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GENE INFLUENCE OF ACTN3 AND NOS3 ON SERUM LEVELS OF NITRIC OXIDE AND ON THE CAROTID CALIBER AFTER ECCENTRIC EXERCISE IN QUILOMBOLAS OVER 50 YEARS OLD

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ABSTRACT

Introduction: There are gaps in the literature related to genetic and hemodynamic influences in the face of the protocols of strength exercise, which hinders the prescription of interventions for health promotion. Objective: To check the gene influence of ACTN3 and NOS3 and the serum levels of nitric oxide on the carotid caliber, post-eccentric exercise, in quilombolas over 50 years old. Methods: This is a quasi-experimental study, performed in a community of Quilombola remnants. The 18 participants were submitted to 10 sets of 10 eccentric repetitions in the extension chair, with 120% of 1RM. Serum levels of the NO and carotid caliber were checked pre- and post-intervention. Mann Whitney was used for comparisons; and Spearman for correlations. 5% alpha was adopted. Results: An increase in serum NO and carotid caliber occurred after exercise (p=0.0001; p=0.021). There was no correlation between serum levels of the NO and carotid caliber (r=-0.23 ; p=0.35). As for the ACTN3 and NOS3 polymorphisms, no statistical differences were observed in the responses induced by eccentric exercise in both parameters (ΔNO = ACTN3 R Homozygous and presence of the X allele (p=0.43); NOS3 T Homozygous and presence of the C allele (p=0.95); Δ carotid caliber = ACTN3 R Homozygous of and presence of the X allele (p=0.41); NOS3 T Homozygous of and presence of the C allele (p=0.52). Conclusion:

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There were no significant variations between serum levels of the NO and carotid caliber for the ACTN3 and NOS3 polymorphisms.

Keywords: Resistance Exercise. Endothelium. Vasodilation. Ethnic Group.

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INTRODUCTION

This study brings relevant information regarding the gene expression of ACTN3, which is a gene that promotes Alpha-actinin-3 in skeletal muscle sarcomeres (1,2), responsible for the morphological structure of the muscle cell, deliberating on the predominance of energy metabolism and magnitude of muscle strength (3,4). Together with the ACTN3 gene, the NOS3 gene was evaluated, responsible for the serum expression of the NO, an important gas for the regulation of endothelial processes in the body (5,6). The whole context of the experimental design occurs through a rare sample (7), living in isolated conditions, with difficult access to the means of transportation and communication, which is the community of Quilombola remnants (8-10 and they have never been submitted to a physical exercise program before, much less to eccentric exercise (11), narrowing the confounding conditions, resulting from adaptations arising from exercise (12). Accordingly, through this context, the gene and hemodynamic responses should be checked, not only to physical exercise, but to every experimental context that exposes the studied variables to aspects inherent to the formation of Quilombola communities (13–16). Thus, the current study has the objective of checking the gene influence of ACTN3 and NOS3 on serum levels of nitric oxide and on the carotid caliber post-eccentric exercise in Quilombolas over 50 years old.

MATERIALS AND METHODS

SAMPLE DESIGN

The current research was conducted in the state of Tocantins and in the Federal District, and it is a study with Quasi experimental design, of randomized field trial with double blind, where the groups were defined after gene sequencing analysis, and the researchers responsible for DNA extraction and biochemical analysis did not have access to the results of body composition evaluation or physical examinations. In turn, the evaluators who performed the clinical and physical examinations, as well as the stressful exercise, did not have access to the biochemical and DNA extraction tests (Fig 1). The study complied with all ethical principles, as stated in opinion nº 1.771.159, issued by the Research Ethics Committee.

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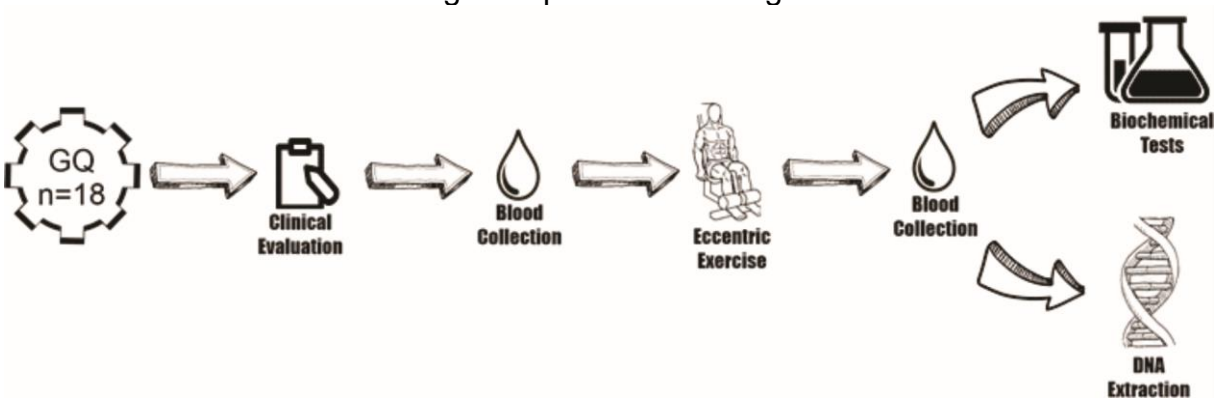
Fig 1. Experimental Design



SAMPLE

The study sample consisted of individuals of both genders, aged 45 years or over, quilombola remnants living in the “Malhadinha” Quilombola Community. As inclusion criteria: being residents of the remaining quilombola communities; having ability to move around without assistance and being physically active according to the International Physical Activity Questionare – IPAQ. Exclusion criteria were: existence of metallic prosthesis; acute painful condition of lower limbs; Central or peripheral nervous system disease; using hormone replacement therapy and/or medications that could interfere with blood pressure levels; having manifestation of cardiovascular disease detected by alteration in blood pressure levels during blood pressure measurement; absence of pulmonary disorder, evaluated according to pulmonary auscultation; having osteomyoarticular problems that could prevent them from performing strength evaluation and strength exercise; not performing any of the study phases. The sample was later stratified, according to the criterion of gene clustering performed by DNA extraction and sequencing by means of the NOS3 and ACTN3 polymorphisms.

PROCEDURES

BODY COMPOSITION EVALUATION

The collection was performed by a qualified professional linked to a laboratory and in the hygienic conditions required by the responsible public agencies. All tubes used are from the Vacutainer brand, while the needles are Greiner Bio-One type, measuring 25X0.8mm, for vacuum blood collection. In order to make the blood comparison, blood was collected before and immediately after the execution of the training session.

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DNA EXTRACTION AND SEQUENCING

Genomic DNA was extracted from 1 ml of whole blood by the salting out method. The genetic variants of the NOS3 and ACTN3 polymorphisms were determined by amplification, using a polymerase chain reaction.

The amplified products from the T-786C locis were hydrolyzed with MspI at 37 °C for 4 hours, which produced fragments of 140 and 40 bp for the wild type allele (T) or 90, 50 and 40 bp for the polymorphic allele (C). The fragments were separated by electrophoresis (12% polyacrylamide gel) and visualized by means of silver staining.

The genotyping of the R577X polymorphism alleles of the ACTN3 gene was performed with a system of two specific primers that provided the sequence where the polymorphism occurs in the gene, in order to amplify them and classify individuals into RR, RX and XX. To this end, the techniques described by Mills, Yang were followed (4).

EVALUATION OF SERUM LEVELS OF NITRIC OXIDE (NO)

The measurement of the NO was performed by the ELISA method (Enzyme-Linked Immunosorbent Assay), according to the specifications of the R&D Systems Quantikine high-sensitivity kit. The intra-assay coefficient of variation (CV) and the sensitivity were determined. In order to perform the detection of nitric oxide (NO2-/NO3-), a nitrite and nitrate concentration determination kit was used with sensitivities of 0.222 µmol/L for NO2 (nitrite) and 0.625 µmol/L for NO3 (nitrate).

ANALYSIS OF CAROTID MORPHOLOGICAL IMAGING

The carotid morphological analyses were obtained by means of a Terason t3000 portable device (Terason, division of Teratech Corporation, USA), with a 12L5 linear model transducer, with a frequency of 5-12 MHz. A conductive gel (Sonic Plus Gel – Hal industry and trade) was used to conduct the sound waves.

The analysis performed by Doppler was with a standard angle of 0º to 60º adjusted according to blood flow. Wall filters have been adjusted so that there is no interference from any artifacts. A color Doppler was used. Parameters such as vessel diameter, peak systolic velocity and resistance index were recorded in each patient's records. The anatomical reference point was 1 cm below the right carotid bulb. Delta analysis of the variation of the area and diameter of the carotid artery between the pre- and post-eccentric exercise moments was performed.

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EVALUATION OF ANTHROPOMETRIC MEASUREMENTS AND BODY COMPOSITION

Body mass was measured with a resolution of 0.1 kg using a digital scale (Filizolla brand). Height was measured with a resolution of 0.1 cm using a stadiometer (CARDIOMED, Brazil). In order to evaluate body composition, the dual energy x-ray absorptiometry (DXA) test was used, equipment from the General Electric-GE brand, with Encore 2013 software.

EVALUATION OF MAXIMUM DYNAMIC AND ISOMETRIC STRENGTH

The maximum strength test (1RM) was performed bilaterally on the extension chair (CybexInternational, Medway, MA). The individuals will be submitted to eight repetitions with 50% of estimated 1RM (according to the capacity of each participant checked in the adaptation session carried out in the previous two days), after a one-minute interval, where three repetitions will be performed with 70% of estimated 1RM. After three minutes, subsequent trials will be performed for one repetition with progressively heavier loads until the 1RM is determined over three trials, using a 3-minute rest between trials. The standardizations of the angulations and movements of the exercises will be conducted according to the descriptions made by Brown et al., (2001)(17). It will be held in order to make sure that the pre-training 1RM will be adjusted before the start of training. The intraclass correlation will be determined between the second and third attempt of the 1RM test. The highest 1RM determined from the last two attempts will be used as the initial measure (18).

As an evaluation of isometric strength, the handgrip test was employed, using a JAMAR palm dynamometer, properly adjusted according to the size of the evaluated individual's hand. Three attempts were performed for each hand, with a 3-minute interval between each attempt. At the end of the 6 repetitions, the highest strength score for each hand was recorded. Relative strength was measured by the ratio between the highest score of the grip strength of the dominant hand and the total body mass (KgF/Kg).

ECCENTRIC TRAINING PROTOCOL

Having possession of the RM of each volunteer, the data was inserted in the application for creating EXCEL spreadsheets, where 120% of 1RM of each individual was calculated. After making this calculation, the training session was started, seven sets with ten repetitions were performed with emphasis on the eccentric phase. In order to make this

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possible, during the concentric phase, the load was lifted by external strenght made by another person; during the eccentric phase, if the volunteer controlled the lowering of the load, an external strenght was also applied with an intent to generate greater damage to the muscles (19).

STATISTICAL ANALYSIS

Statistical analyses were performed with the aid of the SPSS 19 software, which is properly licensed. The homogeneity of allelic frequencies of ACTN3 and NOS3 polymorphisms was checked by means of Levene's test. The results of the numerical variables for the characterization of the sample were expressed as mean and standard deviation, those of the dependent variables related to hemodynamic responses in relation to eccentric exercises were expressed as median ± interquartile range, and the categorical variables were expressed as absolute and/or relative frequencies. Shapiro-Wilk test was used to check the normality distribution of the study variables. As for the correlations between serum levels of the NO and Carotid Caliber, Spearman's test was used. Comparisons between pre- and post-eccentric exercise moments for dependent variables were performed using Wilcoxon test. The current study took into consideration a 5% alpha.

RESULTS

The sample consisted of 18 individuals of both genders (66.7% women), all voluntary Quilombola remnants, without experience with strength training programs. Mean age of 66.00 ± 9.20 years, height of 1.55 ± 0.1 m, total body mass of 63.15 ± 10.28 kg and BMI = 26.26 ± 3.73 kg/m2. The Quilombola volunteers reached 23.56 ± 7.32 KgF of absolute muscle strength on the handgrip and 47.41 ± 12.33 kg of load on the extension chair, making, respectively, 0.37 ± 0.1 KgF/Kg and 0.74 ± 0.13 KgF/Kg of strength relative to total body mass.

Fig 2 represents the expression kinetics of the NO and vasodilator response of carotid diameter, between pre- and post-eccentric exercise, of the 18 Quilombola remnants. The kinetics of the NO was almost tripled at the end of the eccentric exercise. The same behavior occurred in the carotid diameter, with a statistically significant increase ($p<0.05$), but in a lower magnitude.

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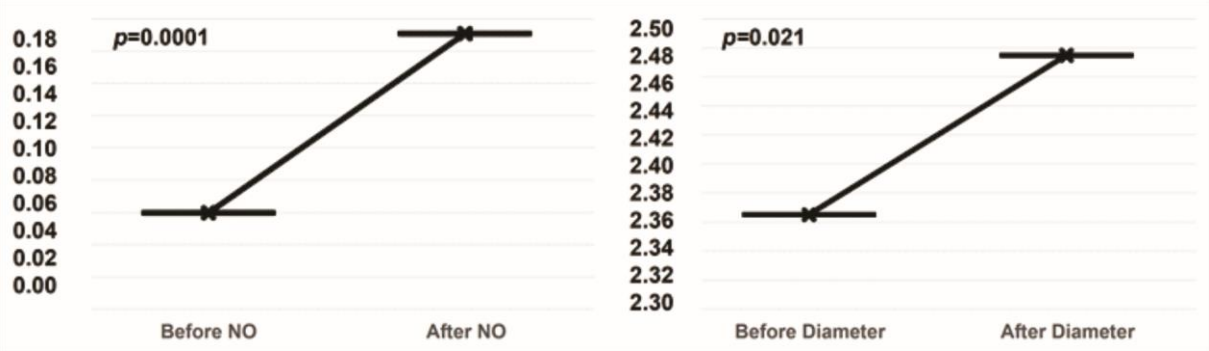
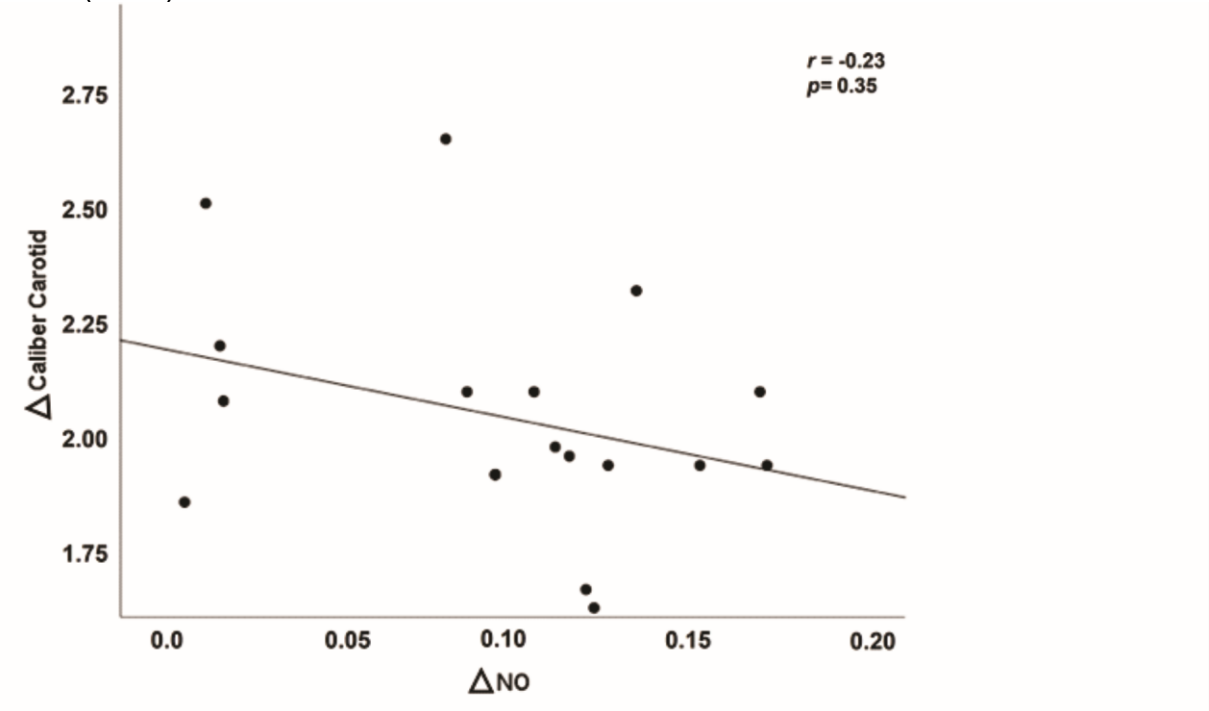
Fig 2. Acute response of the expression of the NO (µmol/L) and carotid diameter (mm) after eccentric exercise (n=18).



A correlational analysis was performed between the variations in serum levels of the NO (µmol/L) and the carotid diameter (mm) post-eccentric exercise, which are expressed in Fig 3. In general, the correlation results proved to be negligible (r<0.3) between carotid vasodilation and production of serum NO, under the condition of physical effort.

Fig 3. Correlation between carotid caliber and serum concentration of nitric oxide after exercise (n=18).



Allelic variations for the ACTN3 and NOS3 polymorphisms showed a pattern of variation similar to the rest of the world population (p>0.05). The stratification according to the ACTN3 and NOS3 polymorphisms are found in Table 1, together with the characteristics of body composition and of age range of each group. The table shows similarities between

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the age ranges of both ACTN3 and NOS3 gene polymorphisms. As for body composition, the NOS3 polymorphisms do not seem to influence this sample, unlike the ACTN3 polymorphisms, where the presence of the X allele has reduced and significant ($p<0.05$) magnitudes in relation to variables related to coronary risk.

Table 1. Characteristics of age range and of body composition according to the ACTN3 and NOS3 polymorphism stratification.

	ACTN3 polymorphism			NOS3 polymorphism		
	Presence of the X allele (n=7)	R Homozygous (n=11)	*p*	Presence of the C allele (n=4)	T Homozygous (n=14)	***p***
Age (years)	70.33±10.8	62.75±6.76	0.11	78.5±0.71	63.92±8.17	0.88
BM (kg)	61.98±10.21	64.03±10.95	0.76	59±6.93	63.84±10.81	0.28
Height (m)	1.57±0.11	1.54±0.1	0.23	1.56±0.23	1.55±0.09	0.51
BMI (kg/m^2)	25.3±3.98	26.99±3.62	0.76	24.8±4.53	26.51±3.76	0.44
WHR	0.97±0.06	0.91±0.05	0.02	0.93±0.06	0.93±0.06	0.80
DAM (kg)	2.38±0.44	2.13±0.74	0.09	2.49±0.41	2.2±0.66	0.90
% FAT	28.6±11.81	41.74±6.43	0.03	27.75±15.77	37.5±10.3	0.30

Legend: BM – Body Mass; BMI – Body Mass Index; WHR – Waist-to-Hip Ratio; DAM - Dominant Arm Mass; % FAT – Fat Percentage.

Regarding the state of muscle strength in groups formed by different allelic configurations of the ACTN3 polymorphisms, the results showed 25.17 ± 7.17 KgF for the group carrying the X allele (n=7) and 23.25 ± 7.54 KgF for the homozygous group of R (n = 11) (p = 0.16) in the handgrip dynamometry of the dominant limb. The same pattern was followed, respectively, for the relative handgrip strength (presence of the X allele = 0.42 ± 0.13 KgF/Kg; R homozygous = 0.36 ± 0.08 KgF/Kg; p = 0 14). As for relative strength of the lower limbs, no statistical differences were also observed between the groups (presence of the X allele = 0.76 ± 0.13 KgF/Kg; R homozygous = 0.70 ± 0.14 KgF/Kg; p = 0.35).

The analysis of muscle strength performance, according to the extratification by different NOS3 polymorphisms, indicated that, for the group carrying the C allele (n = 4), the handgrip strength was 17.00 ± 7.07 KgF. As for the T homozygous group (n=14), the performance shown was 25.25 ± 6.74 KgF (*p* = 0.32). Regarding the performance in relative strength, the groups followed the same previous pattern; however, with relevant

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clinical performance distinctions, where the relative strength was lower in the presence of the C allele (RHGS = 0.30±0.16 KgF/Kg) than in the T homozygote (RHGS = 0.40 ± 0.09 KgF/Kg), but without statistical difference (p>0.05). The evaluation of strength in the lower limbs revealed that the presence of the C allele obtained a score of 0.68 ± 0.07 Kg/Kg and T homozygous = 0.73 ± 0.15 KgF/Kg; (p = 0.99).

The serum levels of the NO and the carotid diameter pre- and post-eccentric exercise are shown in Table 2. The kinetics of the NO in relation to the moments pre- and post-eccentric exercise were significantly (p<0.05) positive for the different ACTN3 polymorphisms; while, for NOS3, only the T homozygote showed a significant increase in serum levels of the NO. There were no statistical differences (p>0.05) in response to exercise between the different polymorphic groups of the ACTN3 and NOS3 genes. Only for the NOS3 gene, static differences (p<0.05) were identified at baseline between the different polymorphisms, where the presence of the C allele showed higher levels of the circulating NO than the T homozygoze. As for carotid diameters, no significant differences were identified with respect to exercise exposure nor with respect to the different polymorphic groups of both genes.

Table 2. Serum levels of nitric oxide and carotid diameters, pre- and post-extension chair exercise with eccentric movement, expressed as median and interquartile range.

	ACTN3 Group			NOS3 Group		
	Presence of the X allele (n=7)	R Homozygous (n=11)	*p*	Presence of the C allele (n=4)	T Homozygous (n=14)	*p*
SNO before (µmole/L)	0.06±0.04$^{\mp}$	0.06±0.01$^{\mp}$	0.17	0.07±0	0.06±0.01$^{\mp}$	0.04
SNO after (µmole/L)	0.17±0.1$^{\mp}$	0.17±0.09$^{\mp}$	0.99	0.17±0	0.17±0,1$^{\mp}$	0.80
Diameter before (mm)	2.42±0.83	2.41±0.49	0.32	2.3±0	2.45±0,47	0.33
Diameter after (mm)	2.5±0.97	2.46±0.37	0.83	2.51±0	2.48±0,37	0.88

Legend: SNO before - Serum Nitric Oxide before intervention; SNO after - Serum Nitric Oxide after intervention. $^{\mp}$ Statistical difference between Pre- and Post-Eccentric Exercise; For statistical differences between different groups of polymorphisms, p ≤ 0.05.

The variations between the serum levels of nitric oxide and the carotid caliber of the different polymorphic groups of ACTN3 and NOS3 are represented in Fig 4. In this, it is observed that all variations both in serum levels of the NO and in carotid caliber were positive, but no static differences (p>0.05) were identified between the different polymorphisms for the ACTN3 and NOS3 genes.

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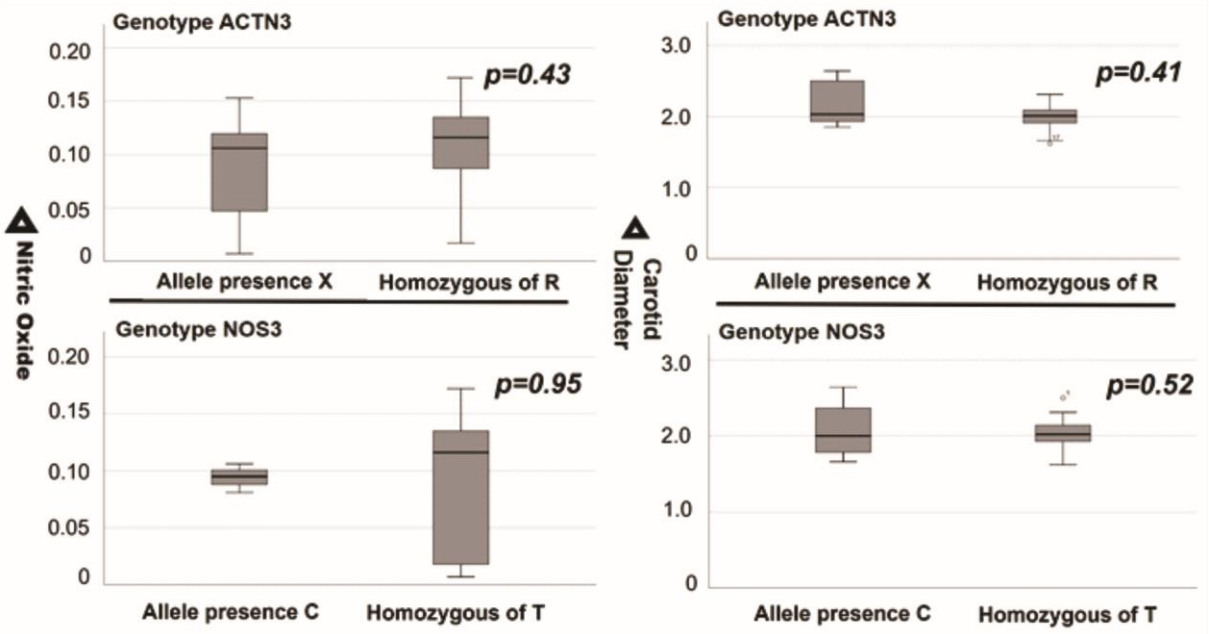
Fig 4. Variations in serum levels of nitric oxide (µmol/l) and carotid diameter (mm) by performing the eccentric exercise.



Legend: ACTN3 Genotype – presence of the X Allele (n=7) and R Homozygous (n=11); NOS3 Genotype – presence of the C allele (n=4) and T Homozygous (n=14).
For statistical differences p≤0.05.

DISCUSSION

In the resting condition, a statistically significant difference was found in the release of serum NO only between gene groups in the presence of the C allele and in T homozygous. Similar results were found in other studies that analyzed the status of the release of serum NO in relation to G894T and T⩾786C promoter genes to evaluate endothelial function(20).

The release of serum nitric oxide is a phenomenon that is observed at different times with different magnitudes in different stages of life, and Casey's group (2015) (21) evaluated the release kinetics of serum NO in different age ranges, identifying peculiarities to each one of them. They were also responsible for raising several questions about the etiology and casuistry of the observed changes, as it has been seen that, since, although the NO is considered by many studies to be only an important vasodilator, other works already indicate it as a precursor of several prophylactic processes linked to senescence or metabolic dysfunctions triggered in the human organism (20,22,23).

By observing the cross-analysis between the NOS3 and ACTN3 promoter genes, it was expected to notice the relationship between their respective gene expressions and the higher production of serum NO, concomitant with the increase in the carotid caliber, as

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mentioned in the study by Eynon and collaborators in 2013 (24). In the study above mentioned, the researchers identified that the higher frequency of the R allele (ACTN3), together with the higher frequency of the T allele (NOS3), would result in higher serum expression of the NO and greater vasodilation of blood vessels. Nevertheless, these results seem to be more linked to the chronic adaptations arising from the training of the athletes participating in the observed studies (27–29), a fact that was not observed in the current study, as it has been seen that, although this sample is composed of Quilombola remnants, a community with rural characteristics and, in turn, with a high level of physical activity (9,25,26), they do not have a history of engaging in sports or physical exercise programs with a high training load.

Furthermore, one could question the efficiency of exercise as a stressful agent to generate changes both in serum levels of the NO and in the change in the caliber of the carotid vessel. Figure 2 shows the significant variations of approximately 0.11 µmol/L in serum levels of the NO (p=0.0001) and 0.11mm in the carotid caliber (*p*=0.021) immediately after exercise. Conversely, when the sample stratified by the ACTN3 and NOS3 polymorphisms is observed, these results are not significant, although they obey the same condition of elevation.

In a study published by WEIHL and GUILDER (2018), the chronic effect of 4 weeks of swimming training with high and low intensity was compared, where it was found that high intensity, although with less training volume, generated greater effects on changes in the endothelium of young female swimmers, as well as O'BRIEN and collaborators (2020) (31), who identified the acute effect of resistance training for the elderly population. Accordingly, when observing the protocols of the studies in question, high training intensities seem to be more effective than high training volumes together with low intensities, in the sense of deliberating on acute and chronic effects on vasodilation.

Even showing that there were changes in the area and diameter of the carotid artery between the pre- and post-eccentric exercise times, it cannot be said that these changes were due to the increased production of this gas, since the correlational test of serum levels of the NO did not identify any correlation with the carotid morphological variables (*r*=0.23; *p*=0.35). These findings were also found in the study published by Casey's group (2015) (32), where a test was performed using a similar protocol and with a sample of individuals consisting of 10 young people and 10 elderly people who performed rhythmic forearm exercises and received doses of inhibitors of nitric oxide; and, even under these

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experimental conditions, they showed vasodilation of the brachial artery, leading to the conclusion that the morphological changes that occurred were not mediated by the NO (33).

In a study directed by Wray and his team (2010) (34), they showed a relationship between NO and vasodilation, when, in their experiment, they used an inhibitor of the NO and noticed that the intra-arterial use of *NG-monomethyl-L-arginine* generated inhibition of vasodilation and blood flow in the highest absolute intensity of strength, compared to the group where the inhibitor of the NO was not used. Therefore, the NO should be interpreted as an important signaling component of vasodilation, and not its precursor, mainly mediated by high intensities of physical exercise.

The study brings important contributions to the understanding of gene relationships in serum levels of the NO and morphological changes in blood vessel caliber, due to the fact that a better understanding of their relationships can identify prescription parameters of physical exercise, in order to generate chronic adaptations that protect the cardiovascular system (35).

According to studies (36-38), coronary heart disease is the world's leading killer. They also point out that black men and women have a rate of systemic arterial hypertension two to four times higher when compared to white men and women (39–41). Although this study did not record any Quilombola remnant with chronic arterial hypertension disease, the ancestry points to the risk for this evil, thus making the experimental design clinically representative and an important prophylactic interventional parameter (40,42,43).

Physical exercise is extremely important for any individual, through it, the biological system undergoes numerous transformations and adaptations that can be acute, that is, immediate, or chronic, which are those that will occur over time. These adaptations can be neurophysiological, metabolic and morphological (44). Numerous studies have been published guaranteeing the importance of physical exercise (45–48), some of them sought to prove the positive effect on improving cognitive function, understood here as the phases of the information process, such as perception, learning, memory, attention, surveillance, reasoning and problem solving (49); in others, possible effects mediated by nitric oxide have been proven (50).

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CONCLUSION

Physical exercise generated an increase in serum levels of the NO for all gene configurations of the ACTN3 polymorphisms, but the same phenomenon was not repeated for the NOS3 polymorphism, where it was significantly responsive only for the homozygosity of the T allele. Even though there were significant changes in serum levels of the NO, the same phenomenon was not observed for morphological measures of vasodilation in carotid arteries.

The evidence found suggests the need for similar interventions that seek to understand the mechanisms of vasodilation not only acutely, but also chronically, as well as to diversify the studied audiences, thus generating a portfolio suitable for the implementation of appropriate programs to check the dose and response of exercise to generate vasodilators.

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PERSPECTIVE

This work seeks not only to contribute to the scientific literature, but also to generate important information about therapeutic alternatives related to a population with a defined stereotype and the presence of diseases in the circulatory system. Thus, the authors seek to generate a theoretical framework capable of assisting in the prescription of physical exercise.

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