Association of the Gly482Ser polymorphism of the PGC-1α gene with aerobic performance and muscle strength

Asociación del polimorfismo GLY482SER del gen PGC-1α con el rendimiento aeróbico y la fuerza muscular

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Abstract

Introduction. The peroxisome proliferator-activated receptor coactivator 1-alpha (PGC-1α) gene has a polymorphism known as Gly482Ser that has been associated with aerobic capacity.
Objective. To explore the association of the Gly482Ser polymorphism of the PGC-1α gene with aerobic performance and strength performance in young adults.
Methods. The cross-sectional study cohort comprised 106 participants. The Gly482Ser polymorphism in PGC-1α was ascertained using the RFLP-PCR genotyping technique. Standardized physical evaluations were administered to assess aerobic capacity and muscular strength.
Results. Participants who possess the homozygous Gly482 genotype demonstrated better physical performance assessed by the 6-minute walk test (6MWT), exhibited a reduced heart rate recovery time. Gly482 homozygous men achieved a greater walking distance. Women had a higher oxygen consumption during the Astrand test. No significant differences were observed in the Ruffier index. In terms of muscle strength evaluated through the push-up test, women with the Gly482 genotype were at a disadvantage, while this genotype did not affect hand grip and maximal isometric strength evaluations. For men, no statistically significant differences in muscle strength were observed measured by the hand grip test, the push-up test, or the maximum isometric strength.
Discussion. The results are consistent with previous reports in which the Gly482 allele shows an association with aerobic performance, while the Ser482 allele has been associated with muscle strength and power.
Conclusions. The findings indicate that the Gly482Ser polymorphism of the PGC-1α gene is correlated with variations in physical performance, with the Gly482 genotype demonstrating superior performance in aerobic capacity assessments among young adults.

Keywords

Gly482Ser; aerobic performance; PGC-1α polymorphism; physical performance tests; young adults.

Resumen

Introducción. El gen del coactivador del receptor gamma 1-alfa activado por el proliferador de peroxisomas (PGC-1α) tiene un polimorfismo conocido como Gly482Ser que se ha asociado con la capacidad aeróbica.
Objetivo. Explorar la asociación del polimorfismo Gly482Ser del gen PGC-1α con el rendimiento aeróbico y fuerza en adultos jóvenes.
Métodos. Un estudio de corte transversal comprendió 106 participantes. El polimorfismo Gly482Ser se determinó utilizando la técnica RFLP-PCR. Se administraron evaluaciones físicas estandarizadas para capacidad aeróbica y fuerza muscular.
Resultados. El genotipo homocigoto Gly482 demostró un mejor rendimiento físico evaluado por la prueba de caminata de 6 minutos (6MWT), y una mejor recuperación de frecuencia cardíaca. Los hombres homocigotos Gly482 lograron una mayor distancia de caminata. Las mujeres tuvieron un mayor consumo de oxígeno durante la prueba de Astrand. No se observaron diferencias significativas en el índice de Ruffier. En la fuerza muscular evaluada a través del test de flexiones, las mujeres con el genotipo Gly482 se encontraron en desventaja, sin diferencias en fuerza de agarre manual y fuerza isométrica máxima. Para los hombres, no se observaron diferencias estadísticamente significativas en la fuerza muscular.
Discusión. Los resultados son consistentes con informes previos en los que el alelo Gly482 muestra una asociación con el rendimiento aeróbico, mientras que el alelo Ser482 se ha asociado con la fuerza y potencia muscular.
Conclusiones. El polimorfismo Gly482Ser del gen PGC-1α se asocia con variaciones en el rendimiento físico, en donde el genotipo Gly482 demuestra un rendimiento superior en evaluaciones de capacidad aeróbica entre adultos jóvenes.

Palabras clave

Gly482Ser; rendimiento aeróbico; polimorfismo de PGC-1α; test de rendimiento físico; adultos jóvenes.

Introduction

Physical performance in an individual, whether sedentary or trained, requires multiple physiological adaptations that allow maintaining an optimal metabolism based on the workload and the type of physical demand imposed. Among the most notable adaptations observed in skeletal muscle associated with aerobic performance, they occur at the mitochondrial level, where trained subjects show greater mitochondrial activity and an improvement in the regulatory and coupling properties of the electron transport chain compared to their untrained peers (Popov, 2020). This is associated with an increase in the levels of mitochondrial enzymes involved in fatty acid oxidation, the Krebs cycle, and the electron transport chain, as well as an increase in mitochondrial biogenesis (Eggelbusch et al., 2024), which depends on the activation of genes present in mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) and is stimulated by microenvironmental changes in the cell (Fiorenza et al., 2018). This process may also be regulated in part by changes involving modifications in the nucleotide sequence, such as mutations and polymorphisms, as well as modifications without changes in the nucleotide sequence, such as methylation, histone modification, among others. The presence of polymorphisms has been associated with multiple health and disease conditions, such as body composition (Moraga Muñoz et al., 2021), strength and speed (Arroyo Moya, 2021), musculoskeletal injuries (Silva Fagundes et al., 2024), among others.

The molecular pathways that favor optimal aerobic capacity involve in part the activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key protein in the stimulation of mitochondrial biogenesis (Popov, 2018). PGC-1α is preferentially expressed in tissues with high oxidative capacity, such as the heart, slow skeletal muscle fibers, and brown adipose tissue (Rius-Pérez et al., 2020). Thus, PGC-1α has been described as a "master regulator" of oxidative metabolism and mitochondrial biogenesis (Qian et al., 2024).

The PGC-1α gene presents multiple polymorphisms that can be associated with the expression of a differentiated physical capacity (Steinbacher et al., 2015). Specifically, a single nucleotide polymorphism (SNP) of this gene has been described as the most promising in terms of its association with aerobic capacity, described in the literature as Gly482Ser (rs8192678), at position 1444, which involves a base change of C>T generating a "missense" variant, which causes a change of glycine to serine in the PGC-1α protein (Bailén et al., 2022; Ramos-Lopez, 2024; Wei, 2023).

Through various studies, the Gly482 allele has been shown to be related to greater aerobic capacity and maximal oxygen consumption (VO2Max) compared to the Ser482 allele, which is more common in speed and strength athletes (Konopka et al., 2022). Thus, in two cohorts of European athletes (Russian and Lithuanian) it has been reported that the homozygous Ser482 genotype is more favorable for strength/power athletes (weightlifters) than for controls (Gineviciene et al., 2016). This association has been more consistent in European and Asian populations, showing contradictory results in participants from other geographic locations (Lucia et al., 2005; Maciejewska-Skrendo et al., 2022; Nishida et al., 2015; Vostrikova et al., 2022; Zhang et al., 2008). Considering that the PGC-1α protein is related to oxidative capacity and with the highest proportion of mitochondrial biogenesis, especially in skeletal muscle, it is possible to mention that Gly482 homozygous subjects present a greater quantity or activity of this protein, enhancing aerobic metabolism. On the other hand, Ser482 homozygous subjects would have worse aerobic metabolism, favoring an anaerobic metabolism, a necessary requirement for the development of muscle strength/power (Varillas-Delgado, 2024). Thus, a review of the literature showed that 44%, 72% and 10% of the variance of the response in the aerobic, strength and power phenotypes, respectively, was explained by genetic influences (Chung et al., 2021). However, it has been recognized that genetic variables can partly explain the variability in physical performance, which should be analyzed in conjunction with nutrition, training and physiological factors (Flück et al., 2024).

Studies of this polymorphism and physical performance have used the comparison of subjects with elite aerobic capacity versus non-trained subjects. Few studies have explored the association between physical performance and the presence of the PGC-1α Gly482Ser polymorphism among the untrained population using a cross-sectional model. However, in a study developed with a population of twins, a greater time dedicated to high-intensity activities was reported in subjects carrying the Ser482 allele (Gielen et al., 2014). Even more relevant, it has been suggested that the rs8192678 polymorphism may affect the abundance of the PGC-1α protein, which in turn may alter mitochondrial biogenesis and function. This polymorphism has been associated with the appearance of metabolic diseases such as obesity, diabetes

mellitus and hypertension, which justifies the need to delve deeper into its association with pathologies and physical fitness in the non-athletic population (Huang et al., 2023).

In Chile, there is an absence of research determining the genotypic and allelic frequency of the Gly482Ser polymorphism in the PGC-1α gene, with even fewer investigations addressing its correlation with physical performance in untrained individuals. Consequently, the aim of this study was to examine the relationship between the Gly482Ser polymorphism of the PGC-1α gene and both aerobic and strength performance in young adults.

Method

A cross-sectional study was designed to explore the possible association between the Gly482Ser polymorphism of the PGC-1a gene and standardized physical tests assessing aerobic capacity and muscle strength. The procedures implemented in this study adhere to the ethical standards outlined in the principles of the Declaration of Helsinki, sanctioned by a Scientific Ethics Committee, with written informed consent obtained from each participant.

Participants

The study sample comprised 106 university students, of which 58 were women with a mean age of 22.1 ± 2.21 years and 48 were men with a mean age of 21.6 ± 1.72 years. The study included university students aged 18 to 27 years, who self-reported as sedentary, considering that they did not perform moderate physical activity at least 3 times per week or vigorous physical activity at least 2 times per week. Participants were excluded if they had any physical impediments that prevented participation in physical tests, exhibited any chronic noncommunicable diseases, whether controlled or not, were pregnant, had a body mass index (BMI) greater than 40 kg/m2, or were diagnosed with metabolic or cardiopulmonary pathologies. Consanguinity with another participant also warranted exclusion. All participants were subjected to interviews and blood pressure, weight, and height assessments. Subsequently, schedules for physical tests and blood sample collection were arranged. Participants were instructed to abstain from food or liquids and from taking any drugs or substances that could affect physical performance. They were also instructed to maintain their dietary habits for 72 hours before their physical evaluation. In addition, they were advised against smoking within an hour before the test and engaged in strenuous exercise during the 72 hours before each test. Physical tests were applied at least 72 hours apart to avoid the effect of fatigue on the subjects.

Procedure

Physical tests

Physical tests were divided into aerobic and muscular strength tests, using clinical tests that required low equipment and a basic level of instruction so that they could be replicated in contexts of low clinical complexity. Aerobic tests focused on functional responses and global physical work capacity through the 6-minute walk test, heart rate recovery responses that reflect the autonomic response to exercise, such as the Ruffier test, and specific heart rate plateau stage responses through the Astrand test on a cycle ergometer. Additionally, upper extremity muscle strength tests were selected by hand grip and arm flexion power by arm curls test, and lower extremity tests by leg extension, providing a global view of the muscular strength of the subjects.

Aerobic capacity

Six-minute Walk test. The 6-minute walk test (6MWT) was administered to evaluate performance through the distance covered in meters. Additionally, the percentage of reserve heart rate (HRR) and the percentage of heart rate recovery (HRrecovery) were employed to assess the physical demand during the test. The peak oxygen consumption (VO2Peak) was calculated using a formula reported in previous studies (VO2max (mL/kg/min) = 12.701 + (0.06 × 6MWD m) − (0.732 × BMI kg/m2)) (Jalili et al., 2018).

Ruffier test. The Ruffier index (RI) was computed to assess the aerobic capacity of the participants. In this context, the resting heart rate (P0) was utilized as the baseline, whereas the heart rate was measured immediately after the execution of 30 squats within 45 seconds (P1) and one minute post-test completion (P2) (Alahmari et al., 2020). Based on the acquired data, the Ruffier index (RI) was determined as: ((P0+P1+P2)-200)/10.

Astrand test. The Astrand test was performed using a cycle ergometer, applying a workload of 450 kp/min for men participants and 300 kp/min for woman participants. The pedaling cadence was maintained at 50 rpm. Heart rate was continuously monitored throughout the procedure with measurements taken at minutes 5 and 6 of exercise used to estimate maximal oxygen consumption (VO2Max). For estimation of VO2Max via the Astrand nomogram, the mean of the heart rates recorded at minutes 5 and 6 was used, with the resulting value corrected by an appropriate factor relevant to the age of the individuals involved (Magrani & Pompeu, 2010; Radovanovic et al., 2009).

Muscular strength

Handgrip strength. Handgrip muscle strength was assessed using a Jamar® hand dynamometer, allowing the participant to familiarize himself with the device. During the assessment, the participant was placed bipedally with his arm in a neutral posture and instructed to exert maximum strength for a duration of 5 seconds. This procedure was performed three times for each hand, incorporating a 30-second interval between trials, with the highest value recorded for each hand. Subsequently, the optimal values from both hands were summed (Amaral et al., 2012; Bohannon, 2008; Peters et al., 2011).

30-second dynamic muscle strength. The arm curls test (ACT) involved the use of a 5-pound dumbbell for women participants and an 8-pound dumbbell for men participants. Utilizing their dominant hand, participants were instructed to execute the maximum number of elbow flexions through a complete range of motion within a duration of 30 seconds. The assessment was based on the number of repetitions executed correctly (Minges et al., 2011).

Leg extension muscle strength test. The maximum isometric strength (MIF) of knee extension was evaluated using a quadriceps chair, whereby muscle strength was quantified utilizing a tension transducer with the knee positioned at 90 degrees of flexion. Three trials were conducted on the dominant lower extremity, with a one-minute rest interval between each trial. The subject received verbal encouragement to ensure achievement of peak performance (de Ruiter et al., 2010).

Blood samples

Peripheral blood samples were obtained using Vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. These blood samples were stored at 4°C for subsequent analytical procedures.

Genotyping analysis

Genomic DNA was isolated from a 10 mL sample of whole blood, anticoagulated with EDTA (1 mg/dL), utilizing the saline precipitation micromethod as described by Salazar et al. (2001) (Salazar et al., 2001). The Gly482Ser polymorphism of PGC-1α was identified via the polymerase chain reaction (PCR) technique followed by analysis through enzymatic restriction (PCR-RFLP), employing primers published by Zhang et al. (2008), Forward: 5'-GGAATATGGTGATCGGGAAC-3'; Reverse: 5'-TGAGAGAGACTTTGGAGGCA-3' (Zhang et al., 2008). The PCR protocol included: 2.5 µL of 10X enzyme buffer, 1 µL of Forward Primer at a concentration of 10000 nM, 1 µL of Reverse Primer at a concentration of 10000 nM, 0.5 µL of 10 mM dNTPs mix, 2 µL $MgCl_2$ at a concentration of 2 mM, 0.1 µL of Dream Taq Green DNA polymerase (#EP0712, Fermentas, Lithuania) at a concentration of 5 U/µL, 2.5 µL of Dream Taq Green buffer (#EP0711, Fermentas, Lithuania), and 1 µL of genomic DNA at a concentration of 25 ng, with sufficient deionized sterile water to reach a final volume of 25 µL. The PCR protocol involved an initial denaturation at 95°C for 5 minutes, followed by 35 cycles consisting of 30 seconds at 95°C, annealing for 30 seconds at 54.6°C, and extension for 30 seconds at 72°C, concluding with a final extension at 72°C for 10 minutes.

The amplified product yielded a fragment measuring 452 base pairs (bp), which underwent enzymatic restriction utilizing the FastDigest Msp1 restriction endonuclease (Thermo Scientific) according to the following protocol: 10 µL of PCR product, 1 µL of restriction enzyme, 2 µL of reaction buffer, and an

appropriate volume of sterile distilled water to achieve a final volume of 30 µL. The reaction mixture was incubated for 10 minutes in a thermal cycler at 37°C. Subsequently, the restriction fragments were separated by electrophoresis for 45 minutes at 100 volts on a 2% agarose gel stained with GelRed®. The homozygous Gly482 genotype was characterized by the presence of a 452 bp fragment; the heterozygous Gly482Ser genotype was characterized by three fragments measuring 452, 308, and 144 bp, and the homozygous Ser482 genotype was characterized by two fragments measuring 308 and 144 bp.

Data analysis

Qualitative variables were presented using absolute frequencies and relative percentages. Quantitative variables were analysed using means with their corresponding standard deviations. The χ-square test (χ^2) was used to assess Hardy-Weinberg equilibrium and to determine whether allele and genotype frequencies are influenced by the sex of the individuals. A one-way analysis of variance test, accompanied by a corresponding Tukey post hoc analysis, was used to compare physical performance between genotypes. In addition, the independent samples t-test was applied to assess performance stratified by sex, using recessive and dominant inheritance models. the assumptions of the analysis of variance and independent samples t test were met; a distribution analysis of normality (Kolmogorov-Smirnov) and homogeneity (Levene) was performed. When the data did not meet any of these assumptions, the nonparametric Kruskal-Wallis tests and the Mann-Whitney U test were used, depending on the number of groups to be compared. A recessive inheritance model was applied comparing subjects with homozygous Gly482 genotype versus the addition of subjects with heterozygous genotype and homozygous Ser482 genotype. For the dominant inheritance model, subjects with homozygous Ser482 genotype were compared versus the addition of subjects with heterozygous genotype and homozygous Gly482 genotype. All analyses were performed using IBM® SPSS® 25 software, with a $p < 0.05$ to determine statistical significance.

Results

The study group consisted of 106 participants, 58 women (57.7%) and 48 men (43.3%). Table 1 presents the general characteristics of the study group.

Table 1. General characteristics of the study group, stratified by sex.

	Woman (n=58)	Men (n=48)	All participants (n=106)
Age (years)	21.5 ± 2.32	21.4 ± 2.07	21.5 ± 2.20
Weight (kg)	58.3 ± 6.25*	69.4 ± 8.46	63.3 ± 9.19
Height (cm)	159.4 ± 5.07*	170.9 ± 6.36	164.6 ± 8.06
BMI (kg/m2)	22.9 ± 2.19	23.8 ± 2.26	23.3 ± 2.25

Showed mean ± s.d. Body mass index = BMI. Comparison between women and men. Student's t test * p< 0,05.

The genotypic frequency was stratified by gender as well as for the entire cohort of subjects (Table 2). Participants conformed to the Hardy-Weinberg equilibrium among women ($\chi2=0.020$, $p=0.888$), men ($\chi2=3.393$, $p=0.065$), and the total subjects ($\chi2=1.443$, $p=0.230$). There were no statistically significant differences observed in genotypic frequencies by gender ($\chi2=2.605$, $p=0.275$). The Ser482 allele was the most prevalent among both men (59.4%) and women (64.7%), as well as within the total cohort (62.3%). No disparities were identified in allele frequencies between genders ($\chi2=0.623$, $p= 0.430$).

Table 2. Description of genotypic and allelic frequency of the Gly482Ser polymorphism of the PGC-1α gene stratified by sex and all subjects

	Genotype % (n=106)			Allelic Frequency	
	Homozygous Gly482	Heterozygous Gly482Ser	Homozygous Ser482	Gly482	Ser482
Woman (n=58)	12.1 (7)	46.6 (27)	41.4 (24)	35.3	64.7
Men (n=48)	22.9 (11)	35.4 (17)	41.7 (20)	40.6	59.4
All participants (n=106)	17.0 (18)	41.5 (44)	41.5 (44)	37.7	62.3

Hardy-Weinberg equilibrium analysis, women, men and all groups. χ^2 test no statistically significant differences

The results of the physical performance tests are presented in Table 3 by genotype, stratified by sex. In women, a higher oxygen consumption was observed during the Astrand test, while a lower performance in the ACT muscle strength test was identified in those who presented a homozygous Gly482 genotype

(p<0.05) compared to heterozygous and homozygous Ser482 subjects. In men, no statistically significant differences were identified in any physical test associated with the present genotype.

Table 3. Comparison of average performances in physical tests by genotype for Woman and Men

		Woman (n=58)			Men (n=48)		
		Homozygous Gly482 (n=7)	Heterozygous Gly482Ser (n=27)	Homozygous Ser482 (n=24)	Homozygous Gly482 (n=11)	Heterozygous Gly482Ser (n=17)	Homozygous Ser482 (n=20)
		Aerobic performance					
6MWT	6MWD (m)	700.5±74.9	737.2±46.5	713.1±68.4	834.1±114.0	788.2±95.8	783.1±60.2
	HRR (%)	83.4±16.18	88.4±11.85	84.4±12.34	75.7±17.76	77.7±12.92	81.0±13.84
	HR $_{Recovery}$ (%)	44.4±9.42	52.6±9.17	51.2±11.40	39.9±12.45	47.0±7.18	48.7±8.25
	VO_{2peak} (ml/kg/min)	38.4±5.15	40.3±4.31	38.4±4.75	44.1±6.27	41.9±4.15	42.2±4.40
Astrand test	VO_{2Max} (ml/kg/min)	27.5±4.91*	23.3±4.22	24.7±4.19	40.9±10.62	41.0±10.16	37.6±10.91
RI		9.3±5.68	11.4±4.90	11.6±5.24	7.9±5.23	9.0±4.40	8.3±3.43
		Muscle strength performance					
HGS	(kg)	51.3±10.20	52.6±10.36	49.6±7.27	86.5±15.44	81.9±10.84	81.5±16.04
MIF	(KN)	0.302±0.107	0.255±0.052	0.273±0.065	0.428±0.095	0.402±0.132	0.424±0.130
ACT	(Rep.)	29.3±3.95*	33.5±4.42	31.3±4.43	35.1±6.50	33.2±7.09	34.8±5.20

Comparison by genotype, stratified by sex. Six-minute Walk test =6MWT; Six-minute Walk distance = 6MWD; Heart rate reserve = HRR; Heart rate recovery = HR $_{Recovery}$; Peak Oxygen Consumption = VO_{2peak}; Estimate maximum oxygen consumption = VO_{2Max}; Ruffier index = RI; Hand-Grip Strength=HGS; maximum isometric strength = MIF; Arm curl test = ACT. One-way ANOVA with Tukey's post hoc test * p< 0,05.

A recessive inheritance analysis model, stratified by sex, was applied to analyse the influence of the Gly482 allele on the performance of the physical tests used, comparing the results between subjects with the homozygous Gly482 genotype with the sum of heterozygous subjects and Ser482 genotypes (Table 4). It was found that in women there is greater heart rate recovery (6MWT), greater oxygen consumption on the Astrand test, and lower performance on the ACT muscle strength test ($p < 0.05$). In men, a greater distance travelled and a better HR recovery in the 6MWT were found ($p < 0.05$). Similarly, no statistically significant differences were found in muscle strength tests.

Table 4. Comparison of physical performance under a recessive inheritance model, stratified by sex

		Woman		Men	
		Homozygous Gly482 (n=7)	Heterozygous Gly482Ser + Homozygous Ser482 (n=51)	Homozygous Gly482 (n=11)	Heterozygous Gly482Ser + Homozygous Ser482 (n=39)
		Aerobic performance			
6MWT	6MWD (m)	700.5±74.89	725.9±61.60	834.1±113.95*	785.4±72.92
	HRR (%)	83.4±16.18	86.6±11.52	75.7±17.76	79.6±13.77
	HR $_{Recovery}$ (%)	44.4±9.42*	51.9±10.01	39.9±12.45*	47.9±8.02
	VO_{2peak} (ml/kg/min)	38.4±5.15	39.4±4.43	44.1±6.27	42.1±5.04
Astrand test	VO_{2Max} (ml/kg/min)	27.5±4.91*	24.1±4.16	40.9±10.62	39.1±10.63
RI		9.3±5.68	11.5±4.65	7.9±5.23	8.6±3.97
		Muscle strength performance			
HGS	(kg)	51.3±10.20	51.2±8.43	86.5±15.44	81.7±14.40
MIF	(KN)	0.302±0.107	0.264±0.065	0.428±0.095	0.414±0.126
ACT	(Rep.)	29.3±3.95*	32.5±4.49	35.1±6.50	34.1±6.14

Comparison under a recessive inheritance model, stratified by sex. Six-minute Walk test =6MWT; Six-minute Walk distance = 6MWD; Heart rate reserve = HRR; Heart rate recovery = HR $_{Recovery}$; Peak Oxygen Consumption = VO_{2peak}; Estimate maximum oxygen consumption = VO_{2Max}; Ruffier index = RI; Hand-Grip Strength =HGS; maximum isometric strength = MIF; Arm curl test = ACT. Student's t test. * p< 0,05. Student's t test.

To determine the influence of the Ser482 allele on the performance of the physical test, a dominant inheritance analysis model was performed. Therefore, the average performance of subjects who had the homozygous Ser482 genotype was compared with subjects who had the homozygous Gly482 genotypes plus heterozygous subjects, as shown in Table 5. No statistically significant differences were found in the dominant inheritance model, stratified by sex.

Table 5. Comparison of physical performance under a dominant inheritance model, stratified by sex.

Woman		Men	
Homozygous Ser482 (n=24)	Heterozygous Gly482Ser + Homozygous Gly482 (n=36)	Homozygous Ser482 (n=20)	Heterozygous Gly482Ser + Homozygous Gly482 (n=30)
Aerobic performance			

6MWT	6MWD (m)	713.1±68.39	729.7±59.26	783.1±60.21	806.9±100.11
	HRR (%)	84.4±12.34	87.4±11.88	81.0±13.84	76.9±15.24
	HR $_{Recovery}$ (%)	51.2±11.40	50.9±9.39	48.7±8.25	44.3±10.25
	VO_{2peak} (ml/kg/min)	38.4±4.75	39.9±4.25	42.2±4.40	42.7±5.98
Astrand test	VO_{2Max} (ml/kg/min)	24.7±4.19	24.2±4.53	37.6±10.91	41.0±10.23
RI		11.6±5.24	11.0±4.51	8.3±3.43	8.6±4.79
			Muscle strength performance		
HGS	(kg)	49.6±7.27	52.3±9.33	81.5±16.04	83.7±13.88
MIF	(KN)	0.273±0.065	0.266±0.077	0.424±0.130	0.411±0.113
ACT	(Rep.)	31.3±4.43	32.6±4.56	34.8±5.20	34.00±6.91

Comparison under a dominant inheritance model, stratified by sex. Six-minute Walk test =6MWT; Six-minute Walk distance = 6MWD; Heart rate reserve = HRR; Heart rate recovery = HR $_{Recovery}$; Peak Oxygen Consumption = VO_{2peak}; Estimate maximum oxygen consumption = VO_{2Max}; Ruffier index = RI; Hand-Grip Strength =HGS; maximum isometric strength = MIF; Arm curl test = ACT. Student's t test. * p< 0,05. Student's t test.

Discussion

In the present study, we investigated the association between the Gly482Ser polymorphism of the PGC-1α gene and physical performance in sedentary young adult subjects. Genotypic analysis, dominant inheritance analysis and recessive inheritance analysis were performed to investigate whether one or both copies of the Gly482 allele are necessary to establish an influence on aerobic capacity and/or muscle strength of the subjects tested (Flores-Alfaro et al., 2012). In our study, the homozygous Gly482 genotype was associated with higher levels of oxygen consumption estimated by the Astrand test, showing better aerobic capacity in these participants. Furthermore, when recessive inheritance analysis was performed, this association was again evident, confirming that two copies of the glycine allele are necessary to establish this advantage, to which a better recovery of heart rate was added after 6MWT execution. 6MWT has been used in various populations with a wide range of ages, particularly in the evaluation of functional capacity in patients with cardiorespiratory pathologies (Hoeper et al., 2003; Larsen et al., 2001; Siafakas et al., 1995). Since the 6MWT is considered a submaximal test, it is often questioned whether the measured performance corresponds to the best effort of the individual, so it is interesting to investigate the physiological cost during its development, in addition to evaluating the post-test recovery. Therefore, in our investigation, it was observed that in response to 6MWT, men walked a longer distance and had greater heart rate recovery in the homozygous presence of the Gly482 homozygous genotype. Therefore, it is plausible to say that if subjects had better performance on walked meters, it was because their effort was greater; however, this same group had a lower HRR and a higher HR recovery. In this sense, subjects who undergo aerobic training have an accelerated decrease in heart rate after physical effort (Lakin et al., 2013; Otsuki et al., 2007). Post-exercise heart rate recovery has also been proposed to be an indicator of cardiac function and has been used to classify the work capacity of children after a submaximal exercise test (Jankowski et al., 2015). Heart rate recovery after physical exercise has been studied on cardiopulmonary tests and has been associated with morbidity and mortality in patients with heart failure (Lindemberg et al., 2014), and is also considered a predictor of all-cause mortality (Georgoulias et al., 2009). Heart rate recovery has been shown to be slower in patients with heart failure and faster in sprinters (Morise, 2004).

Our results show that subjects expressing the homozygous Gly482 genotype had a better response in relation to the physiological cost of a submaximal effort with aerobic characteristics than subjects expressing the homozygous Ser482 genotype, this through a recessive inheritance model showing that two copies of the Gly allele are required to exhibit better performance in aerobic characteristics. In this context, the expression of the Ser482 allele has been associated with a higher frequency of appearance in strength athletes compared to control subjects (Eynon et al., 2011) indicating a specificity of the different alleles to determine an advantage in physical performance, associating Gly482 with aerobic performance and the Ser 482 allele with anaerobic performance. This is complemented by the results reported in the Danish adult population where it was found that the presence of the Ser482 allele was inversely correlated with the mRNA levels for PGC-1α and the maximum oxygen consumption of the subjects evaluated (Ling et al., 2004). Therefore, it has been suggested that the presence of the Ser482 allele is considered a disadvantage for aerobic performance (Tural et al., 2014). Thus, an association has been demonstrated between the Ser482 allele and a reduced oxidative capacity, which directly affects performance in aerobic activities, with limited capacity for efficient energy generation resulting in a greater tendency to muscle fatigue and less recovery between training sessions, although the effects of the Ser482 allele are not universally negative and may vary depending on the specific sporting discipline

and interactions with other genetic and environmental factors (Petr et al., 2018). However, this behavior is not homogenous in various populations, since it has been reported that the Gly482 allele represents a highly significant positive effect on muscle strength in Caucasian populations, having a null effect in Asian populations (Steinbacher et al., 2015).

In muscular strength, in women the presence of the homozygous genotype Gly482 represented a disadvantage for performance in the arm curl test, these results being confirmed under a recessive inheritance analysis, where again the presence of two Gly482 alleles is necessary to generate a disadvantage in relation to muscular strength. This was evidenced by Eynon et al., (2010), in Israeli athletes, reporting a higher frequency of the Ser482 allele in sprinters compared to endurance or aerobic athletes (Eynon et al., 2010). This situation was replicated in Lithuanian athletes, where the presence of the Gly482 allele was negatively associated with anaerobic muscle power, while the Ser482 allele was negatively associated with the Ruffier index (Kučinskas et al., 2010). In young Chinese women (aged 16-18 years), no associations were found between grip strength performance and any of the PGC-1 genotypes, as we found in our study where no differences were observed in this test when comparing the different genotypes (Chiu et al., 2012). In men, no differences associated with aerobic performance or muscle strength were found in a genotype analysis for the Gly482Ser polymorphism in any genotype or under a dominant inheritance analysis model. These findings are similar to those reported by He et al. in Chinese subjects, where oxygen consumption was assessed in a submaximal and maximal test, and no differences in physical performance were found before or after 18 weeks of aerobic training when comparing the different genotypes (He et al., 2008). Similarly, no differences were found in terms of energy used during regular physical activity when comparing subjects with different genotypes in an English population (Franks et al., 2003). In this regard, a study of Chinese children of both sexes showed significant differences between the sexes in the abdominal index, demonstrating that sex-related differences in muscle development can lead to differences in physical function, since muscle strength is proportional to the cross-sectional area of the muscle and the strength growth curve is essentially the same (Wei, 2023). This difference has also been shown by other authors where through muscle biopsy they found notable differences between men and women in the presence of the Gly482Ser polymorphism, which the researchers explained by several factors, such as gender differences in the composition of muscle fibers and the conversion of fibers with age or hormonal activity, mitochondria playing a crucial role in the biosynthesis of sex steroid hormones and, in turn, sex steroid hormones such as estrogen, progesterone and testosterone can regulate mitochondrial function (Yvert et al., 2020).

The research presented is analyzed under a cross-sectional model with field tests that can contribute to the evaluation of diverse populations without specialized equipment or laboratories with complex technologies. Usually, the analysis of the influence of polymorphisms has been addressed mainly under a case-control model, which is different from the model presented and may represent a simpler methodological contribution to the analysis of polymorphisms, either in health or disease. For the Gly482Ser polymorphism of PGC-1α, the comparison of the presence of the homozygous Gly482 genotype in elite athletes has been established in contrast to sedentary subjects. Therefore, it has been observed that as subjects increase their level of aerobic physical performance, the homozygous genotype Gly482, especially in Caucasian subjects, has been observed. In addition, the Ser482 allele has been shown to be more frequent in nonathlete subjects (Lucia et al., 2005).

According to evidence, individual variability in learning ability is a normal biological phenomenon, which could partly reflect genetic diversity (Sarzynski et al., 2017). Thus, previous studies show that a genetic component in the response to physical training can explain up to 80% of the variability in aerobic, strength, and power adaptations in an individual's response, and that in response to physical training, results vary significantly depending on the environmental stimuli and exercise administered (Chung et al., 2021). Other authors argue that these genetic variants are only capable of explaining 20% of aerobic performance and capacity, indicating that more consistent research is still required to reach an acceptable consensus (Flück et al., 2024). A relevant factor corresponds to the training capacity and the changes induced by these since it has been established that PGC1-α alters its expression in human skeletal muscle during adaptation to resistance training compared to pre-training, non-exercise and resistance training states, indicating a differentiated regulation according to the cellular microenvironment (Vissing & Schjerling, 2014).

The genotypic characteristics of our population showed an equal frequency for heterozygous and homozygous Ser482 subjects (41.5%) and a lower frequency for homozygous Gly482 subjects (17%). In the Latin American population, there are few publications; however, what was observed in this research was similar to what was reported in the Venezuelan population with a lower frequency of Gly482 with 8.3% (Zambrano et al., 2009), and different from what was observed in Argentines of 39.2% (Gianotti et al., 2008) and Brazilians of 47.3% (Geloneze et al., 2012), where homozygous subjects of Gly482 were higher. A lower frequency of Gly482 has also been found in the Asian population of Japan 20.5% (Hara et al., 2002), India 3.0% (Vimaleswaran et al., 2006) and China 18.0% (Li et al., 2011) and 22.6% (Zhu et al., 2009). However, there is variability in the reports of Japanese and Chinese populations, where higher frequencies of Gly482 have also been reported compared to Ser482, showing in the Japanese population 28.6% (Nishida et al., 2015; Tobina et al.) and in China 27.4% (Wei, 2023), 32.5% (Weng et al., 2010), 27.5% (He et al., 2008). On the contrary, in the European population a higher frequency of homozygous Gly482 subjects has been reported, with a frequency of 31.9% (Yvert et al., 2020) and 10.6% (Muniesa et al., 2010) in the Spanish population, 40.9% in the Poles (Maciejewska et al., 2012), 43.2% in the Russians(Maciejewska et al., 2012), 45.5% in the Danes (Ling et al., 2004), 42.8% in the Germans (Stumvoll et al., 2004) and 38.9% in the English (Franks et al., 2003).

This study has some limitations that are important to highlight, such as the lack of gender parity among subjects, the possibility that cofactors such as sleep time, eating habits, or prior training history were not considered in the analysis of the results, and the fact that physical testing was only performed in one instance. On the other hand, it presents the strengths of using field tests with standardized protocols, robust and widely used biological analyses, and the fact that, to date, according to the authors' review, there are no reports of Gly482Ser polymorphisms in the Chilean population.

Conclusions

This study investigated the relationship between aerobic capacity and muscle strength in relation to the Gly482Ser polymorphism of the PGC-1α gene (rs8192678). The data suggest that the presence of the homozygous Gly482 genotype may confer a beneficial effect on aerobic physical performance in both sexes. On the contrary, in terms of muscle strength, the expression of this genotype in women seems to be disadvantageous. The results obtained allow us to investigate the genetic profiles of the Latin population where there are few studies related to genetic variants and physical performance, contributing to the generation of analytical tools that allow us to understand physical performance from a genetic point of view, as well as to provide training for sports talents. Despite these findings, further research is warranted to elucidate these associations.

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