
PHYSICAL ACTIVITY AND CARDIOVASCULAR AGING: THE MECHANISM AND RECENT EVIDENCES

Theressia Handayani¹, Stephanie Wijayanti¹, Dana Daniati¹, Cynthia Lawrence¹, Angelia Ongko Prabowo¹, Luh Putu Liana Indayana Dewi¹, Luh Gede Wiwin Witsari Dewi¹, Ni Luh Okta Saktiadewi Tanjung¹, Indira Vidiari Juhanna²

¹ Anti-Aging Medicine Post Graduate Program Biomedic Medical Faculty Universitas Udayana, 80234, Denpasar, Indonesia

² Physiology Department Medical Faculty Universitas Udayana, 80234, Denpasar, Indonesia
Email: theressdr@gmail.com

ABSTRACT

Lower the health burden and maintain the wellbeing is a definition of successful aging in population. There are some factors that influence the successful aging, such as physiological, mental, social, and lifestyle variables. The one of most significant lifestyle factors that can reducing the chronic diseases, improving health and survival, and enhancing cognitive and physical functions in elderly is physical activity. Recent systematic review showed the benefit of exercise for overall health and cardiovascular system. In the younger population, physical activity promotes successful aging. To explain the correlation between exercise and successful aging was the main aim of this narrative review.

Keywords: *exercise; healthy life style; cardiac aging*

INTRODUCTION

Aging is a neither simple nor very complex process. The definition of aging is a gradual physiological integrity loss that occurs depending on time. This process ultimately leads to decreased physical function¹. molecular and cellular damage over the life cycle of the organism frequently contributes to pathological conditions associated with age².

These days, aging becomes a global health problem. The data from World Health Organization showed that the elderly population (aged 65 years or older) will rise to 1.6 billion in 2050 and constitute up 16 % of the global residents³. The increase of aging population is linked with many health condition problems and large medical cost. Non-communicable diseases and chronic including diabetes, cardiovascular disease, dementia, blood pressure disease and cancer are common disease that we found in elderly⁴.

There is a need for senior citizen to experience morbidity and disability to protect their roles successfully⁵. Being able to preserve the quality of life and reduce the burden of wellbeing is considered as successful aging⁶. Many factors, including physiological, psychological, social, and lifestyle factors, affect successful aging⁷. One of the most important lifestyle factor that can prevent chronic diseases, boosting durability as well as sustainability, and also develop physical functions and cognitive in elderly is physical activity^{6,7}. Therefore, to explain the correlation between exercise and successful aging is the main aim of this narrative review.

DISCUSSION

Mechanism of physical activity and aging prevention

Genomic instability, mitochondrial dysfunction, telomere protection, and low grade inflammation plays very important role in aging⁸. One of the important process that caused aging is genetic injury accumulation during the person's lifespan⁹. The two main factors in the process of genomic instability are exogenous & endogenous which cause translocations, mutations, losses and gains in chromosomes, destruction of gene and shortening of telomeres. Exogen factors were made

from physical, chemical, and biological, while endogen factors consisted of deoxyribonucleic acid (DNA) replication defects, uncontrolled hydrolytic responses, and reactive oxygen species (ROS)¹⁰.

Exercise and good physical activity plays important role in preserving genomic integrity. A result shows that aerobic physical activity enhances the repairing mechanism of DNA and the signaling of nuclear factor kappa B (NF- κ B) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) in a study using animal models¹¹. The increased number of DNA repairs combined with the lowered amount of DNA damages (up to 77%) are able to overcome aging process and make the disease that related to cardiovascular risk reduce, which can be done through physical exercises¹².

Mitochondrial dysfunction plays important part in aging¹⁰. Some mechanisms are linked to mitochondrial integrity and biogenesis, including mitochondrial deficiencies that enhance their predisposition in the presence of stress, thus triggering inflammatory reactions mediated by ROS (Reactive Oxygen Species) and permeabilization-facilitated, which also speed up the aging process¹³.

One of positive effect of daily physical activity is on mitochondrial function. The previous study showed people that train their endurance has expression of mitochondrial proteins, mtDNA, and TFAMs in higher levels¹⁴. An animal-based study found that mtDNA systemic mitochondrial biogenesis was induced by a 5-month aerobic physical activity program and enhanced multi-organ oxidative capacity, offering phenotypic protection and minimizing the risk of premature mortality and multisystem pathology¹⁵.

Low grade inflammation plays important role in aging. Regular physical activity reduces inflammatory markers in older adults. Furthermore, inflammation of the low-grade, including chronic illness, has been related to most of the elements of good aging and can speed down the aging process^{16,17}. A recent study in population showed that the chance of life free of chronic conditions, cognitive decline and physical disability for an additional 10 years increases with higher level of physical activity¹⁸.

Recent studies have shown that the activation of telomerase will reverse aging, to be specific, in premature aging mice which lacked in telomerase when the reactivation of the enzyme occurs¹⁹. Aging promotes the accumulation of DNA damage, particularly in very sensitive chromosome areas like the telomeres. Latest research shows that there would be a protective function for physical activity against stress-related telomere loss. Physical activity gives a massive effect on telomere length, es in chronic design and moreover in older people in contrary to age-induced decline in telomere reduction. A few possible pathways have been reported to correlate workout and reduced telomere longevity with altered activity of telomerase, inflammation, oxidative stress, and lowered composition of skeletal muscle satellite cells²⁰.

Physical activity has been connected to increased regulation of protective proteins (like telomeric repeat-binding factor 2) and proteins of DNA repair pathway (like Ku protein) and also the decreased control of negative regulatory proteins of cell cycle growth (like p16) in middle-aged athletes that hold up such association²¹. Antioxidant activity and decreasing ROS levels, holding up the REDOX balance, defending against DNA destruction and consequently diminishes telomere alleviation are affiliated with regularly physical activity^{20,21}.

Recent evidences

An epidemiological studies showed that the risk of all-caused deaths and the risk of developing conditions such as type 2 diabetes and cardiovascular disease is lower for older adults who regularly exercise at a moderate level²². Physical activity, health and all – causes mortality were reported to have a strong inverse relationship, as shown in epidemiological studies²³. A prospective cohort study showed a 40 – 50% reduction in certain cause, cardiovascular disease and cancer mortality rates and were associated with a higher physical activity level compared to the lower activity levels²⁴.

Mortality is strongly attributed to objectively measured cardiovascular fitness²⁵. Functional independence has been strongly linked to muscle strength and aerobic fitness. Enhancements in muscle strength and aerobic fitness also show in functional independence in older adults without disabilities²⁶. A reduced risk of approximately 30-50% of functional limitations and disability was shown in older adults who performed physical activity of adequate amount and duration has been carried out as reported in a systemic review recently²⁶.

A recent review showed a positive association among high levels of cardiovascular fitness and great health. There may be advantages of some kind of physical activity that increases cardiovascular fitness. Improving cardiovascular fitness in older adults means improving their health. The same benefit is also offered by starting from a low level of cardiovascular fitness²⁷.

Physical exercise and cardiac aging

Aging makes changes in the heart on structural and functional changes that are associated with a levitating risk of cardiovascular disease and weakened functional capacity in the elderly. Advanced age is considered a major independent risk factor for HF (heart failure). The accumulating effect of repetitive insults and injuries to the heart during its lifespan, such as myocardial infarctions and hypertension, is irrefutably a major cause of maladaptive myocardial remodeling in the elderly. Cardiac aging also developed from intrinsic aging that occurs at a cellular and molecular level that the role of the heart can influence²⁸. Stress response, metabolism of fatty acids, hypertrophy, contractility, inflammation of mitochondrial function, and development of extracellular matrix have been identified as key molecular phenotypes of cardiac aging associated with transcriptional pathway alterations²⁹.

Desensitization of β -adrenergic receptor (β -AR) is a mechanism of sympathetic dysregulation in the aged core. During normal aging, circulating levels of norepinephrine rise by 10-15 percent per decade²⁹. Post-synaptic machinery desensitization is triggered by higher β -AR catecholamine occupancy, which activates a compensatory mechanism in aged cardiomyocytes^{28,29}.

Prolonged Ca^{2+} transients that occurred in aging myocardium is caused by the decreasing amount of sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a), and changes that is related to aging in the proteins involved on EC coupling can prevent the restoration of the Ca^{2+} intracellular impairments³⁰.

A study using animal model showed result that training in aerobic physical activity causes a faster increase and decay of Ca^{2+} transients in cardiomyocytes and subsequent improvement in systolic and diastolic activity. Via more efficient coupling of L-type Ca^{2+} channels and RyR receptors, increased SERCA2a and NCX expression, enhanced SERCA2a function through transient CaMKII activation or PLB inhibition, and enhanced Ca^{2+} myofilament sensitivity, the mechanisms for such modification induced by physical activity in Ca^{2+} cycling in young hearts are potentially mediated³⁰.

Recent systematic review showed the benefit of exercise for overall health and cardiovascular system. Physically active middle-aged and older adults were more likely than sedentary adults to age successfully (OR=1.64, 95 % CI: 1.40–1.94). In the younger group (OR=1.71, 95 percent CI: 1.41–2.08), the impact of physical activity was greater than in the older group (OR=1.54, 95 percent CI: 1.13–2.08)³¹.

CONCLUSION

Our review showed that there was good evidence of physical inactivity in older adults for chronic health problems. They must increase regularly exercise to minimize mortality and morbidity. The research shows that daily exercise is good for healthy and vulnerable elderly people. If physical exercises are regularly done, the probability of acquiring serious cardiovascular and metabolic diseases, osteoporosis, obesity, falls, cognitive problems, and weak muscle will be reduced. Regular physical activity is effective to prevent aging for middle-aged and older adults, particularly among the younger population.

REFERENCES

1. López-Otín C, Blasco MA, Partridge L, Serrano M KG. The hallmarks of aging. *Cell* 2013;153:1194–217. <https://doi.org/10.1016/j.cell.2013.05.039>.
2. Gems D PL. Genetics of longevity in model organisms: debates and paradigm shifts. *Annu Rev Physiol* 2013;621–44. <https://doi.org/10.1146/annurev-physiol-030212-183712>.
3. Organization, World Health UNI of A. Global Health and Aging n.d.

4. Avendano M, Glymour MM, Banks J MJ. Health disadvantage in US adults aged 50 to 74 years: a comparison of the health of rich and poor Americans with that of Europeans. *Am J Public Heal* 2009;540–8. <https://doi.org/10.2105/AJPH.2008.139469>.
5. Michel JP SR. “Healthy Aging” Concepts and Measures. *J Am Med Dir Assoc* 2017;460–4. <https://doi.org/10.1016/j.jamda.2017.03.008>.
6. Nosraty L, Pulkki J, Raitanen J, Enroth L JM. Successful Aging as a Predictor of Long-Term Care Among Oldest Old: The Vitality 90+ Study. *J Appl Gerontol* 2019;553–71. <https://doi.org/10.1177/0733464817716968>.
7. Young Y, Frick KD PE. Can successful aging and chronic illness coexist in the same individual? A multidimensional concept of successful aging. *J Am Med Dir Assoc* 2009;87–92. <https://doi.org/10.1016/j.jamda.2008.11.003>.
8. Rebelo-Marques A, De Sousa Lages A, Andrade R et al. Aging Hallmarks: The Benefits of Physical Exercise. *Front Endocrinol* 2018;258. <https://doi.org/doi:10.3389/fendo.2018.00258>.
9. Moskalev AA, Shaposhnikov MV, Plyusnina EN, Zhavoronkov A, Budovsky A, Yanai H et al. The role of DNA damage and repair in aging through the prism of Koch-like criteria. *Ageing Res Rev* 2013;12:661–84. <https://doi.org/10.1016/j.arr.2012.02.001>.
10. JH H. DNA damage, aging, and cancer. *N Engl J Med* 2009;361:1475–85. <https://doi.org/10.1056/NEJMra0804615>.
11. Cash SW, Beresford SA, Vaughan TL, Heagerty PJ, Bernstein L, White E et al. Recent physical activity in relation to DNA damage and repair using the comet assay. *J Phys Act Heal* 2014;11:770–6. <https://doi.org/10.1123/jpah.2012-0278>.
12. A I. Genomic biomarkers and clinical outcomes of physical activity. *Ann N Y Acad Sci* 2011;1229:103–14. <https://doi.org/10.1111/j.1749-6632.2011.06091>.
13. Ristow M SS. Extending life span by increasing oxidative stress. *Free Radic Biol Med* 2011;51:327–36. <https://doi.org/10.1016/j.freeradbiomed.2011.05.010>.
14. Kong Y, Trabucco SE ZH. Oxidative stress, mitochondrial dysfunction and the mitochondria theory of aging. *Aging (Albany NY)* 2014;39:86–107.
15. Lanza IR, Short DK, Short KR, Raghavakaimal S, Basu R, Joyner MJ et al. Endurance exercise as a countermeasure for aging. *Diabetes* 2008;57:2933–42. <https://doi.org/10.2337/db08-0349>.
16. Brinkley TE et al. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. *J Gerontol A Biol Sci Med Sci* 2009;64:455–61.
17. Vasto S et al. Inflammation, ageing and cancer. *Mech Ageing Dev* 2009;130:40–5.
18. Gopinath, B., Kifley, A., Flood VM et al. Physical Activity as a Determinant of Successful Aging over Ten Years. *Sci Rep* 2018;8:10522. <https://doi.org/doi.org/10.1038/s41598-018-28526-3>.
19. Jaskelioff M, Muller FL, Paik J-H, Thomas E, Jiang S, Adams AC et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature* 2011;469:102–6. <https://doi.org/10.1038/nature09603>.
20. Puterman E, Lin J, Blackburn E, O’Donovan A, Adler N EE. The power of exercise: buffering the effect of chronic stress on telomere length. *PLoS One* 2010;5:10837. <https://doi.org/10.1371/journal.pone.0010837>.
21. Arsenis NC, You T, Ogawa EF, Tinsley GM ZL. Physical activity and telomere length: impact of aging and potential mechanisms of action. *Oncotarget* 2017;8:45008–19. <https://doi.org/10.18632/oncotarget.16726>.
22. Ueshima K, Ishikawa-Takata K, Yorifuji T et al. Physical activity and mortality risk in the Japanese elderly. A cohort study. *Am J Prev Med* 2010;38:410–8.
23. Iijima K, Iimuro S, Shinozaki T et al. Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type2 diabetes mellitus beyond traditional

-
- risk factors: the Japanese elderly diabetes intervention trial. *Geriatr Gerontol Int* 2012;12:77–87.
24. Oguma Y S-TT. Physical activity decreases cardiovascular disease risk in women: review and meta-analysis. *Am J Prev Med* 2004;26:407–18.
 25. Gregg EW, Cauley J, Stone K et al. Relationship of changes in physical activity and mortality among older women. *JAMA* 2003;289:2379–86.
 26. Paterson D W d. Physical activity and functional limitations in older adults: a systematic review related to Canada’s physical activity guidelines. *Int J Behav Nutr Phys Act* 2010;7:38.
 27. Stratton JR, Levy WC, Caldwell JH, Jacobson A, May J, Matsuoka D MK. Effects of aging on cardiovascular responses to parasympathetic withdrawal. *J Am Coll Cardiol* 2003;41:2077–83.
 28. Leosco D, Parisi V, Femminella GD, Formisano R, Petraglia L, Allocca E BD. Effects of exercise training on cardiovascular adrenergic system. *Front Physiol* 2013;4:348.
 29. Bhella PS, Hastings JL, Fujimoto N, Shibata S, Carrick-Ranson G, Palmer MD, Boyd KN, Adams-Huet B LB. Impact of lifelong exercise “dose” on left ventricular compliance and distensibility. *J Am Coll Cardiol* 2014;64:1257–66.
 30. Roh J, Rhee J, Chaudhari V RA. The Role of Exercise in Cardiac Aging: From Physiology to Molecular Mechanisms. *Circ Res* 2016;118:279–95. <https://doi.org/doi:10.1161/CIRCRESAHA.115.305250>.
 31. Lin YH, Chen YC, Tseng YC, Tsai ST TY. Physical activity and successful aging among middle-aged and older adults: a systematic review and meta-analysis of cohort studies. *Aging (Albany NY)* 2020;12:7704–16. <https://doi.org/doi:10.18632/aging.103057>.