ANÁLISIS DE LA VARIABILIDAD EN LA LONGITUD TELOMÉRICA DE PACIENTES CON ENFERMEDAD CARDIOVASCULAR, SOMETIDOS A UN PROGRAMA DE EJERCICIO FÍSICO EN UN CENTRO MÉDICO DE LA CIUDAD DE BARRANQUILLA.

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RESUMEN

Las Enfermedades cardiovasculares (ECV), son desordenes de origen multifactorial, que según la Organización Mundial de la Salud (OMS), constituyen la principal causa de mortalidad en Colombia y a nivel mundial. El desarrollo de estas patologías se relaciona con diversos factores de riesgo ambientales, metabólicos y genéticos; entre los factores genéticos, se encuentran biomarcadores con potencial para predecir el riesgo de ECV. Uno de estos biomarcadores es la longitud de los telómeros (TL), los cuales son estructuras al extremo del cromosoma, que actúan como marcador del envejecimiento biológico. Esto se debe a que con el tiempo reducen su longitud por la división celular, lo que genera inestabilidad cromosómica y senescencia celular. Además de la división celular, factores como enfermedades o estilos de vida se han relacionado con cambios en la TL; entre estos, la actividad física es asociada con efecto protector sobre la TL, siendo también un protocolo recomendado en pacientes para el tratamiento de ECV. Sin embargo, se desconoce la relación causa-efecto entre la actividad física, la TL y las ECV. El presente trabajo se propuso analizar el efecto de un programa de ejercicio sobre la Longitud de Telómero en pacientes diagnosticados con ECV de la ciudad de Barranquilla. Los participantes del estudio se seleccionaron teniendo en cuenta los criterios de inclusión y exclusión, a partir de un listado de pacientes atendidos por enfermedad cardiovascular. Los pacientes seleccionados se citaron a una valoración por cardiología, donde se registró la presencia de factores de riesgo cardiovascular

(FRCV), y se realizó toma de una muestra de sangre venosa, para determinar la TL previo intervención. Posteriormente se entregó a cada paciente el protocolo de ejercicio para 3 meses, y al finalizar el protocolo se citó a los participantes a una segunda toma de sangre para determinar la TL post intervención. Las muestras se procesaron por triplicado utilizando la técnica de Reacción en Cadena de la Polimerasa Cuantitativa en tiempo real (qPCR). Para cada muestra se realizó una primera reacción dirigida a telómero y una segunda dirigida al gen 36B4, el cual se utilizó como referencia para determinar el número de copias del genoma por reacción, para cada paciente. Adicionalmente, se determinó una curva de calibración, utilizando diluciones seriadas de oligómeros sintetizados de tamaño conocido de secuencia de telómero y del gen 36B4, para calcular una TL absoluta (aTL). Los datos obtenidos se exportaron y analizaron utilizando los softwares Excel y IBM-SPSS 26.0, utilizando pruebas estadísticas no paramétricas. Los resultados muestran una TL post ejercicio 5,54% más larga que la aTL pre-ejercicio, aunque no se evidenció una diferencia estadísticamente significativa entre las aTL pre y post intervención (p=0,750). Así mismo tampoco se observó una diferencia significativa en la variación de la TL entre los pacientes, respecto a la presencia de FRCV como comorbilidades (p=0,396), perfil de lipídico elevado (0,762), hipertensión arterial (p=0,659) o ECV (p=0,81). Estos resultados sugieren un posible efecto de mantenimiento de la TL debido al programa de ejercicio, independientemente del estado cardiovascular inicial del paciente; sin embargo, teniendo en cuenta que este estudio solo contempló la Actividad física, el efecto observado puede estar influenciado, por factores, como la dieta, los cuales pueden actuar como factores de protección adicional; por tal motivo no es posible relacionar la actividad física con un efecto de mantenimiento del telómero en pacientes con ECV, por lo que se hace necesario realizar un estudio que incluya la supervisión de otras posibles variables que puedan influenciar en la TL.

Palabras clave: Longitud Telomérica, Actividad física, Telómero, enfermedad Cardiovascular.

ABSTRACT

Cardiovascular diseases (CVD) are multifactorial disorders that, according to the World Health Organization (WHO), are the leading cause of mortality in Colombia and worldwide. The development of these pathologies is related to various environmental, metabolic and genetic risk factors; among the genetic factors, there are biomarkers with the potential to predict the risk of CVD. One of these biomarkers is telomere length (TL), which are structures at the end of the chromosome that function as a marker of biological aging. This is because over time they reduce in length due to cell division, which generates chromosomal instability and cellular senescence. In addition to cell division, factors such as diseases or lifestyles have been related to changes in TL; among these, physical activity is associated with a protective effect on TL, being also a recommended protocol in patients for the treatment of CVD. However, the cause-effect relationship between physical activity, TL and CVD is unknown. The present study aimed to analyze the effect of an exercise program on telomere length in patients diagnosed with CVD in the city of

Barranquilla. The study participants were selected considering the inclusion and exclusion criteria, from a list of patients treated for cardiovascular disease. The selected patients were scheduled for a cardiology evaluation, where the presence of cardiovascular risk factors (CVRF) was recorded, and a venous blood sample was taken to determine the pre-intervention TL. Subsequently, each patient was given the exercise protocol for 3 months, and at the end of the protocol, the participants were summoned to a second blood sampling to determine the post-intervention TL. The samples were processed in triplicate using the real-time quantitative polymerase chain reaction (qPCR) technique. For each sample, a first reaction targeting the telomere and a second reaction targeting the 36B4 gene were performed, which was used as a reference to determine the number of genome copies per reaction for each patient. Additionally, a calibration curve was determined, using serial dilutions of synthesized oligomers of known size of telomere sequence and 36B4 gene, to calculate an absolute TL (aTL). The data obtained were exported and analyzed using Excel and IBM-SPSS 26.0 software, using nonparametric statistical tests. The results show a post-exercise TL 5.54% longer than the pre-exercise aTL, although there was no statistically significant difference between the pre- and post-intervention aTL (p=0.750). Likewise, there was no significant difference in the variation of TL between patients with respect to the presence of CVRFs such as comorbidities (p=0.396), elevated lipid profile (0.762), arterial hypertension (p=0.659) or CVD (p=0.81). These results suggest a possible maintenance effect of TL due to the exercise program, independently of the patient's initial cardiovascular status; however, taking into account that this study only contemplated physical activity, the effect observed may be influenced by factors, such as diet, which may act as additional protective factors; for this reason it is not possible to relate physical activity with a telomere maintenance effect in patients with CVD, so it is necessary to conduct a study that includes the monitoring of other possible variables that may influence TL.

Key Words: Telomere Length, Physical Activity, Telomere, Cardiovascular disease.

REFERENCIAS BIBLIOGRÁFICAS

1. Doroschuk NA, Postnov AY, Doroschuk AD, Ryzhkova AI, Sinyov V V., Sazonova MD, et al. An original biomarker for the risk of developing cardiovascular diseases and their complications: Telomere length. Toxicol Rep [Internet]. 2021;8:499–504. Available from: https://doi.org/10.1016/j.toxrep.2021.02.024
2. Goldsborough III E, Osuji N, Blaha MJ. Assessment of Cardiovascular Disease Risk. A 2022 Update. Endocrinology and Metabolism Clinics of NA [Internet]. 2022; Available from: https://doi.org/10.1016/j.ecl.2022.02.005

3. World Health Organization. Cardiovascular-Diseases-(Cvds) [Internet]. 2021. Available from: http://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
4. World Health Organization. WHO MORTALITY DATABASE Interactive platform visualizing mortality data [Internet]. 2022. Available from: https://platform.who.int/mortality/themes/theme-details/topics/topic-details/MDB/cardiovascular-diseases
5. Departamento Administrativo Nacional de Estadística DANE. Estadísticos por tema, Tabla publicada en Página oficial. 2023 [cited 2023 Sep 25]. Defunciones No Fetales 2023 - Preliminar. Available from: https://www.dane.gov.co/index.php/estadisticas-por-tema/salud/nacimientos-y-defunciones/defunciones-no-fetales/defunciones-no-fetales-2023
6. Baena Díez JM, del Val García JL, Pelegrina JT, Martínez Martínez JL, Peñacoba RM, Tejón IG, et al. Epidemiología de las enfermedades cardiovasculares y factores de riesgo en atención primaria. Rev Esp Cardiol [Internet]. 2005;58(4):367–73. Available from: http://dx.doi.org/10.1157/13073893
7. Huzen J, Wong LS, van Veldhuisen DJ, Samani NJ, Zwinderman AH, Codd V, et al. Telomere length loss due to smoking and metabolic traits. J Intern Med [Internet]. 2014;275(2):155–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24118582
8. Zhan Y, Hägg S. Telomere length and cardiovascular disease risk. Vol. 34, Current Opinion in Cardiology. Lippincott Williams and Wilkins; 2019. p. 270–4.
9. Lanier JB, Bury DC, Richardson SW. Diet and physical activity for cardiovascular disease prevention. Am Fam Physician [Internet]. 2016;93(11):919–24. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L610598352
10. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. Physical activity and telomere length: Impact of aging and potential mechanisms of action [Internet]. Vol. 8, Oncotarget. 2017. Available from: www.impactjournals.com/oncotarget/
11. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. Journal of Physiology. 2016;594(8):2061–73.
12. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andrés V. Biological Versus Chronological Aging: JACC Focus Seminar. J Am Coll Cardiol. 2020;75(8):919–30.
13. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science (1979). 2015;350(6265):1193–8.
14. Lai TP, Wright WE, Shay JW. Comparison of telomere length measurement methods. Philos Trans R Soc Lond B Biol Sci [Internet]. 2018;373(1741). Available from: http://www.ncbi.nlm.nih.gov/pubmed/29335378

15. Kalmbach KH, Fontes Antunes DM, Dracxler RC, Knier TW, Seth-Smith ML, Wang F, et al. Telomeres and human reproduction. Fertil Steril [Internet]. 2013 Jan;99(1):23–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23273986
16. Li JSZ, Denchi EL. How stem cells keep telomeres in check. Differentiation [Internet]. 2018;100:21–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29413749
17. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, et al. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. Am J Epidemiol. 2007;165(1):14–21.
18. Shadyab AH, LaMonte MJ, Kooperberg C, Reiner AP, Carty CL, Manini TM, et al. Association of Accelerometer-Measured Physical Activity With Leukocyte Telomere Length Among Older Women. J Gerontol A Biol Sci Med Sci [Internet]. 2017;72(11):1532–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28329327
19. Du M, Prescott J, Kraft P, Han J, Giovannucci E, Hankinson SE, et al. Physical activity, sedentary behavior, and leukocyte telomere length in women. Am J Epidemiol [Internet]. 2012;175(5):414–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22302075
20. Colon M, Hodgson A, Donlon E, Murphy JE. Effects of Competitive Triathlon Training on Telomere Length. J Aging Phys Act [Internet]. 2018;1–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30507277
21. Sousa C V, Aguiar SS, Santos PA, Barbosa LP, Knechtle B, Nikolaidis PT, et al. Telomere length and redox balance in master endurance runners: The role of nitric oxide. Exp Gerontol [Internet]. 2019;117:113–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30481549
22. Chilton W, O'Brien B, Charchar F. Telomeres, aging and exercise: Guilty by association? Int J Mol Sci. 2017;18(12).
23. Espinosa-Otalora RE, Flórez-Villamizar J, Esteban-Pérez CI, Forero-Castro M, Marín-Suarez J. Lifestyle effects on telomeric shortening as a factor associated with biological aging: A systematic review. Nutr Healthy Aging. 2021;6(2).
24. World Health Organization. Centro de prensa OMS. 2022 [cited 2023 Sep 25]. Envejecimiento y salud. Available from: https://www.who.int/es/news-room/fact-sheets/detail/ageing-and-health
25. Iqbal M, Nanda M, Isa M, Muhammad K, Ku N, Muhammad N, et al. Cardiovascular disease detection from high utility rare rule mining. Artif Intell Med [Internet]. 2022;131(July):102347. Available from: https://doi.org/10.1016/j.artmed.2022.102347
26. Ciumărnean L, Milaciu MV, Negrean V, Orășan OH, Vesa SC, Sălăgean O, et al. Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. Int J Environ Res Public Health. 2022;19(1).
27. Adams V, Linke A. Impact of exercise training on cardiovascular disease and risk. Biochim Biophys Acta Mol Basis Dis [Internet].

2019;1865(4):728–34. Available from: https://doi.org/10.1016/j.bbadis.2018.08.019

28. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary Behavior, Exercise, and Cardiovascular Health. Circ Res. 2019;124(5):799–815.
29. Huang YC, Wang CY. Telomere attrition and clonal hematopoiesis of indeterminate potential in cardiovascular disease. Vol. 22, International Journal of Molecular Sciences. MDPI; 2021.
30. Franco OH, de Laet C, Peeters A, Jonker J, Mackenbach J, Nusselder W. Effects of physical activity on life expectancy with cardiovascular disease. Arch Intern Med. 2005;165(20):2355–60.
31. Opresko PL, Shay JW. Telomere-associated aging disorders. Ageing Res Rev [Internet]. 2017;33:52–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27215853
32. Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mech Ageing Dev [Internet]. 2018; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29604323
33. Victorelli S, Passos JF. Telomeres and Cell Senescence - Size Matters Not. EBioMedicine [Internet]. 2017;21:14–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28347656
34. Flores I, Benetti R, Blasco MA. Telomerase regulation and stem cell behaviour. Curr Opin Cell Biol [Internet]. 2006;18(3):254–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16617011
35. Boniewska-Bernacka E, Pańczyszyn A, Klinger M. Telomeres and telomerase in risk assessment of cardiovascular diseases. Vol. 397, Experimental Cell Research. Elsevier Inc.; 2020.
36. Gomes NM, Shay JW, Wright WE. Telomere biology in Metazoa. FEBS Lett [Internet]. 2010;584(17):3741–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20655915
37. von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci. 2002;27(7):339–44.
38. Sahin E, Colla S, Liesa M, Moslehi J, Muller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature [Internet]. 2011;470(7334):359–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21307849
39. Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. Lancet Oncol. 2013;14(11):1112–20.
40. Wright DL, Jones EL, Mayer JF, Oehninger S, Gibbons WE, Lanzendorf SE. Characterization of telomerase activity in the human oocyte and preimplantation embryo. Mol Hum Reprod. 2001;7(10):947–55.
41. Cherkas LF, Aviv A, Valdes AM, Hunkin JL, Gardner JP, Surdulescu GL, et al. The effects of social status on biological aging as measured by white-blood-cell telomere length. Aging Cell. 2006;5(5):361–5.

42. Gallicchio L, Gadalla SM, Murphy JD, Simonds NI. The effect of cancer treatments on telomere length: A systematic review of the literature. Vol. 110, Journal of the National Cancer Institute. Oxford University Press; 2018.
43. Lin J, Epel E, Blackburn E. Telomeres and lifestyle factors: roles in cellular aging. Mutat Res [Internet]. 2012;730(1–2):85–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21878343
44. Shadyab AH, LaMonte MJ, Kooperberg C, Reiner AP, Carty CL, Manini TM, et al. Leisure-time physical activity and leukocyte telomere length among older women. Exp Gerontol [Internet]. 2017;95:141–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28552815
45. Tucker LA. Physical activity and telomere length in U.S. men and women: An NHANES investigation. Prev Med [Internet]. 2017;100:145–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28450121
46. Dimauro I, Scalabrin M, Fantini C, Grazioli E, Beltran Valls MR, Mercatelli N, et al. Resistance training and redox homeostasis: Correlation with age-associated genomic changes. Redox Biol [Internet]. 2016;10:34–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27687219
47. O'Callaghan NJ, Fenech M. A quantitative PCR method for measuring absolute telomere length. Biol Proced Online. 2011;13(1):1–10.
48. Piplani S, Alemao NN, Prabhu M, Ambar S, Chugh Y, Chugh SK. Correlation of the telomere length with type 2 diabetes mellitus in patients with ischemic heart disease. Indian Heart J [Internet]. 2018;70:S173–6. Available from: https://doi.org/10.1016/j.ihj.2018.09.007
49. Ludlow AT, Roth SM. Physical activity and telomere biology: Exploring the link with aging-related disease prevention. Vol. 2011, Journal of Aging Research. 2011.
50. Hoffmann T, Worrall L. Designing effective written health education materials: considerations for health professionals. Disabil Rehabil [Internet]. 2004;26(19):1166–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15371031
51. Deng Y, Li Q, Zhou F, Li G, Liu J, Lv J, et al. Telomere length and the risk of cardiovascular diseases: A Mendelian randomization study. Front Cardiovasc Med. 2022 Oct 24;9.
52. Rehkopf DH, Needham BL, Lin J, Blackburn EH, Zota AR, Wojcicki JM, et al. Leukocyte Telomere Length in Relation to 17 Biomarkers of Cardiovascular Disease Risk: A Cross-Sectional Study of US Adults. PLoS Med. 2016 Nov 1;13(11).
53. Koriath M, Müller C, Pfeiffer N, Nickels S, Beutel M, Schmidtmann I, et al. Relative telomere length and cardiovascular risk factors. Biomolecules. 2019 May 1;9(5).
54. Brandao CFC, Nonino CB, de Carvalho FG, Nicoletti CF, Noronha NY, San Martin R, et al. The effects of short-term combined exercise training on telomere length in obese women: a prospective, interventional study. Sports Med Open. 2020 Dec 1;6(1).

55. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, et al. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. Med Sci Sports Exerc. 2019 Jun 1;51(6):1270–81.
56. Marin C, Yubero-Serrano EM, Lopez-Miranda J, Perez-Jimenez F. Endothelial aging associated with oxidative stress can be modulated by a healthy mediterranean diet. Int J Mol Sci [Internet]. 2013;14(5):8869–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23615475
57. Garcia-Calzon S, Moleres A, Martinez-Gonzalez MA, Martinez JA, Zalba G, Marti A, et al. Dietary total antioxidant capacity is associated with leukocyte telomere length in a children and adolescent population. Clin Nutr [Internet]. 2015;34(4):694–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25131600
58. Canudas S, Becerra-Tomas N, Hernandez-Alonso P, Galie S, Leung C, Crous-Bou M, et al. Mediterranean Diet and Telomere Length: A Systematic Review and Meta-Analysis. Vol. 11, Advances in Nutrition. Oxford University Press; 2020. p. 1544–54.
59. Barragán R, Ortega-Azorín C, Sorlí J V., Asensio EM, Coltell O, St-Onge MP, et al. Effect of physical activity, smoking, and sleep on telomere length: A systematic review of observational and intervention studies. Vol. 11, Journal of Clinical Medicine. MDPI; 2022.
60. Tucker LA. Dietary Fiber and Telomere Length in 5674 U.S. Adults: An NHANES Study of Biological Aging. Nutrients [Internet]. 2018;10(4). Available from: http://www.ncbi.nlm.nih.gov/pubmed/29570620