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Regular exercise in adolescents with ACE gene polymorphism helps preventing cardiovascular risk factors

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ABSTRACT

Introduction: Polymorphisms can influence the expression and production of regulatory components in the endocrine system. These include the renin-angiotensin-aldosterone system (RAAS), which plays, along with other environmental factors, a fundamental role in the pathogenesis of essential arterial hypertension in both adults and adolescents. **Objective:** To analyze the influence of the level of physical activity and the polymorphism in the ACE gene on cardiac autonomic modulation and the chance of cardiovascular risk in adolescents. **Methods:** 136 adolescents were divided into active (AG) and sedentary (SG) groups. The genotypic frequencies in SG group are DD (38), DI (12) and II (10); and AG group are DD (38), DI (15) and II (23). Blood pressure, body composition, physical activity level, and sexual maturation were assessed to characterize the groups. Afterward, an electrocardiogram was performed to analyze heart rate variability and oral mucosal cells were collected for the genotypic of angiotensin-converting enzyme. **Results:** The AG presented lower systolic blood pressure and sympathetic modulation when compared to the SG DD. Additionally, the odds ratio for the cardiovascular events was increased in the SG DD compared with that in AG with DD allele (AG DD) adolescents, as verified for the autonomic variables LF%, HF%, LF/HF, and SBP. **Conclusion:** Regular physical activity in adolescents can contribute to the maintenance of blood pressure levels, preventing autonomic imbalance and cardiovascular risk factors in adolescents with ACE gene polymorphism.

Keywords: adolescent; Angiotensin-converting enzyme inhibitors; exercise; Autonomic Nervous System; cardiovascular system.

INTRODUCTION

Understanding the genetic influence on health issues and preventing cardiovascular diseases is paramount. Epidemiological studies have shown that genetic factors influence about 30% to 50% of blood pressure variation[1,2], contributing to hypertension and cardiovascular diseases. Polymorphisms can influence the expression and production of regulatory components in the endocrine system. These include the renin-angiotensin-aldosterone system (RAAS), which plays, along with other environmental factors, a fundamental role in the pathogenesis of essential arterial hypertension in both adults and adolescents[3].

Insertion/Deletion (I/D) angiotensin-converting enzyme (ACE) gene polymorphisms (rs1799752) stand out among these polymorphisms that contribute to unfavorable changes in blood pressure control. Individuals with the D allele display serum and cardiac ACE elevated levels. Thus, the ACE gene polymorphism is a genetic variant that can alter cardiovascular physiological function in individuals with a higher amount of angiotensin II[4]. This condition can increase the chances of developing cardiovascular diseases due to changes in several mechanisms such as electrolyte and endothelial imbalance, autonomic dysfunction, and decreased heart rate variability (HRV)[5].

Studies showed that HRV impairment is an independent predictor of cardiovascular disease and mortality[6,7]. Additionally, HRV can be influenced by factors such as general and abdominal obesity, higher blood pressure, and physical inactivity in different populations[8,9]. These risk factors may occur as early as childhood, as shown by the study[10], and may be influenced by genetic factors[11].

Additionally, a sedentary lifestyle strongly contributes to all risk factors and is increasingly present in adolescents[12]. Given this fact, identifying autonomic dysfunctions in adolescents with ACE polymorphism becomes relevant, as their cardiac autonomic modulation may be altered even before the development of cardiovascular diseases. Regular physical exercises can protect against these comorbidities[13]. However, few studies have studied the impact of polymorphism on the ACE gene (rs1799752) and the level of physical activity on autonomic dysfunction in adolescents.

Thus, this study aimed to analyze the influence of the level of physical activity and the polymorphism of the ACE gene (rs1799752) on cardiac autonomic modulation and cardiovascular risk in adolescents.

METHODS

Sample collection

This analytical and cross-sectional study included adolescents of both sexes, aged between 11 and 18, from a state public school. The study included 136 adolescents (47 boys and 89 girls), which was divided into an active group (GA), composed of 76 individuals, and a sedentary group (GS), consisting of 60 individuals. The samples were classified into one of the three genotypes resulting from the ACE gene's polymorphism: two homozygous (DD and II) and one heterozygous (ID) genotype.

Students of the selected age group were invited to participate in the study upon furnishing the informed consent form (ICF) signed by the parents or guardians, which authorized their participation and starting data collection in September 2018 in the city of São Luís-MA, Brazil. This study followed the recommendations of the Helsinki Declaration and Resolution No. 466/2012 of the National Health Council of the Brazilian Ministry of Health. It was approved by the Permanent Ethics Committee in Research Involving Human Beings of the Federal University of Maranhão (2,673,791).

The following exclusion criteria were used for the study sample: participants who did not attend all the study visits, those who presented any pathophysiological changes during the study, and those undergoing pregnancy or lactation. The data was collected during a single session on the scheduled days.

Collection of oral mucosal cells

Exfoliated oral mucosal cells were obtained from the participants by gently brushing the buccal mucosa and buccal groove using a sterile swab. The collected cells were then stored at –20 C° until DNA isolation.

Clinical assessment and body composition analysis

An anthropometric evaluation was performed with the participant in the orthostatic position. The weight was measured using a Balmak digital scale (kg), while the height was measured using a compact stadiometer, type EST 23 (in mm). A trained professional performed all the measurements according to NHBLI[14].

The bioelectrical impedance method (BIA) was carried out with the Maltron device, model BF906 (Maltron; Essex, UK), tetrapolar, 50 kHz. The procedure was performed during the morning after fasting for 10-12 hours in a supine position. The electrodes were placed on the dorsal surfaces of the right hands and feet, close to the metacarpophalangeal and metatarsophalangeal joints and medially between the distal prominences of the radius and ulna, between the tibial and fibular malleolus. Resistance was obtained and fat-free mass (FFM) was calculated using the equations proposed by Houtkooper et al.[15].

Evaluation of sexual maturation

For the evaluation of sexual maturation, the criteria used by Tanner were adopted[16]. It is a self-evaluation method using images, considering the development of breasts in girls, penis in boys, and hair on genitals in both genders.

Subsequently, the individuals were classified into one of the following five stages: 1st stage: Indicates that the individual is still in childhood (pre-pubertal), 2nd stage: Represents the beginning of the maturational period, 3rd and 4th stages: Shows the continuity of the maturation process, 5th stage: Indicates that the individual is a complete adult.

Measurement of blood pressure

The protocol for blood pressure measurement (Omron® HEM-711 and Omron® 905) followed the norms of the Brazilian Guideline of Hypertension[2] and the IV Report on the Diagnosis, Evaluation, and Treatment of Hypertension in Children and Adolescents[17]. An optimal cuff size was used according to the arm size of the participants.

Assessment of the heart rate variability

The HRV data were obtained in a supine position with spontaneous breathing. The time series of HR was acquired (Micromed Biotecnologia, WinCardio) by determining the RR interval with a 12-lead electrocardiogram, 1000 Hz sample rate, during 10 min and was analyzed in the time domain through the analysis of standard deviation of the range of regular beats (SDNN) and root-mean-square differences of successive R-R intervals (RMSSD). After visual inspection, the series of RR intervals was made by tuning the frequency cubic spline interpolation (fi=250 Hz) and reducing the number of dots per decimation (18 times).

Then each beat was identified using the algorithm by Matlab™ program (Welch's method) that generates the result of spectral analysis with the respective bands of interest (HF, high-frequency: 0.4 to 0.15 Hz; LF, low-frequency: 0.15 to 0.04 Hz). Normalized LF and HF components of R–R variability were considered markers of cardiac sympathetic and parasympathetic modulation, and the ratio between them (LF/HF) was considered an index of the heart's autonomic modulation[18]. The results were expressed in absolute values (HF ms^2 and LF ms^2) and percentages (HF% and LF%).

Physical Activity Level Assessment

The physical activity level was analyzed using the International Physical Activity Questionnaire (IPAQ). The data were converted into METS (Metabolic Equivalent of Task) for better visualization. The IPAQ allows the evaluation of the physical activity conducted by the individual during the previous week, classifying it as high (greater than 1500 MET-min/week) vs. low levels of physical activity (less than 600 MET-min/week)[19].

DNA Extraction and PCR

The DNA extraction from the oral mucosa cells was conducted using the Axyprep™ Mailsource Genomic DNA Miniprep Kit (Axygen Scientific - USA), following the manufacturer's instructions. The DNA was quantified, and subsequently, the DNA fragment containing the polymorphic site I/D of the ACE gene was sequenced using polymerase chain reaction (PCR). The primers used in this PCR allowed the amplification of sequences with 190 base pairs (bp) for the DD genotype and 490 bp for the II genotype. Used the sequences hECAf (5′-CTG GAG ACC ACT CCC ATC CTT TCT-3′) and hECAr (5′-GAT GTG GCC ATC ACA TTC GTC AGA T -3′). The presence of both fragments served to identify the heterozygotes (ID).

PCR was performed in a final reaction mixture of 12 µL volume, comprising 6 µL of Go Taq (Promega, cat. No. M7122), 0.06 µL of primers (hECAr e hECAf), 1 µL of DNA, and 5 µL of ultrapure water. The reaction conditions in the thermocycler alternated between temperatures of 95.55 °C and 75 °C, following: 5 min at 95 °C, 40 cycles of 10 s at 95 °C, 10 s at 58 °C, 20 s at 72°C, and 5 min at 72 °C. The steps in this protocol promoted denaturation of the DNA, annealing the primers to sample DNA strands, and then an extension of the DNA strands, respectively.

The PCR products were separated into 1% agarose gel, using 6 µL of the sample and 490 bp and 190 bp markers. The samples were run for 1 h 40 min at 80V. Afterward, the samples were stained with ethidium bromide (40 min), and electrophoresis was performed at 100V. The fragments were subsequently observed under ultraviolet light. The samples were classified into one of the three genotypes resulting from the polymorphism of the ACE gene: two homozygous (DD and II) genotypes and one heterozygous (ID) genotype.

To increase the specificity of the genotyping, the samples that presented the DD genotype were re-evaluated by a second PCR, using a specific primer for the incorporation were used the sequences: sense (5' TGG GAC CAC AGC GCC CGC CAC TAC-3'), hECAf, and anti-sense (5'-TCG CCA GCC CTA CCA TGC CCA TAA -3'), hECAr.

Statistical analysis

Data were subjected to the Kolmogorov-Smirnov normality test. To analyze the differences between the groups, t-tests, and two-way ANOVA with Bonferroni post-hoc test were used. The chi-squared test was performed to evaluate the association between qualitative variables and the Hardy-Weinberg balance. The level of significance was established at $p<0.05$. Data is represented as mean ± standard error of the mean. Statistica® 5.0 software was used for data analysis.

RESULTS

The study included 136 adolescents (47 boys and 89 girls), with an average age of 14. The sedentary group (SG) consisted of 60 individuals, 23 boys, and 37 girls, and the active group (AG) was composed of 76 individuals, 24 boys and 52 girls. The statistical

analysis did not reveal significant differences related to sex, indicating that the groups were homogeneous.

The Hardy-Weinberg balance was calculated, and the data were distributed in the frequency of the D alleles (n=88 /73.3%) and (n=91 / 59.8%) and I (n=32 / 26.7%) and (n=61 / 40.1%) between the SG and AG groups, respectively, based on the Chi-squared test (χ^2=3.37 and p-value 0.66). The DD genotypes (n=38) in both groups, DI (n=12) and (n=15), and II (n=10) and (n=23) between the SG and AG groups, respectively, based on the Chi-squared test (χ^2=3.62 and p-value 0.16). There was no difference in distribution frequency after a Fisher's test and demonstrating a balance in the observed sample (Table 1).

For the division of sexual maturation between tanner stages, there were no differences in distribution between groups. With the following distribution of internships: 1: n=5 (5.29%) and n=7 (6.71%), 2: n=15 (14.12%) and n=17 (17.88%), 3: n= 30 (34.41%) and n= 48 (43.59%), n= 4: 10 (6.18%) and n=4 (7.82%) between the SG and AG groups, respectively, based on the Chi-squared test (χ^2=5.37 and p-value 0.14) (Table 2).

Table 3 shows the body composition, Age (years), Weight (kg), Height (cm), BMI (kg/cm²), WC (cm), heart rate, SBP, and DBP of the SG and AG groups. Each group was divided into three subgroups, considering Alleles D and I. Reduced values of SBP were observed in AG-DD compared to SG-DD and SG-DI. HR values were reduced in AG-DD as compared with SG-DI.

In Table 4 of the autonomic evaluation, in time-domain, RR (ms), SDNN (ms), RMSSD (ms), SD1(ms), and SD2(ms) nowhere was a difference among the groups. In the frequency domain, the SG group with the DD allele had higher values for sympathetic modulation (LF%); lower values for parasympathetic modulation (% HF%), and higher sympathovagal balance (LF/HF) when compared to the AG group with DD, DI, and II allele.

Table 1: Frequency of the D and I alleles and the genotypes

	SG	AG	χ^2
Allele D	88 (73.3%)	91 (59.8%)	[3.37] 0.66
Allele I	32 (26.7%)	61 (40.1%)	
Genotype DD	38	38	
Genotype DI	12	15	[3.62] 0.16
Genotype II	10	23	

SG: sedentary group; AG: active group; Statistical difference (p<0.05), based on Chi-squared test (χ2).

Table 2: Sexual maturation of adolescents

Sexual maturation	SG (n=74)	AG (n=214)	χ^2
Stage 1	5 (5.29%)	7 (6.71%)	[5.37] 0.14
Stage 2	15 (14.12%)	17 (17.88%)	
Stage 3	30 (34.41%)	48 (43.59%)	
Stage 4	10 (6.18%)	4 (7.82%)	

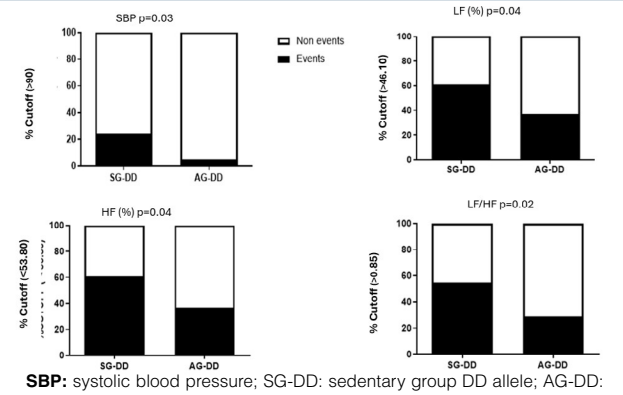
SG: sedentary group; AG: active group.
Statistical difference (p< .05), based on Chi-squared test (χ**2).**

Table 3: Body composition, heart rate, SBP, and DBP of SG divided into genotypic frequencies group

	SG (n=60)			AG (n=76)		
	DD (n=38)	DI (n=12)	II (n=10)	DD (n=38)	DI (n=15)	II (n=23)
Age (Years)	15 ± 1.5	15 ± 1.6	15 ± 1.5	15 ± 1.4	15 ± 1.9	15 ± 2
Weight (kg)	57 ±12	58 ± 14	50± 13	51 ± 8	55 ± 10	54 ± 11
Height (cm)	162 ± 8	161 ± 9	162 ± 11	161 ± 7	157 ± 27	162 ± 11
BMI (kg/cm²)	21 ± 4	21 ± 5	19 ± 2	19 ± 3	21 ± 4	20 ± 2
WC (cm)	71 ± 8	72± 11	67 ± 6	66 ± 5	68 ± 5	69 ± 7
DBP (mmHg)	82 ± 12	89 ± 10	81 ± 12	79 ± 13	77 ± 18	80 ± 14
SBP (mmHg)	114 ± 11	118.5 ± 13	110 ± 15	107 ± 12 * #	113 ± 9	111 ± 2.0
HR (bpm)	67 ± 7	72 ± 10	66 ± 7	64 ± 8 #	67 ± 9	62 ± 6

SG: sedentary group; AG: active group
Waist circumference (WC); BMI: Body Mass Index; HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure (*) comparison between SG vs. AG DD, () comparison between SG DI vs. AG DD with statistical difference p <0.05, two-way ANOVA and Bonferroni posthoc test).

Additionally, when we evaluated the odds ratio for a cardiovascular event to occur in a group, we found that the SG DD has a higher chance of occurrences compared to the AG DD, as verified for the variables LF%, HF%, LF/HF, and SBP (Table 5 and Figure 1).



SBP: systolic blood pressure; SG-DD: sedentary group DD allele; AG-DD: active group DD allele.

Figure 1: Cutoff points for detecting cardiovascular risk factors.

DISCUSSION

This study aimed to analyze the influence of physical activity level and polymorphism in the ACE gene (rs1799752) on cardiac autonomic modulation and cardiovascular risk in adolescents. It is essential to mention that our study was the first to show relationships between the variables of the ACE gene polymorphism

Table 4: Heart rate variability in time and frequency domain divided into genotypic frequencies group

	SG (n=60)			AG (n=76)		
	DD (n=38)	DI (n=12)	II (n=10)	DD (n=38)	DI (n=15)	II (n=23)
Time Domain						
RR (ms)	772 ± 86	735 ± 95	735 ± 111	799 ± 85	778 ± 113	788 ± 122
SDNN (ms)	57 ± 21	45 ± 14	43 ± 14	51 ± 13	49 ± 18	53 ± 16
RMSSD (ms)	55 ± 28	41 ± 17	40 ± 16	51± 23	50 ± 24	55 ± 24
SD1 (ms)	40 ± 19	31 ± 14	32 ± 15	40 ± 12	40 ± 18	40 ± 18
SD2 (ms)	70 ± 25	56 ± 18	56 ± 18	66 ± 11	64 ± 22	65 ± 18
Frequency Domain						
LF (ms^2)	1787 ± 341	552 ± 452	735 ± 644	781 ± 681	660 ± 516	852 ± 663
HF (ms^2)	1240 ± 619	997 ± 358	832 ± 267	1714 ± 426	1658 ± 249	1397 ± 1083
LF (%)	60 ± 14	44 ± 15	49 ± 14	40± 14*	44 ± 20*	41 ± 14*
HF (%)	40 ± 14	56 ± 15	51 ± 14	60 ± 14*	56 ± 20*	59 ± 14*
LF/HF	1.16 ± 0.79	0.96 ± 0.79	1.04 ± 0.70	0.80 ± 0.49*	0.78 ± 0.34*	0.80 ± 0.52*

SG: sedentary group; AG: active group
RR: normal RR interval; SDNN: Standard deviation from the mean of normal RR intervals; RMSSD: Root mean square of the successive differences; LF: low-frequency component in absolut (ms^2) and percentual values (%); HF: high-frequency component; in absolut (ms^2) and percentual values (%); * p <0.05 in SG DD vs AG. two-way ANOVA, Bonferroni posthoc.

Table 5: Cutoff points and indicators for detecting Heart rate variability and systolic blood pressure as cardiovascular risk factors in GS and GA with DD alleles.

	Cutoff	Odds ratio	SG DD	AG DD (events/ nonevents)	95% CI	p-values
SDNN (ms)	< 63.70	0.5128	25/13	30/8	[0.183-1.434]	0.20
RMSSD (ms)	< 49.60	0.8944	23/15	24/14	[0.354-2.251]	0.81
LF (%)	**> 46.10**	**2.6286**	**23/15**	**14/24**	**[1.0412-6.636]**	**0.04**
HF (%)	**< 53.80**	**2.6286**	**23/15**	**14/24**	**[1.0412-6.636]**	**0.04**
LF/HF	**> 0.85**	**3.0321**	**21/17**	**11/27**	**[1.1739-7.831]**	**0.02**
SD1(ms)	< 35.10	1.2346	20/18	18/20	[0.501-3.038]	0.64
SD2(ms)	<84.80	0.6724	26/12	29/9	[0.244-1.852]	0.44
SBP (mmHg)	**> % 90**	**5.5862**	**9/29**	**2/36**	**[1.118-27.901]**	**0.03**

SG: sedentary group; AG: active group
CI: confidence interval; SDNN: Standard deviation from the mean of normal RR intervals; RMSSD: Root means square of the successive differences.
LF: low-frequency component; HF: high-frequency component.
SBP: Systolic blood pressure.

and the physical activity level in adolescents, together with cardiac autonomic modulation and risk of cardiovascular disease.

Thus, the most significant findings of this study demonstrate that the SG DD had higher blood pressure levels accompanied by higher sympathetic modulation and less vagal modulation than GA DD. Also, SG DD has been shown to increase cardiovascular disease risk. This data suggested that regular physical activity provides protective action to physically active individuals even when the ACE gene polymorphism is present.

Studies show that the single D allele of the ACE gene polymorphism is sufficient to increase serum ACE production in individuals with it[20,21]. As a result, individuals with the DD genotype showed twice as much ACE activity as homozygotes II. Individuals with the ID genotype have an intermediate level of ACE activity between groups[22]. Thus, individuals with the DD genotype may be more exposed to higher levels of angiotensin II than those with genotype II.

Thus, the increase in the synthesis of ACE potentiates the increase in sympathetic activity and the systemic vasoconstrictor responses due to greater angiotensin II production and other mechanisms as a decrease in the endothelial signaling pathways triggered by bradykinin, which has vasodilating action, consequently increasing blood pressure[23].

On the other hand, physical exercise may decrease ACE activity, allowing higher blood flow and vascular conductance, which would be beneficial during exercise[24]. Furthermore, physical exercise reduces sympathetic activity and increases the vagal tonus.

Our results also demonstrate that the AG DD had higher vagal modulation values of HF (nu). The reduction in parasympathetic modulation of the SG DD is also implicated in the low values for HF (nu) since the importance of this frequency domain index reflects vagal tone. These values are associated with increased cardiovascular abnormalities due to impaired autonomic function. The association of the ACE DD genotype with the decrease in the HRV high-frequency band leads to an autonomic imbalance, increasing the risk of cardiovascular events[25].

Due to regular physical activity, our study improvement in autonomic modulation is well observed and was consistent with previous investigations. These results show that physical activity stimulates the predominance of parasympathetic modulation and the reduction of cardiac sympathetic modulation, reducing the risk factors for cardiovascular diseases[26]. This is evidenced in our study, where the AG DD, DI, and II groups showed higher vagal modulation accompanied by a reduction in sympathetic modulation compared to the SG DD group. Parallel, there is also a reduction in the sympathovagal balance, in which studies report that the lower this index, the greater the individual's vagal predominance[27].

Studies show that exercise promotes cardiovascular benefits. In the active vs. sedentary comparison, better cardiac autonomic modulation of the active group was also demonstrated, along with reduced SBP and DBP values, proving the effectiveness of physical exercise in improving autonomic modulation[28] and decreases in blood pressure[29] and weight control[30]. However, ACE polymorphism is not explored in these studies. Additionally, our study did not observe any difference in adolescents' weight.

In the association between heart rate variability parameters (HRV) with the duration of leisure-time physical activity in adolescents, it was observed that leisure-time physical activity is associated with better HRV. These associations were improved when adolescents were physically active for more than six months[31].

The relationship between sports practice, school physical education, habitual physical activity, and cardiovascular risk indicators in adolescents observed that sports practice was related to more significant heart rate variability during rest[32]. With this, studies demonstrate that physical exercise, in addition to reducing ACE activity, would reduce the action of Ang II on ANS and can improve baroreflex control[33] by increasing the sensitivity of the aortic depressor nerve, leading to an attenuation of the sympathetic tone[34,35].

Experimental evidence has shown that physical activity effectively reduces RAS activity and improves cardiac autonomic control, reducing the risk of cardiovascular diseases[36].

Our results demonstrated that the odds of developing cardiovascular disease increased after the association of a sedentary lifestyle and DD genotype with indexes in the frequency domain of heart rate variability and systolic blood pressure. This result is evidenced by reduced parasympathetic modulation (HF%) and increased sympathetic modulation (LF%) and SBP.

The results have significant clinical applications since the monitoring of HRV values that discriminate cardiovascular risk in adolescents can help the multidisciplinary health team identify cardiovascular risk through HRV[37]. Considering that the frequency domain parameters are the best cardiovascular risk discriminants in adolescents, monitoring cardiac autonomic modulation in the initial stages of life is emphasized, as it is considered an independent predictor of mortality[6].

Our results also reinforce the importance of regular physical activity in promoting health in young people. According to Zaffalon et al.[38], the sedentary lifestyle associated with genetic factors induces impairment of cardiac autonomic modulation, compromising the quality of life, even before changing any cardiovascular or metabolic clinical parameters.

However, the importance of interpreting these research results is emphasized by some limitations, one of which is using accelerometer sensors in mobile and biochemical marks.

Conclusion

Regular physical activity in adolescents can contribute to maintaining blood pressure levels and preventing autonomic imbalance and cardiovascular risk factors in adolescents with ACE gene polymorphism.

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