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Influence of physical exercise on cognition and polymorphisms of the APOE, ACE and ACTN3 gene in the elderly: A systematic review

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ABSTRACT

The objective of this study was to carry out a theoretical deepening on the influence of physical exercises on cognition and genetic polymorphism in the elderly. This article is a systematic review of studies published between 2017 and 2022 in the following databases: PubMed, Medline, Lilacs, Scopus, SciELO. We searched and selected 10 articles included in this research, in which they tell us about the importance of physical exercises and their influence on cognition and genetic polymorphism in the elderly, thus giving priority to combined strength and aerobic training. However, it is concluded that physical exercises have beneficial effects in elderly people with cognitive impairment and dementia, as well as some genes that influence exercise, thus improving quality of life and a better prescription of specific training for this population.

Keywords: Elderly, Physical exercises, Cognition, Genetic polymorphisms.

INTRODUCTION

Currently, aging has not yet been portrayed naturally by most elderly people; However, most of them are not aware of the importance of physical activity for their lives and especially for the maintenance of health and longevity. According to the IBGE projection (2018), the aging index points to a change in the age structure of the Brazilian population, however, any individual aged 60 years or over is considered elderly, thus having 28 million people in this age group in Brazil, representing 13% of the country's population and may double in the coming decades.

Population aging in poorer and developing countries requires greater attention to the life expectancy of this population, however there are declines in several functional variables of the body, thus decreasing muscle mass, loss of bone mass, increase in body fat, as well as cognitive declines, being factors of impact in the promotion of the lifestyle of the elderly population (PEREIRA; TEIXEIRA; SANTOS, 2012).

As reported by Dantas and Santos (2017), regardless of where the exercises are performed, they characterize many benefits for the elderly population, exemplifying the improvement in blood circulation, muscle strength and improvement in the lubrication of synovial fluid in the joints, thus having better mobility of locomotion, muscle power, balance and motor coordination.

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Body composition refers to relative percentages of body weight consisting of fat and fat-free body tissue; Its evaluation is a common and important component of the assessment of global physical fitness, but it is known that excess body fat is harmful to health. Anthropometry includes measurements of height, weight, and circumference of various body segments and areas (ACSM, 2017).

The improvement in physical fitness, through physical exercises, improves functional capacity, increasing the life expectancy of the elderly who practice regularly, in addition to further delaying the aging process (ABDALA et al., 2017).

When talking about the genome, many doubts arise in most people, man has been conquering in the construction of time a fantastic decipherment in relation to genetics, the applicability of genetic tests is increasingly on the rise to prevent diseases not yet developed, that is, even before having the disease, preventive medicine already begins, this deciphering of humanity's DNA and genetic code is one of the greatest employability studies ever existing.

There are many studies of genetic association of the ACE gene- Angiotensin-Converting Enzyme, which is located on chromosome 17 of the human genome, corresponding to the insertion (I allele) or deletion (D allele) of 287 base pairs in the intron, however individuals carrying deletion on both chromosomes (DD genotype), may have higher plasma ACE activity, compared to other genotypes (TIBANA et al., 2014). ACE converts angiotensin I to II, which are part of the renin-angiotensin-aldosterone system and are responsible for the control of body fluids and especially for the control of blood pressure, thus the variants associated with ACE are associated with a higher percentage of type I fibers than individuals with the DD genotype, and also seem to be associated with a superior performance of muscular endurance, therefore, the DD genotype is associated with short-term and explosive activities (GUTH, L.M.; ROTH, S.M., 2013).

A study of great value cited by Tibana et. al (2014) was carried out by Thomis et al (1998), where they reported that several factors related to genetics were associated with strength training, relating that 20% of the strength found is based on some genes in muscle phenotypes, however a gene that makes a difference in strength gain is the angiotensin-converting enzyme (ACE).

The Alipoprotein E (apoE) gene and its polymorphisms are important risk factors for the development of Alzheimer's disease (AD), the human gene is mapped on the long arm of chromosome 19 (19q13.2), it encodes a glycoprotein with 317 amino acids, thus playing an important role in the catabolism of the triglyceride-rich components of our human body (OJOPI, E.P.B; BERTONCINI, A.B.; DIAS NETO, E., 2004).

In humans, there are 3 alleles of the apoE gene, resulting from only two DNA alterations, called ε2, ε3 and ε4. The identification of the ε4 variant of the apoE gene as the most common genetic risk factor for late-onset AD suggests that cholesterol must play a direct role in the pathogenesis of the disease,

however, the mere presence of the apoE ε4 allele is neither necessary nor sufficient to cause AD; This allele only increases the individual's risk of developing the disease, indicating that there are other important environmental and genetic factors in the development of the disease (OJOPI, E.P.B; BERTONCINI, A.B.; DIAS NETO, E., 2004).

Aging is one of the main risk factors for AD, and there are also other associated factors such as: low schooling and low occupational demand, there is a drastic reduction in physical and mental activities and head trauma, in addition to factors associated with vascular disease including hypercholesterolemia, hypertension, atherosclerosis, coronary artery disease, smoking, obesity and diabetes (FRANCE, 2011).

The ACTN3 gene, called ALPHA ACTININ -3 is associated with the muscle strength and power of our body, this gene encodes a protein present in fast-twitch or type 2 muscle fibers, thus promoting faster muscle contraction, being associated with strength and muscle power exercises. Individuals who have genotypes C/C and C/T tend to have a better response to exercise training that requires muscle strength and power, as an example in short-distance running and explosiveness, in some studies the C allele is represented by the letter "R", and the T allele is represented by "X", in this case, the genotypes are equivalent to: R/R (C/C); R/X (C/T); X/X (T/T),(ALFRED, et.al, 2011).

The production of the ACTN3 protein is done in the musculature of type 2 fibers, which are fast-twitch and potent, however, people who have the "C" allele (C/C and C/T) have the ability to produce this protein, people who have this allele can give priority to weight training and burst runs, However, people who do not have the "C" allele or with the T/T genotype, do not produce the protein for the ACTN3 gene, having a greater predisposition to slow-twitch fibers, with more resistance to fatigue, giving greater emphasis to long-duration sports such as marathons (ALFRED et.al, 2011).

Pereira et al. (2013), investigated the genetic variations of human ACE I/D and ACTN3 R577X polymorphisms and verified improvements in muscle power and functional capacity of 139 elderly women who performed for 12 weeks of training, 3 x per week, vertical jump exercises and medicine ball throwing, thus relating that this program significantly increased the increase in functional/muscular capacity and a significant increase in the polymorphism in the performance indexes thus understanding that the ACE and ACTN3 genotypes exerted beneficial responses to high-speed training.

OBJECTIVE

With the significant increase in the number of elderly people in the world, and the prevalence of chronic-degenerative diseases and cognitive problems, the present review study will seek to associate the influence of physical exercise on cognition and polymorphisms of the Apoe, Eca and Actn3 genes in the elderly.

METHODOLOGY

This research was a systematic review study, carried out using the PRISMA method, relating the following question: What is the influence of physical exercises on cognition and polymorphisms of the Apoe, ACE and Actn3 genes in the elderly? All selected articles should be based on articles published between 2012 and 2022 in the following electronic databases: PubMed Medline-Library of Medicine, Lilacs-Latin American and Caribbean Center on Health Sciences Information, SciELO-Scientific Electronic Library Online, and Scopus. The search was carried out in November 2022, using the following keywords: elderly, physical exercises, cognition, genetic polymorphism and their respective synonyms, in Portuguese and English. There were reasons for excluding some articles from the titles and not being related to the objective of this systematic study, so articles with elderly people aged 60 years or older that addressed the theme of physical exercises and genetic polymorphism were also selected.

In the searches for the articles, a total of 3,810 articles were initially identified, however, all those that did not contain titles similar to the study carried out here were excluded, as well as with the help of the Mendeley Software, 107 articles were selected for the reading of the abstracts and soon after, 43 articles were selected to end with the reading of them. A total of 10 articles were viable, where those that did not answer the question of the present study and the review were excluded. The selected articles are from studies from countries such as: Spain, Brazil, South Korea, Taiwan, United States.

DEVELOPMENT

The literature tells us that physical exercises are effective in improving muscle response, taking into account the genetic polymorphism of each individual studied, however, it is worth reading this work to better understand how the body of an elderly individual relates to tests that show the improvement of power, muscle mass, cognition among other associated factors. Muscle mass, as well as strength, are aspects that are performed of great importance for daily and motor tasks, giving more quality of life, longevity and health to perform the sports part, however several studies have reported a drop in the risk of increased chronic-degenerative diseases, in addition to early death and decreased motor skills in the elderly.

Chart 1 below presents a summary of the articles that make up this review, highlighting: author(s)/year, title, type of study, collection tool, location/sample, main findings related to physical exercises, and genetic polymorphism.

Table 1. Summary of the articles selected in the systematic review

Author(s) Year	Type of Study	Collection Tool	Location/ Sample	Main findings in E.g. Physics and Genetic Polymorphism
Salles et. al. 2022	Transverse	ACTN-3 gene polymorphism in functional fitness (measured by the Senior Fit test) and cognitive ability (assessed by the Stroop test) of the elderly (*n= 347), both men and* women.	Alto Tietê, state of São Paulo/recruited 347 individuals aged 60 years or older, of both sexes,	The genotypic distribution of the ACTN3 R557X polymorphisms was 110 (31%) for the RR genotype, 148 (42%) for the RX genotype and 89 (25%) for the XX genotype. Nutritional variables and schooling also showed no significant difference between the genotypes studied.
Blanco et. al. 2020	Transverse	Tests adapted from the Senior Fitness Test. The genotyping of the polymorphisms was obtained from the DNA of the participants by means of buccal swabs.	300 non-institutionalized elderly women from six regions of Spain, all over 60 years of age.	The analysis of *the ACE* polymorphism revealed no differences between the genotypes. The analysis of the *R577X* polymorphism showed a favorable effect for the *ACTN3 XX* genotype in leg strength tests (p:0.001) after training, in relation to the other genotypes, and also in the analysis of the combined effect of the polymorphism (*ACE II + ACTN3 RX/XX*). The intragroup effect revealed an improvement in arm strength for carriers of the X allele after 24 months of training ($p <$ 0.05). Resistance values worsened significantly in all study groups.

Seok-ki-min et.al. 2016	Transverse	Weight and height and % of fat to height were averaged using an X-Scan Plus body composition analyzer (Jawon Medical, Jawon Medical, Jawon Medical, Jawon Medical, Jawon Medical, Jawon Medical, VO2 max was measured in cycle ergometer. DNA extracted through PCR.	Sixty-eight elderly women (67.38 ± 3.68 years) were recruited from a Seongbuk-Gu Medical Services Public Health Center (Seoul, Korea).	The present study is the first of its kind to investigate the associations between ACTN3 genotypes and BMD and physical fitness in elderly women. The main finding of the study was the presence of associations of BMDs of the pelvic trunk and spine and BMC of the arms with the ACTN3 polymorphism.
Araque et.al.2021	Transverse	Anthropometric data, chronic diseases, prescribed medications, quality of life, handgrip strength, physical activity, and nutritional status were collected.	The associations of *the ACTN3 R577 polymorphism* with quality of life and muscle strength in an elderly Spanish population were correlated. A total sample of 281 older adults participated in this study.	Evidence of gender-specific associations of the ACTN3 R577X polymorphism with muscle strength, quality of life, and morbidity in the elderly population was found, the results support the hypothesis that a lack of alpha-actinin-3 may cause a more rapid decrease in muscle function with increasing age.
Colovati *et.al.* 2021	Bibliographic Research	Analysis of articles that verified the effects of physical exercise on cognitive function in carriers of the APOEε4 allele, particularly in AD patients.	A total of 1,548 articles were found, of which 828 articles were excluded by title and 664 were excluded by abstract, leaving 56 for the study.	The influence of physical exercise on cognitive function in carriers of the APOE ε4 allele showed that carriers of the ε4 allele for the APOE gene were more responsive to the beneficial effects of physical exercise on cognitive function compared to non-carriers, so studies with larger samples will provide more precision on this relationship.

Freire et.al. 2015	Transverse	The association of ACE I/D polymorphism and hemodynamic response (BP), heart rate (HR) and rate-pressure product (RPP)) to resistance exercise in healthy young people was investigated.	ACE I/D polymorphisms were studied by PCR analysis in 75 healthy men from Bahia, Brazil.	Patients with ACE DCS have greater cardiac work during resistance exercise, and some future studies should focus on the influence of the resistance training period with different workloads on the hemodynamic response in healthy individuals with different ACE genotypes.
Zhou et. al. 2022	Transverse	The effects of high-intensity aquatic acute intermittent jumping (HIIJ) on blood pressure (BP) and arterial stiffness in postmenopausal women with different angiotensin-converting enzyme (ACE) genotypes were investigated.	The study included 12 postmenopausal women with the ACE deletion/deletion (DD) genotype and 61 with the insertion/insertion or insertion/deletion (II/ID) genotype. Location: Taiwan.	Postmenopausal women with the DD genotype have a greater increase in post-exercise SBP than those with genotype II/ID, These findings suggest that the aquatic exercise program has better effects on lowering blood pressure in postmenopausal women with genotype II/ID.
Izzicupo et.al.2013	Transverse	The study investigated the effects of walking training on adrenal steroid and cytokine levels and cardiovascular parameters in postmenopausal women with ACE I/D genotypes.	Thirty-six sedentary postmenopausal women participated in a 13-week program of moderate-intensity walking training.	The ACE I/D polymorphism is linked to different levels of adrenal steroids and cytokines, and ACE I allele carriers showed better adrenal activity and systemic inflammatory profile, however walking training positively influences menopausal immunoneuroendocrine changes, regardless of ACE I/D genotype.

Dhana et. al.2021	Transverse	A population-based longitudinal epidemiological study of AD and other health conditions among adults aged 65 years was conducted.	3,886 subjects underwent regular clinical and cognitive assessments from 1993 to 2012. 1,269 (32.7%) were APOE* E4 carriers in 3 neighborhoods of Chicago, Illinois.	The etiology of AD is multifactorial, involving genetic and environmental factors. Previous studies have shown that the presence of the ε4 allele of the apolipoprotein E gene (*APOE*E4*) contributes to the development of AD, however other studies have identified several lifestyle factors, including a high-quality diet, physical activity, not smoking, moderate alcohol use, and cognitive activities, that reduce the risk of AD.
Buford et. al. 2014	Transverse	The association of ACE I/D genotypes with changes in physical function among elderly Caucasians was evaluated.	Sample of 283 Caucasian older adults after 12 months of structured multimodal physical activity or health education. Florida/USA.	Exercise improved gait speed by 0.06 ± 0.01 m/s and SPPB score by 0.72 ± 0.16 points among those with at least one D allele (ID/DD carriers), but function did not improve among II carriers.,however ACE I/D genotype plays a role in modulating functional responses to exercise training in the elderly.

Source: Authors (2024)

In the study by Salles et. al. (2022), investigated the effect of the ACTN3 gene polymorphism on functional fitness with the Senior Test Fit tests and evaluated cognitive ability by the Stroop test in 347 elderly men and women in Bahia, Brazil, where they did not find the effect of the genotype on functional fitness, but found a positive effect of the ACTN3 gene polymorphism on executive function, with the presence of the X allele of the ACTN3 gene in the elderly studied, a better performance in the Stroop test with shorter response time was thus correlated, thus demonstrating that the polymorphism of the ACTN3 gene ends up affecting the cognitive function and not the functional function.

Blanco et.al. (2020) reports the effect of two genetic polymorphisms of ACTN3 and ACE, with a sample of 300 elderly women over 60 years of age with a training program over a period of 2 years, where they used the Senior Fitness Test to verify strength tests. Genotyping was obtained by buccal swabs, however ACE analysis did not reveal differences between genotypes, but indicated a difference for the leg

strength test for ACTN3. The combination of ACE and ACTN3 was effective, revealing an improvement in upper limb strength for carriers of the X allele after two years of the training program, however, the authors report that ACTN3 has a very important role in muscle strength, where it provided a positive effect of the X allele in the elderly investigated.

In developing countries, work of this nature is still timid, however, several studies indicate that lifestyle and levels of regular physical activity are the main factors that modify the risk of dementia and cognitive decline. The present study aimed to verify the influence of physical exercise on cognition and polymorphisms of the Apoe, Eca and Actn3 genes in the elderly.

Another study of great relevance was by Seok-Ki-Min et.al. (2016), where they verified the association of the ACTN3 genotype and the relationship with Bone Mineral Density (BMD), with 68 elderly women in a Public Health Center in Seongbuk-Gu (Seoul, Korea). They related muscle strength, muscular endurance, flexibility, agility, balance and VO2 max. For the evaluation of anthropometry they analyzed with Dexa rays and for genotyping of the genes the Taqman approach was used. The results showed differences in BMD for pelvis, trunk and spine between the ACTN3 genotypes, with no significant differences for: head, arms, legs and ribs, thus having a greater tendency of the RR genotype in relation to other genotypes, and there were also no significant differences for physical fitness between the ACTN3 genotypes.

For a systematic review, we also obtained from Colovati et.al.(2021), relating studies on physical exercise and the polymorphism of the APOE gene on cognitive function in patients with Alzheimer's disease (AD). However, they report that it focused on the effect of physical exercise on the cognitive function of the polymorphism of the APOE gene, but these studies were related to the fact that it was related to the cognitive function of the APOE gene polymorphism, but these studies were related to the fact that physical exercise was associated with less neural damage, with improvements in the test for memory scores, obtaining in other studies a failure in the detection of physical exercises in the cognitive improvement of healthy individuals or those with AD (Alzheimer's Disease).

Some studies do not agree with the literature on the effects of physical exercise on cognitive function, however, it improves social interaction and the sense of well-being, thus contributing to a better quality of life for the elderly, however, the influence of physical exercise on cognitive function in carriers of the APOE ε4 allele, tends to demonstrate that these carriers of the APOE allele 4, obtained greater beneficial effects of physical exercise on cognitive function compared to non-carriers.

Freire et. al. (2014), demonstrates in his study the association of ACE polymorphism and hemodynamic response (BP) (HR) and frequency-pressure product to resistance exercise in healthy young people, however he concludes that ACE polymorphism is associated with hemodynamics to resistance

exercise, that healthy individuals with the ACE D allele relate more certain responses, having a phenotypic difference in load, and have greater cardiac work during resistance training.

Some studies suggest that progressive strength training with moderate to high intensity can be performed with tolerance in healthy elderly, thus performing strength increase, regardless of gender, however a combined strength and aerobic training helps the elderly population in the prevention of several degenerative diseases, and the increase of several components of physical fitness. such as the gradual improvement in aerobic and functional capacity.

Dahna et.al.(2021) related population data from 3,886 individuals (Chicago-Illinois) who were surveyed between 1993 and 2012, coming to the conclusion that a healthy lifestyle in cognition, especially among people with a genetic predisposition, will be less vulnerable to cognitive decline as they are aging.

Reports from the study by Buford (2014), which evaluated the association of ACE genotypes I/D, with 283 elderly Caucasians, all with physical alterations who underwent 12 months of multimodal physical activity, where gait speed at normal pace and performance in the physical performance battery were included, however, there was an improvement in exercise and gait speed among individuals who had at least one D allele and no improvement in carriers II, it was concluded that the ACE genotype plays an important role in the functional responses to physical training of the elderly.

According to Izzicupo et.al. (2013), the effects of walking training between cytokine levels and cardiovascular parameters in menopause with ACE genotype, is linked to different levels of adrenal steroids and cytokines, with carriers of ACE allele I having a better adrenal activity, i.e. walking positively influences several immunoneuroendocrine changes in menopause, whether ACE genotype I or D.

Araque el.al (2021) examines the associations of the ACTN3 gene with the relationship between quality of life and muscle strength in the elderly population in Spain. A total of 281 elderly participants in the study were investigated, however, anthropometric data, medications used, chronic diseases, quality of life and physical activity, nutritional status, handgrip strength and genotyping of the ACTN3 gene by the Taqman protocol were collected. The results found in women an association between the ACTN3 genotype and the regression coefficient, while in men there was a significant difference between handgrip and regression coefficient.

Thus, in the context of the above-mentioned framework of studies, we conclude with Zhou et.al. (2022), who refers us to their study that investigated the effects of high-intensity aquatic acute intermittent jumping on blood pressure and arterial stiffness in postmenopausal women with different angiotensin-converting enzyme (ACE) genotypes. The study was carried out in Taiwan, with a sample of 12 postmenopausal women with ACE genotype/deletion (DD) and 61 carriers of the insertion/insertion or insertion/deletion (II/ID) genotype. It is concluded that postmenopausal women with genotype DD

obtained a greater increase in SBP in the post-exercise period, compared to those with genotype II/D, suggesting that aquatic exercises played an improvement in BP reduction in postmenopausal women with genotype II/D. increasing them a better lifestyle, thus relating to health, physical, mental and social well-being, and especially longevity, exceeding expectations of a healthier life, thus inserting new research so that this population has a higher quality of life and health, thus correlating with cognition and genetics.

FINAL THOUGHTS

Considering the data found in this review, it was found that the literature and its various researches on aging, cognition, physical exercises and genetic polymorphism, propose that they are all interconnected through genetic studies, many of them relate that physical exercises cause beneficial effects in relation to genetics, but it is worth noting that future research should be analyzed through other variables such as: To evaluate the gender, social, economic and emotional conditions with different protocols, to relate the current performance of the physical fitness of the elderly population, it will increasingly contribute to the prevention of other risk factors associated with age and if there can be a positive influence of physical exercise.

In this way, it is expected that this work will provide and encourage the practice of physical activities aimed at the public of elderly people, increasing them a better lifestyle, thus relating to health, physical, mental and social well-being, and especially longevity, exceeding expectations with a healthier life, and with more genomic studies to further map the human body and its aging.

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