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The Effects on Antiaging Molecules of Physical Exercise

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Abstract
Regular physical activity has anti-aging effects and reduces the risk of injuries in older individuals. Both aerobic and resistance exercise training exert multiple beneficial effects on the aging body. In humans, aging changes many biological processes, from the molecular to the physical level, and affects mental health and cardio-respiratory health, body composition and muscle function. Muscle morphology, fiber size, and functional properties including strength, are preserved by lifelong physical activity. The molecular mechanisms by which older humans maintain musculoskeletal function are of emerging interest, particularly in developed nations with aging populations. In cells, telomerase activity and nicotinamide adenine dinucleotide (NAD+) are indispensable anti-aging factors for cellular survival. Physical activity induces the increase in telomerase activity and NAD+ level with anti-aging effects in the cells. This review will assess recent studies that correlated NAD+ as a signaling molecule, telomerase as an indicator, to exercise and the aging process.

Keywords: Anti-ageing, Exercise, Health, NAD+, Physical activity, Telomerase activity.

1. Introduction

With advances in health care and improved living standards, human life expectancy is now projected to exceed 80 years in industrialized countries. Subsequently, the proportion of the elderly population has steadily increased. And by 2050, almost a quarter of the world's population will be over the age of 65. As the population grows and ages, the cost of providing health care has also increased, among other socio-economic challenges. Unfortunately, healthy life expectancy lags far behind overall life expectancy, implying a longer course of complications. To help reduce this financial impact and improve overall health, primary prevention strategies that include lifestyle choices of healthy diet and regular exercise have been promoted [1,3].

Physical activity and increased physical exercise are known to decrease the likelihood of morbidity and mortality from a variety of causes such as reduced cardiovascular disease, insulin resistance, and hypertension with concomitant increases in longevity. Regular physical activity has antiaging effects and reduces the risk of injuries in older individuals. In humans, aging impairs multiple biological processes from a molecular to organismal level, and affects mental and cardio-respiratory health, body composition, and muscle function. Both aerobic and resistance exercise training exert multiple beneficial effects on the aging body. In humans, aging impairs multiple biological processes from a molecular to organismal level, and affects mental and cardio-respiratory health, body composition, and muscle function. Muscle morphology, fiber size, and functional properties including strength, are preserved by lifelong physical activity. The molecular mechanisms by which older humans maintain musculoskeletal function are of emerging interest, particularly

in developed nations with aging populations [4,5].
NAD+ is a coenzyme that is involved in cellular redox reactions and is a substrate for NAD-dependent enzymes. The involvement of NAD+, nicotinamide phosphoribosyl transferase (NAMPT) and SIRT1 in the regulation of metabolism and aging has been systematically presented by researchers. The NAD+/NADH ratio may influence ROS formation and oxidative stress due to the regulation of intracellular ATP production, redox state, and metabolic enzymes. With age, NAD+ and nicotinamide mononucleotide (NMN) levels decrease and NADH levels increase. The NAD+/NADH ratio plays an important role in regulating the intracellular redox state, and several enzymes involved in regulating metabolism are regulated by the NAD+/NADH ratio. The NAD+/NADH ratio is an indicator of cellular reduction potential and is regulated by small changes in NAD+ concentration. Aging appears to be enhanced when the NAD+/NADH ratio shifts toward NADH [6,8].
In cells, telomerase activity and nicotinamide adenine dinucleotide (NAD+) are indispensable antiaging factors for cellular survival. Telomere length is a primary biomarker of cellular aging that has recently been associated with cardiovascular disease, insulin resistance and hypertension, and morbidity and mortality. In certain cells, the ribonucleoprotein, telomerase, maintains and lengthens telomeres, allowing continued mitotic activity without progression to senescence. In cells with telomerase activity, telomere length can be maintained, therefore delaying senescence and tissue aging. In addition, there is growing research interest in studying the physiological effects of NAD+ given that increased NAD+ levels are related to an increase in longevity and NAD+ levels fluctuate in response to exercise and nutritional stimuli. It is clear that physical activity and exercise induce to increase in telomerase activity and NAD+ level with antiaging properties in the cells [9,4].

In order to find the relationship between NAD+ as a signaling molecule and telomerase as an indicator, with exercise and the aging process, we conducted a review on several studies in order to fund direct relationship between diet, type of exercise and intensity.

2. Telomerase Activity in the Physical Exercise

Whereas the reduction of disease end points will necessarily increase longevity, whether physical activity also directly affects cellular aging remains unclear for either rodents or humans. Telomere length is a primary biomarker of cellular aging that has recently been associated with cardiovascular diseases, insulin resistance and hypertension, and morbidity and mortality. In the present study, we explored the correlation of physical activity levels with telomere length and telomerase enzyme activity. Telomeres are found on the ends of linear chromosomes and act as a mitotic clock, which shortens with every cell division until cellular senescence. Thus, telomeres are considered an important aging biomarker. Telomeres and their length are not, however, static entities but rather are a dynamic system. In certain cells, the ribonucleoprotein, telomerase, maintains and lengthens telomeres, allowing continued mitotic activity without progression to senescence. In cells with telomerase activity, telomere length can be maintained, thus delaying senescence and tissue aging. Human cells with telomerase activity include germ line cells, embryonic and stem cells, and adult proliferating cells such as those found in the immune system [10].

3. NAD+ Level in the Physical Exercise

NAD+ is an indispensable molecule for cellular survival. For example, NAD+ is an essential redox molecule used for ATP production and it is a substrate for poly-ADP ribose polymerases (PARPs), which are involved in repairing DNA damage. NAD+ is also important for the generation of Ca2+-mobilising second messengers. In both humans and rodents, NAD+ concentrations and sirtuin activity reportedly decline with aging in a tissue-specific manner. Diminished sirtuin activity in human skeletal muscle may impair oxidative capacity and mitochondrial function, and lead to sarcopenia [11]. Nicotinamide adenine dinucleotide (NAD+) and its phosphorylated form (NADP+) are key molecules in ubiquitous bioenergetic and cellular signaling pathways, regulating cellular metabolism and homeostasis. Thus, supplementation with NAD+ and NADP+ precursors emerged as a promising strategy to gain many and multifaceted health benefits. In this proof-of-concept study, we sought to investigate whether chronic nicotinamide riboside administration (an NAD+ precursor) affects exercise performance and as we know, there is growing research interest in studying the physiological effects of nicotinamide adenine dinucleotide (NAD+) given that increased NAD+ levels are related to an increase in longevity and NAD+ levels fluctuate in response to exercise and nutritional stimuli. NAD+ is continuously consumed as a substrate in adenosine diphosphate (ADP)-ribosylation, cyclization, and deacylation reactions that influence many physiological processes. Exercise really does influence how we age, and a new study shows how regular exercise in later life can help offset the decline of NAD+ and NAMPT, two important molecules that facilitate cellular energy production, in skeletal muscle [12].

4. Effects of Training Modality and Type of Physical Activity on Telomere Biology

According to the upcoming studies, it seems that the training method is an important factor that should be investigated in terms of its effect on telomere dynamics. However, such consideration of different teaching methods in telomere biology is rare. In a study, researchers compared the effect of different exercise methods (such as resistance training or RT, endurance training, and interval training) on the activity of telomere length (TL) and telomerase. Endurance and interval training protocols increased TL and telomerase activity. However, RT did not register any such difference. Therefore, although RT can be integrated into other exercise modalities, RT alone may not be sufficient as a substitute for endurance or interval training to induce any changes in TL [13].

Regarding the type of exercise, an observational study by Loprinzi et al. Comparing different physical activities with different metabolic demands (eg, weightlifting, basketball, cycling, running) showed that only running could be positively related to TL maintenance. This association of TL maintenance with running may also help explain the protective effects of aerobic exercise on the incidence of cardiovascular disease and all-cause mortality (14) and that several chronic diseases are associated with telomere attrition [15].

Exercise intensity is a critical factor not only in sports training programs but also in the telomere environment and aging. However, selected studies provide conflicting findings on whether moderate or vigorous exercise has a beneficial effect on telomere dynamics. Researchers examined participants enrolled in the large-scale Nurses' Health Study and showed that moderate exercise is sufficient to maintain leukocyte TL in women. That is, the relationship between the level of physical activity (in terms of intensity and frequency) and TL was described as an inverted U-shaped curve, which indicates that the average level of exercise has a beneficial effect on TL [16].

5. NAD+ depletion influences ATP production, ROS generation and antioxidative defense

It seems that with age, the level of NAD+ decreases and the level of NADH increases. In other words, dysfunctional mitochondria and increased glycolysis create a state of "reduced stress", in which NADH is overproduced and NAD+ is reduced [17]. Depletion of NAD+ affects mitochondrial ATP production, "reduction stress" and ROS production, as well as impairment of antioxidant defense and DNA repair. For example, mitochondrial dysfunction with aging was reported when cells lacked sufficient NAD+. The level of NAD+ is required for the formation of NADPH, which is required for the regeneration of glutathione and catalase inactivated by H_2O_2 and is important in the thioredoxin antioxidant system [18-20]. One study found that increasing NAD+ levels in mice using nicotinamide mononucleotide (NMN), a precursor to NAD+, was able to improve their energy metabolism, reduce DNA damage, and increase lifespan [21]. Similarly, other research has shown that boosting NAD+ levels can help protect against age-related diseases and improve overall health [22-23]. There are several factors that can contribute to the decline of NAD+ levels with age, including oxidative stress, inflammation, and the loss of certain enzymes [24].

6. Conclusions

The review of various research shows a direct relationship between exercise and changes in telomere size and NAD+ level, both of which have a direct effect on the aging process. But the point that is thought-provoking in all studies is the existence of a relationship between the intensity and duration and the manner of physical exercises and biological molecules in the aging process. As a result, the type and intensity of exercises are decisive in the process of reducing aging through signaling molecules and should be included in the agenda of studies.

This conducted reviw shows that most studies emphasize the positive effects of physical activity on telomere dynamics, there is no consensus on the most beneficial type of exercise and exercise method (intensity, duration and frequency). In addition, physical inactivity is a major risk factor for cardiovascular disease and several other chronic diseases, independent of exercise. It should be noted that the reduction of sedentary behavior has a profound and positive effect on maintaining and/or increasing TL. Calorie restriction and physical activity are the best strategies to improve NAD+ levels. Although most studies emphasize the beneficial role of physical activity on telomere dynamics, NAD+ levels, and aging, the molecular events in maintaining and/or increasing TL length and NAD+ levels are not well understood. The levels of NAD+ and NADH in the body change with age in ways that can impact health and longevity. Boosting NAD+ levels using supplements and other interventions may have potential benefits for age-related diseases and overall health. Future studies should provide more detailed information about the participants' physical fitness level as well as the characteristics of the exercise training method for standardization and comparison in order to reach a more definitive conclusion.

In order to reach a consensus on the direct relationship between aging and telomere length and NAD+ level, we need to set up a regular program that includes important factors such as proper planning of physical exercises at weak, moderate, and intense levels, as well as proper diet planning. food and finding the relationship between calorie intake and the level of molecular markers.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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