behavior.

In this sense, regarding this relationship of physical activity and the genetic component, more precisely the ACE I/D polymorphism that is the object of study of this review, the studies reported here have confronted
aspects of in some cases in which the hypertensive population had a higher genotype II as well as a higher level of physical activity.

It is crucial to observe this aspect because the literature presents the presence of ACE genotype II as a possible predictor of higher physical performance because of having higher levels of cininins that consequently would increase blood flow and the supply of oxygen, substrates, and glucose to the muscles [35, 36].

Studies such as Winnick have sought to make this relationship between genetic component and physical activity in a group of mild hypertensive patients, indicating that it is a specific factor associated with physical activity levels, but not yet very well defined. Mainly because of this, other studies did not investigate the effect of the genotype on habitual physical activity and not only on moderate and vigorous activity [37]. Let us then recite Mäestu (2013), who also demonstrated an association between ACE I/D polymorphism and varying physical activity levels.

Therefore, there is still a scarcity of studies on this relationship, and the literature still seeks a better definition for this question.

5. Conclusion

We can conclude in this review article that despite the scarcity of studies that related SAH in adolescence, its relationship as polymorphism of the ACE gene and the regular practice of physical activity. Has been advanced in the consolidation of the DD genotype as the most significant predictor of SAH and sought to increase the consensus of the influence of ACE I/D polymorphism with a predisposition to physical activity and functionality as a SAH attenuator agent.
References


12. de JS Soares-Junior N, Dias-Filho CA, Dias CJ et al. Active Lifestyle can Contribute to Attenuation of Cardiac Autonomic Dysfunction in Adolescent Offspring of Hypertensive Parents. 2019; 22


15. Eleni S, Dimitrios K, Vaya P et al. Angiotensin-I converting enzyme gene and I/D polymorphism distribution in the Greek population and a comparison with other European populations. 2008; 87: 91-93


22. Fuentes RM, Perola M, Nissinen A et al. ACE gene and physical activity, blood pressure, and hypertension: a population study in Finland. 2002; 92: 2508-2512


3963

Revista Contemporânea, v. 4, n. 1, 2024. ISSN 2447-0961

27. Goleva-Fjellet S, Bjurholt AM, Kure EH et al. Distribution of allele frequencies for genes associated with physical activity and/or physical capacity in a homogenous Norwegian cohort-a cross-sectional study. 2020; 21: 1-11


33. Harrap SB, Davidson HR, Connor JM et al. The angiotensin I converting enzyme gene and predisposition to high blood pressure. 1993; 21: 455-460


37. Nader PR, Bradley RH, Houts RM et al. Moderate-to-vigorous physical activity from ages 9 to 15 years. 2008; 300: 295-305