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Original Article

Sports and aging: the role of physical activity in slowing the shortening of telomeres, a key molecular marker of cellular senescence

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Abstract
Dozens of data prove that the DNA damage accumulates during human aging and that lifestyle factors contribute to the accumulation of DNA alteration. Telomeres are nucleoprotein complexes located at the ends of chromosomes, serving to protect DNA integrity by acting as caps. Telomere length decreases with age, which promotes cell senescence. Shortened telomeres accelerate aging and can lead to cells apoptosis. Telomere shortening is associated with biological aging and can be influenced by factors such as inflammation and oxidative stress. Recent evidence supports that telomere length of skeletal muscle cells and leukocytes may be positively associated with healthy living and inversely correlated with the risk of age-related syndromes, including obesity, cancer, chronic pain, diabetes, cardiovascular disease, and stress. In this paper, recent studies are summarized to examine the possible influence of exercise on telomere length. Higher levels of exercise or physical activity are related to longer telomere lengths in several populations, and athletes tend to have longer telomere lengths than non-athletes. This relationship is particularly clear in older individuals, proposing a role of physical activity in preventing the typical age-induced decrements in telomere length. It is proposed that physical activity has a positive effect on the rate of telomere length shortening. In particular, the athletes tend to have longer telomere than sedentary individuals. Exercise has a beneficial outcome on telomere length compared with usual care or inactivity. The evidence gathered to date shows that especially aerobic exercise slows the decline in telomere length. It is fundamental to emphasize how this is important not to overdo it, that is, overtraining must be avoided. Anyway, physical activity and exercise can have both restorative and protective effects and, as such, show great probable to improve well-being and increase longevity. Future studies is needed to mechanistically examine the properties of diverse modalities of exercise on telomere length in middle-aged and older subjects.
Key Words: **exercise, healthy aging, overtraining, telomere length, telomerase.**

Introduction

The social and medical advances achieved during the 20th century have led to a notable in-crease in lifespan, doubling life expectancy worldwide (Dzau et al, 2019; Szychowska and Drygas, 2022). The expression "successful aging" was coined by Rowe and Kahn in the 1980s and is a model that is based on the absence of chronic syndromes, physical disabilities, and risk factors for diseases in old age. Lifestyle factors, such as exercise and diet, have identified as key events in achieving healthy aging and in recent decades, a lot of articles have been published on the health effects of **physical activity** (**PA**) (Szychowska and Drygas, 2022; Dempsey et al, 2022).

In the 1970s, Tromsø, the largest city in Norway, had high mortality rates due to cardiovascular disease. To help combat them, research was launched and between 1974 and 2016, 7 health surveys have been conducted on large cohorts. PA has been found to be related to a reduction in mortality and the subjects who practiced an adequate level of PA for their age reported being in good health up to 15 years longer than not highly active subjects. Furthermore, higher intensity of PA was related to a greater healthy action (Opdal et al, 2020).

Gopinath *et al.* found that Australian adults who practiced elevated levels of PA (over 5,000 MET min/week) were twice as likely to age successfully than those who practiced less intense PA (Gopinath et al, 2018). Feng *et al.* proven that in older Chinese, at least 150 minutes per week of energetic to modest PA was related to better quality of life, better cognitive function, and fewer depressive symptoms. These health results are key elements of healthy/successful aging (Feng et al, 2019).

Nelson *et al.* and Garatachea *et al.* performed a synthesis of the anti-aging effects of physical exercise; they reported the attenuation of neurodegeneration and cognitive alterations, the decrease in blood pressure levels and the increase in numerous cardio-vascular functions, the improvement of respiratory function caused by better ventilation and gas exchange, an improvement in muscle function which determines a better motor control and joint mobility, a reduction in body weight and adiposity in favor of an increase in muscle mass and bone density (Nelson et al, 2007; Hernandez-Segura et al, 2018).

Regular PA particularly practiced by the elderly population, especially a type of resistance and aerobic training, plays a significant action at a multisystem level, preventing muscle atrophy, supporting cardiorespiratory fitness and cognitive function, increasing metabolic and so improving functional independence.

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Exercise is the most powerful non-pharmacological intervention for extending healthy lifespan. Exercise can increase motivation to change lifestyle behaviors, improve aerobic ability and physical function, control fatigue, and improve quality of life. Dozens of studies have shown that mortality decreases with increasing PA, even among high-risk subjects; mortality from coronary syndrome is much lower in physically active people than in inactive people; the risk of syndromes, such as breast cancer, type 2 diabetes, hypertension, and cancer tend to be markedly lower in active subjects than in their sedentary counterparts. There are several mechanisms through which constant PA could reduce disease onset and mortality (Zhu et al, 2023). For example, the practice of PA reduces age-related oxidant status and proinflammatory signals and can activate pathways involved in anabolic and mitochondrial biogenesis in skeletal muscle. PA can improve endothelial function and reduce arterial stiffness by decreasing markers of oxidative and inflammatory damage in vascular tissue together with an improvement in the synthesis of enzymes with antioxidant power and the availability of nitric oxide (Zhu et al, 2023).

Aging is an intraindividual and complex process, often defined as a progressive and time-dependent loss of the individual's physiological integrity, which leads to a deterioration of physical function (López-Otín et al, 2013). Cellular and molecular damage accumulated over the individual's lifetime often leads to age-associated pathological conditions and therefore makes them more prone to death (Foreman et al, 2018). One of the most complicated questions that biological research has yet to understand is the specific molecular and cellular mechanisms involved in the aging process.

López-Otín *et al*. proposed nine molecular and cellular characteristics involved in the aging process, including epigenetic alterations, genomic instability, loss of proteostasis, telomere attrition, deregulated feeling of nutrients, cellular senescence, mitochondrial dysfunction, stem cell exhaustion and impaired intercellular connections (López-Otín et al, 2013) (**Figure 1**). These distinctive traits would be ex-pressed during the normal aging process; their intensification can accelerate senescence and, conversely, their improvement can delay the aging process, thus increasing lifespan.

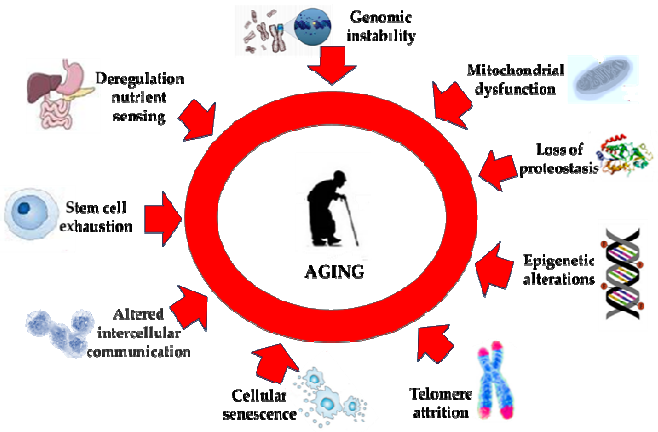

Figure 1. Telomere length and other principal hallmarks involved in aging.

As showed in figure 1, the research into the biology of aging has looked to discover "biomarkers" of aging. Among these, telomere length is considered a fundamental biomarker of aging since telomeres shorten as individuals age and such markers can be considered as a reliable biological clock (Hernandez-Segura et al, 2018; Chakravarti et al, 2021).

Experimental evidence published in the last decade suggests that one of the pathways through which stress can accelerate cellular aging is by acting on the length of telomeric DNA confined to the ends of chromosomes.

Consequently, the **telomere length** (**TeLe**) is currently considered an excellent biomarker of the biological age of the cell and therefore, in general, of the living being. The telomeres are nucleoprotein structures that serve as guardians of genome stability by ensuring protection against both cell death and senescence.

Telomere length is a hallmark of biological aging, and it shortens during cell division. A short TeLe is associated with several age-related syndromes and mortality. Telomere health is found throughout the lifespan by a combination of both genetic and non-genetic influences.

The probable impact of PA on TeLe and aging continues to be a topic of interest in sports medicine research and beyond and in this paper summarizes data from recently published studies looking at the role of lifestyle variable such PA on telomere dynamics and support the idea that engaging in constant PA, as well as following a correct diet and a lifestyle with less stress, seems to be able to slow down the shortening of telomeres.

This paper summarizes data from newly published studies looking at the role of PA on telomere dynamics in active subjects and suggesting that engaging in constant PA could slow down the shortening of telomeres.

Material & methods

A narrative review was conducted of telomere length literature within sport and exercise. The databases searched included SCOPUS, Google Scholar, and PubMed (MEDLINE). All papers were chosen based on a title search, year of publication (between 2014 and 2024), abstract screening, and full article screening for relevance to physical performance testing. Addition criteria included articles that assessed physical performance tests such as aerobic, anaerobic, strength, power, or speed tests in athletes to decide performance differences. Articles were excluded if participants were not healthy or assessed specific sporting performance. Search words included a combination of words: "exercise", "physical activity", "performance", "telomere", "telomerase", and "telomere length". Boolean operators "OR" and "AND" were taken into consideration alone or as combined terms, excluding duplicates. Articles that did not have their full text available were not included in the definitive analysis. Research was included and pick out based on their importance to assessing physical performance on the telomere length.

Results

Telomeres are protein structures present in DNA molecules; they are located at the ends of the chromosomes; their role is to preserve the genome integrity (Puterman et al, 2018; Mehrsafar et al, 2020; Blackburn, 1991; Herrmann et al, 2015). Telomeres can be compared to small plastic cylinders inserted at the end of shoelaces: telomeres protect the DNA "lace" by preventing the double helix from unraveling during moments that occur in the cell division.

In human cells, the telomeres are made up of 10 to 15 kilobases of a highly conserved hexameric tandemly repeated DNA sequence (TTAGGG) (Herrmann et al, 2015; Turner et al, 2019). They form a ring-shaped structure; their terminal regions are hidden, and the ends of the chromosomes would not be identified as double-strand breaks (Herrmann et al, 2015; Turner et al, 2019). By shortening a telomere to a critical length, ring structures could not form. Therefore, the resulting telomere would be recognized as a nick in double-stranded DNA, activating DNA damage responses, resulting in the induction of aging and apoptosis (Blackburn, 2010).

In 1962, Leonard Hayflick developed the telomere theory known as the "Hayflick limit" which hypothesizes the maximum potential length of human life at 120 years, i.e., the time in which cells with extremely short telomeres are so many that they can no longer replicate . (Hayflick, 2020; Blackburn, 2000). 50 years later, new science has expanded our understanding of our genetic potential. The data suggested that the enzyme called "telomerase" was able to function as a reverse transcriptase and could add nucleotides to the end of each chromosome, ensuring greater stability and therefore blocking short telomeres (Blackburn, 2000; Blackburn, 2001).

Blackburn, Greider and Szostak received the Nobel Prize in 2009 for the discovery of "how the enzyme telomerase was able to preserve the length of telomeres" These data led to the development of the idea that aging can potentially be delayed and/or controlled by activating telomerase and consequently reducing the rate of telomere erosion (Blackburn, 2010).

Scientific data from the last 10 years suggests that stress can also affect health through more rapid cellular aging, measured by the length of telomeric DNA (Puterman et al, 2018). As a result, TeLe appeared as a reliable biomarker of biological age. TeLe, therefore, can be considered a measure of physiological age and is linked to numerous age-related syndromes, lifespan and lifestyle factors (Jylhävä et al, 2017).

In somatic cells, TeLe is a "mitotic clock" capable of controlling the number of mitoses that each cell can undergo. Two mechanisms have been hypothesized that could explain the process of telomere shortening. First, it has been proposed that oxidative damage, caused by the overproduction of ROS, may lead to breaks in the 5'-TTAGGG-3' repeats, causing shortening of TeLe. Second, telomere replication presents a natural replication problem during mitosis. DNA sequences located at the ends of chromosomes cannot be fully replicated (Herrmann et al, 2018; Turner et al, 2019).

During cell divisions, TeLe is reduced to a critical minimum size, to the point of preventing further mitosis, resulting in apoptosis or cellular senescence, a phenomenon referred to as the replication end problem. The activity of the telomerase enzyme responds to the problem of final replication by improving telomere lengthening (Nguyen et al, 2019). Most mammalian somatic cells do not synthesize this enzyme, which explains the progressive loss of chromosome ends as well as the reduced proliferative ability found in some cells cultured in vitro. This enzyme deficiency in humans has been linked to premature manifestations of chronic syndromes mainly linked to the reduced recreational ability of the tissues.

Human telomerase forms two significant subunits, an RNA template, and a catalytic enzyme human telomerase reverse transcriptase (TERT). The enzyme telomerase uses its RNA template to synthesize TTAGGG sequences to resolve the obstacle of telomere shortening. **Telomerase activity** (**TA**) is managed by post-translational modifications of the TERT protein, such as phosphorylation and nuclear translocation, or transcriptional control of human TERT (Rubtsova et al, 2020). Some researchers have shown that modifications in TA could occur within a few minutes or some hours following exposure to molecular stimuli, such as stress hormones, inflammatory cytokines, and growth factors that cause post-translational changes of the TERT protein (Mehrsafar et al, 2020; de Punder et al, 2019). TERT is the catalytic subunit of the telomerase, and it is critical for enzymatic action. Upregulation of TERT expression and next telomerase action is found in most

malignancies. This upregulation translates into continued cell proliferation and avoidance of cell aging and apoptosis (McKelvey et al, 2020).

In addition to its telomere lengthening function, the telomerase performs other tasks independent of TeLe (extratelomeric activity), such as cell survival, increasing stress resistance, protecting mitochondrial activity, mediating the DNA damage response, inhibition of apoptosis and promotion of neuroprotective signaling (Veverka et al, 2019). These abilities are crucial for the anti-aging process.

Is it possible to stave off aging simply by managing to lengthen telomeres and prevent them from wearing out? American scientists administered modified mRNA, encoding TERT, enzyme capable of increasing the length of telomeres by adding repetitive DNA sequences, to a cell culture. Three other cell groups were used as 'controls'; one was administered mRNA encoding an inactive form of TERT; to another the solution through which the TERT was administered; at the end, no treatment. The "telomere lengthening" treatment was evaluated on different cell types, such as fibroblasts and myoblasts. Stanford researchers proved that cells can be subjected to this treatment several times, and in this way their ability to divide is improved (Ramunas et al, 2015).

Telomere shortening also occurs through oxidative damage and other events that can occur during mitosis. Telomeres become dysfunctional due to shortening, collapse of the complex telomere structure itself and Shelterin aggregates. A physiological response to this damage to the DNA strands and a loss of cell proliferation are triggered, resulting in senescence and/or apoptosis (Herrmann et al, 2018; Turner et al, 2019). The shortening of the ends of DNA strands can also be conditioned by epigenetic and genetic factors, and by parameters such as age, sex, body fat, inflammation, socioeconomic factors, ethnicity, and PA level (Herrmann et al, 2018; Turner et al, 2019; Prasad et al, 2017). In fact, many manuscripts have proven how physical exercise can play a significant role in improving genomic stability.

Environmental exposures to which living beings are subjected (sedentary lifestyle, unhealthy food, smoking, medicines) which cause an increase in ROS also result in the shortening of telomeres (Barnes et al, 2019). Non-functional mitochondria synthesize a greater amount of ROS. A vicious circle is therefore created in which telomeres can further be subjected to the negative consequences of oxidative stress. Accumulated scientific evidence from animal and human models supports the hypothesis that oxidative injury to telomeric DNA may manage accelerated telomere shortening (Aeby et al, 2016).

The usual genomic DNA damage repair mechanisms are not effective during aging, TeLe decreases contributing to the cellular senescence, and therefore TeLe could be considered a possible marker of biological aging (Wang et al, 2019). The **leukocyte telomere length** (**LTeLe**) is positively associated in subjects leading a healthy life. The association between chronic inflammation and increased proinflammatory cytokines [cytokine tumor necrosis factor (TNF-α) and interleukin (IL)-6] and shortened leukocyte telomeres has been proposed by many authors (Engin & Engin, 2021). For example, the cytokine TNF-α appears to have a precise role in down-regulating telomerase action, producing telomere shortening. Dozens of studies have shown how diet can affect TeLe (Cassidy et al, 2010; Navarro-Ibarra et al, 2019). In fact, the literature of recent years suggests, for example, that in subjects who follow a diet that involves the consumption of plant foods, vitamins such as fruit, vegetables, seeds, and nuts such as the Mediterranean Diet, they have shorter telomeres (Boccardi et al, 2013; Boccardi et al, 2016). Since plant-based foods have high antioxidant power and TeLe is also influenced by oxidative stress, researchers believe that this is the association between consumption of plant-based foods and reduction of the effects of friction that telomeres undergo during some years. Vitamins, carotenoids, polyphenols, omega-3 fatty acids, and fiber could help slow the telomeres shortening. Phytochemicals, such as polyphenols, modulate the redox state of cells (D'Angelo, 2020a; D'Angelo, 2020b; D'Angelo & Cusano, 2020; Vuoso et al, 2020; Boccellino & D'Angelo, 2020; Ferrara et al, 2022; Ferrara & D'Angelo, 2023), can alter cell signaling and help prevent the accumulation of damage in molecules such as proteins, nucleic acids, and lipids. Several studies, for example, propose that polyphenols can influence the TeLe and prevent their shortening (D'Angelo, 2023). As proof of this theory, some works have shown that LTeLe is longer in people who follow the Mediterranean diet (Gomez-Delgado et al, 2018). Conversely, high consumption of processed meat, sugary drinks, and proinflammatory diets is associated with shortened telomeres.

Action of physical activity on telomere length. Shortening of TeLe has been linked to health problems and poor lifestyle. These topics have also attracted attention among sports scientists. Regular PA is a well-established plan to combat and prevent different pathologies. PA stimulates the synthesis of metabolites and inflammatory mediators. A controlled and well-organized exercise program, e.g., moderate to vigorous intensity, with adequate rest can reduce the concentration of circulating proinflammatory cytokines. Therefore, PA promotes the circulation of anti-inflammatory signals capable of decreasing systemic inflammation, decreasing the infiltration of macrophages into adipose tissue, reducing the expression of Toll-like receptors (TLR4 and TLR2) in immune cells, and other molecules involved in signaling pathways to reduce inflammation. The scientific Literature proposes that a precise health behavior, such as PA, can modest the impact of stress on cell senescence (Puterman et al, 2018). Recent research proves that supporting a PA lifestyle is linked to greater TeLe. It is guessed that one of the mechanisms of telomere lengthening associated with physical exercise may occur through the increase in TA (Puterman et al, 2018; Ludlow et al, 2011). Although the potential mechanism has not yet been fully elucidated, PA shows a favorable impact on the TeLe especially in older subjects,

antagonizing the classic age-induced reduction in TeLe. Different mechanisms propose that the association between PA and the reduction of TeLe is linked to changes in telomerase activity, oxidative stress, inflammation, and a decrease in satellite cells present in skeletal muscle.

In 2008, Cherkas *et al.* investigated the hypothesis that leisure-time PA level in the past 12 months was related to LTeLe in healthy subjects. They studied 2401 white twins, including 2152 women and 249 men, by administering specific questionnaires on PA level, smoking habits, and socioeconomic status. LTeLe was positively associated with increased leisure time PA level. The LTeLe of the most active individuals were 200 nucleotides longer than those of the least active individuals (7.1 and 6.9 kb, respectively). This finding was confirmed in a small group of twin pairs discordant in PA level (on average, the LTeLe of the more active twins was 88 nucleotides longer than that of the less active twins) (Cherkas et al, 2008). Considering this data, it is possible to assert that the sedentary lifestyle, in addition to a high body mass index, smoking, and low socioeconomic status, could influence LTeLe and can accelerate senescence. This information is a powerful message that could be used by healthcare workers to promote the potential anti-aging effect of regular PA.

In 2009, Werner *et al.* showed how PA can control proteins that stabilize telomeres and therefore have a protective property from stress-induced vascular apoptosis. Telomere biology was analyzed in leukocytes of young and middle-aged track and field athletes (Werner et al, 2009). Exercise has been linked to upregulation of defensive proteins (such as telomere repeat binding factor 2) and DNA repair proteins, as well as downregulation of negative regulatory proteins of cell cycle progression in athletes middle aged. So, leukocytes isolated from endurance athletes owed an increased telomerase enzymatic activity, an increase expression of telomere-stabilizing proteins, and downregulation of cell cycle inhibitors compared to untrained subjects (Werner et al, 2009). This data suggests how a long-term resistance training could decrease leukocyte telomere shortening confronted to untrained subjects.

Although it improves oxidative stress, continuous PA is associated with antioxidant activity and inferior ROS value, favoring REDOX balance, protecting from DNA damage and therefore from the attrition of shorter telomeres.

Østhus *et al.* hypothesized that VO2max was positively linked to TeLe; they have proven how training with long-term resistance exercises can have a protective action on TeLe in the muscle cells of the elderly. The average TeLe was calculated as the number of repeat copies of telomeres/number of copies of a single gene (T/S), where T indicates nanograms of standard DNA coinciding with the experimental sample per copy number of the telomere template; S instead is the nanograms of standard DNA that corresponds to the experimental sample in number of copies of the single copy gene. Older endurance-trained athletes had longer TeLe than older people with aver-age activity levels (T/S ratio 1.12 vs. 0.92). Instead, the TeleLe of young resistance-trained athletes was not diverse from that of young non-athletes (1.47 vs. 1.33) (Østhus et al, 2012).

Table 1 summarizes more recent observational studies on the action of PA on TeLe. For example, in a study published in 2016, Diman et al. proved that moderate-intensity exercise can slow the aging process. The volunteers underwent stationary cycling sessions for 45 minutes; Researchers have proven that nuclear respiratory factor 1 protects telomeres, thus helping DNA, and so cells, to stay "younger" and control aging. To increase nuclear respiratory factor 1 levels, even moderate PA seems to be sufficient (Diman et al, 2016). Therefore, it is possible to assert that data support the idea that exercise may defend against aging.

It is possible to hypothesize that long-term endurance exercise training may provide a protective effect on muscle TeLe in older subjects. Borghini *et al.* reported that an acute exposure of ultra-distance endurance trail race reduced salivary telomere length in athletes, yet chronic endurance training provided protections against such shortening (Borghini et al, 2015).

In a randomized, controlled study, the authors tried to evaluate any variations of telomerase levels (primary outcome) and TeLe (secondary outcome) caused by aerobic PA in inactive healthcare workers. Puterman *et al.* proposed that exercise could induce a simple lengthening of telomeres even if the molecular mechanisms involved are not yet clear. This study, however, once again underlines the importance of increasing individuals' involvement in aerobic exercise to improve health markers and attenuate cellular aging (Puterman et al, 2018).

Tucker *et al.* conducted a cross-sectional statistical study of 5,823 adults who taken part in the National Health and Nutrition Examination Survey, measuring their LTeLe. The results highlighted how LTeLe did not differ between participants who did not play sports or those who carried out a sporting activity with low or moderate frequency; on the contrary, however, LTeLe appeared to be significantly longer in individuals who carried out PA with a high frequency, leading in some cases to a reduction in cellular aging equal to 9 years (Tucker et al, 2017). So, it is possible to assert that people are generally exposed to a shortening of their life expectancy unless they take part in sport very often.

Simoes *et al.* compared TeLe of high-level master sprinters and non-athlete age matched controls and analyzed the relationship of TeLe with performance and body fat. Studies on biochemical and biomolecular parameters were performed on blood samples.

Experienced sprinters had longer TeLe, lower body fat and BMI, and a better lipid pro-file than age-matched subjects. An important negative correlation was proven between TeLe and performance decline per decade and a positive correlation between TeLe and performance level. TeLe appeared to be an indicator of health status, and

it seemed be considered a marker of sporting longevity, as both the actual performance level and its reduction over the years were correlated with TeLe (Simoes et al, 2017).

The lifestyle of professional athletes can affect oxidative status, chronic inflammation and TeLe and lead to a reduction in the risk of these conditions, thus slowing senescence and performance deterioration. Sousa et al. evaluated TeLe and athletic performance, and their relationship with adiposity, oxidative stress, and inflammation in experts, endurance and sprint/power (SPW) athletes. A positive correlation was found between relative performance and LTeLe in both groups and in the entire sample. Body mass index proved a negative correlation with TeLe for the endurance group and for the analysis of the entire sample. Thus, masters' athletes TeLe was associated with relative performance regardless of training model (endurance or sprint/power), while inflammation and adiposity were associated with shorter telomeres (Sousa et al, 2020). Data on telomere/telomerase dynamics in elite athletes are currently still limited, but research has proven that young elite athletes have longer telomeres than their inactive peers (Muniesa et al, 2017).

In a meta-analysis, Abrain *et al.* proved that elite subjects owned a longer TeLe than sedentary and non-elite athletes. They described that chronic high-level physical training (aerobic and resistance training) can predict protective effects on TeLe (Abrahin et al, 2019). This is another study that showed that elite athletes had longer TeLe compared with TeLe of control subjects (sedentary) and suggest that high level chronic physical training may provide protective effects on TeLe.

The impact of PA on aging considering TeLe as a molecular marker of senescence is currently not yet fully understood. In 4 recent systematic reviews the author the authors tried to compare a physically active lifestyle or structured exercise program to physically inactive lifestyle or control groups on telomere length.

Valente *et al.* considered 30 manuscripts with a total of 7418 participants; they declared said, with a low level of certainty, that physically active subjects have longer telomeres and that this action was probably overestimated (Valente et al, 2021).

Aguiar *et al.* examined 11 studies related to expert athletes; they declared that experienced athletes had longer telomeres than age-matched controls (Aguiar et al, 2021).

Song *et al*. analyzed only randomized clinical trials and found inconclusive results among the seven randomized clinical trial manuscripts considered, which included principally female subjects and subjects diagnosed with tumor (Song et al, 2022).

Schellnegger *et al.* reported that regular aerobic training of modest to vigorous intensity appears to help protect TeLe (Schellnegger et al, 2022). Despite these results, it seems clear how the best intensity, duration of PA, and type of exercise still need to be further investigated. Along with TeLe or telomerase enzyme activity, participants' fitness level, PA type, and training modality should be assessed at different time points in future studies, with the long-term follow-up plan. Further molecular characterization of telomere biology in dissimilar cell types and tissues is needed to draw definitive conclusions about how PA could affect TeLe shortening and therefore indirectly aging. Sánchez-González et al. reported the actions on TeLe in healthy subjects through a systematic review, meta-analysis, and meta-regression. They concluded that, in a healthy population, a high-intensity interval training appears to have a positive effect on TeLe compared to other types of exercise such as resistance training or aerobic exercise. They recommended that future research focus on evaluating the effects of high-intensity PA interventions in several healthy age groups to evaluate the effect of these interventions in subjects with different syndromes and to prove the clinical relationship between increased length of telomeres and relevant clinical variables (Sánchez-González et al, 2024).

However, it is also essential to highlight the variables present in the studies that can affect the outcome of TeLe. For example, elite athletes are often forced into difficult lifestyles and subjected to stress both during competition and during the championship period which can also lead to injury or illness. This can negatively affect their state of well-being and also induce more rapid aging throughout their lives (Tanaka et al, 2008).If this data will be confirmed by future studies, the lifestyle associated with training-competition demands and dietary needs could be studied to control inflammation markers and redox status, easing healthier aging and athletic performance.

Discussion

Effect of overtraining on telomere length. In a recent systematic review, van Paridon et al. have showed how some parameters are associated with competition-related psychophysiological changes in athletes (van Paridon et al, 2017). In humans, a dose-response effect is generally associated with the beneficial effects of PA. Moderate to vigorous PA levels (≥ 450 minutes/week, therefore above the minimum international recommendations of 150 minutes/week) are often linked to longer life expectancy. Elite athletes, such as former Tour de France cyclists or former Olympic marathon runners, generally live longer. PA has a significant effect on the expression of a part of the genome, which has evolved to improve aerobic metabolism in conditions of food deficiency. AP is certainly not capable of reversing human aging, but it is capable of attenuating and/or slowing down harmful effects at a systemic and cellular level (Garatachea et al, 2015).

There is an upper limit to the amount of intense PA that can be performed without disrupting metabolic homeostasis, beyond which, for example, after a period of progressively more intense training that exceeds expected physiological changes (e.g., overtraining), negative effects on metabolism. .

Rae et al. proven that DNA testing in skeletal muscle tissue cells in experienced endurance runners can help understand the effects of chronic exposure to endurance exercise. The researchers compared the length of the minimal terminal restriction fragment (TRF) in the vastus lateralis muscle of experienced endurance runners with that of sedentary subjects. The runners had covered almost 50,000 km in training and racing over 15 years. The minimum TRF lengths in the muscles of both groups were comparable and within the normal range. The minimum duration of TRF in runners, however, was inversely proportional to the years spent running and the hours spent training. Therefore, since endurance running may affect the minimum TRF length and proliferative potential of satellite cells, chronic endurance running may also be a possible stressor, i.e., exert a negative effect on skeletal muscle tissue (Rae et al , 2010). In competitive sports it is well known that a correct stimulus to exercise improves performance, while excessive training leads to tiredness and reduced performance.

Table 1 - Effects of physical activity on telomere length: observational studies

Subjects	Physical activity	Influence on Telomere Length	Reference
68 healthy subjects	40 min of aerobic exercise 3-5 times per week	Significant TeLe changes across time	Puterman et al, 2018
10 healthy young volunteers	Stationary cycling sessions for 45 minutes	TeLe protection	Diman et al, 2016
6503 healthy adults	Movement-based behaviors, as walking/cycling for transportation	A clear dose-response relation between movement-based behaviors and leukocyte telomere length.	Loprinzi et al, 2015
582 healthy adults	Self-reported PA	No significant associations between PA and LTeLe	Soares-Miranda et al, 2015
62 healthy adults	Endurance training	Longer salivary TeLe in endurance athletes vs. sedentary controls.	Borghini et al, 2015
477 healthy adults	Self-reported PA	More vigorous PA was associated with longer LTeLe.	Latifovic et al, 2016
6474 healthy adults	Self-reported PA	Associated with longer LTeLe.	Loprinzi et al, 2016
5,823 healthy adults	PA with a high frequency	LTeLe appeared to be significantly longer than their untrained peers	Tucker et al, 2017
46 healthy adults	Intensive training: training ≥ 5 days/week; moderate training: playing volleyball, basketball, or running less than 6 km, 2-3 days/week	Longer LTeLe in trained *vs*. untrained adults.	Silva et al, 2016
11 healthy adults	Elite master sprinters	LTeLe was longer than their untrained peers	Simoes et al, 2017
203 healthy schoolteachers	Objectively measured PA	Habitual PA was not associated with LTeLe.	von Känel et al, 2017
22 healthy adults	World- master class athletes. Endurance or sprint/power performance	A positive association was observed between relative performance and LTeLe	Sousa et al, 2020
815 healthy adults	Self-reported PA	PA was positively associated with LTeLe. Practicing a sport for > 10 years associated with longer telomeres.	Saßenroth et al, 2015
61 young subjects	Elite athletes	Athletes had on average, higher LTeLe than control subjects	Muniesa et al, 2017

Some studies have shown how excessive PA can cause a partial arrest of mitochondrial respiration. Flockhart *et al.* have proven that excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in health subjects. The amount of training associated with best adaptations is likely lower in subjects not accustomed to exercise training, while elite athletes should tolerate a higher training load after years of training (Flockhart et al, 2021).

In animal models, moderate exercise increases the synthesis of oxidative phosphorylation complexes (OXPHOS), improves mitochondrial energy efficiency through the induction of mitochondrial enzymes. Instead, intense PA causes a significant de-crease in OXPHOS chain complexes, a reduction in mitochondrial OXPHOS and a reduction in ATP synthesis (Sanguesa et al, 2022). Therefore, from what has been showed, it seems to be essential to practice moderate PA to support mitochondrial homeostasis at normal levels. Furthermore, various

research supports how a high synthesis of ROS and proinflammatory cytokines causes greater cellular and/or DNA damage, increasing the rate of cell division by inducing greater shortening of telomeres (Assis et al, 2022).

Laye *et al.* conducted research on 8 professional marathon runners and found that telomerase activity in peripheral blood leukocytes before and after running 7 marathons in 7 days was not significant different, showing that the influence of PA on TA can saturate in subjects involved in elite endurance athletic exercises (Laye et al, 2012). Considering the data reported, it is possible to say that, overall, the telomere biology is an extraordinarily complex process, and recent research support that there are differences in the regulation of TL and telomerase in different tissue- and cell-types. Sedentary and inactivity behavior are reported to influence telomere biology, with strong association with worse health outcomes and higher cardiovascular disease risk.

The amount of reduction in sedentary behavior has a profound and positive effect on preserving and/or increasing TeLe. PA has a beneficial effect on TeLe compared with inactivity. However, further studies are needed to decide the effect of various ages, diseases, or exercise intensities on telomere length.

Many studies prove the positive effects of PA on telomere dynamics; Unfortunately, precise information on the type of exercise and the most helpful training method (intensity, duration and frequency) is currently lacking. Numerous studies agree that elite athletes will on average have increased TeLe compared to inactive controls throughout their lives. Unfortunately, the fundamental molecular events for the preservation and/or elongation of TeLe are not well showed. Furthermore, in addition to fully understanding the biology of telomeres and the potential harmful events involved at the molecular level (e.g., oxidative stress), it is also necessary to understand the differences that can occur between various tissue types. Furthermore, future studies should provide more detailed information on participants' fitness level, as well as training modality characteristics, for standardization and comparison, to draw more definitive conclusions.

It is essential to differentiate PA based on the characteristics of the subjects. Intensive exercise, in general, is encouraged as former elite athletes have lower mortality rates and appear to live longer than the general population. However, both athletes and those who wish to improve their health through exercise should carefully check their response to training, as overtraining could have negative effects on health and even on telomere length. In future studies, parameters such as the type of sport and competition, the periodization of the competitive season and the intensity of the exercise, with the contemporary association to gender and age should also be investigated. Each of these variables deserves to be placed at the center of attention in studies on the telomere biology. Furthermore, attention should be paid to the effect of overtraining on TeLe shortening, which increases the pieces of the complex puzzle of mechanisms to be investigated.

Therefore, it stays a challenge to decide which molecular pathways influence telomere biology through physical exercise.

Conclusions

This paper summarizes and supports the growing body of evidence that PA has an impact on telomere attrition and thus on the aging process. To prevent telomeres from shortening rapidly, on the one hand it is possible by paying attention to what causes them, and on the other by knowing what, exactly, can increase the production of the telomerase enzyme. To date, it is still impossible to produce an elixir of youth that artificially increases telomerase, because there is a risk that the cells will no longer stop dividing. It is possible, however, to consider a natural defense of the telomeres. For example, with physical exercise: a study on 1,200 pairs of twins, which therefore allows us to isolate the effects of physical exercise from genetic factors, proves that the more active twin has longer telomeres than the inactive one. The causes can be multiple. One of these is a hormone that muscles release after exercise, irisin: it burns fat and protects bones. Even moderate exercise, such as cycling, performed three times a week for three-quarters of an hour, doubles telomerase activity in six months.

How to prevent telomeres from becoming too short? PA may be beneficial for keeping telomere length in both healthy and chronically middle-aged people. Telomere length is not only an indicator of aging, but also concerns the ability to protect DNA from damage and associated consequences. PA can have both protective and restorative effects and, as such, show immense potential to improve well-being and increase longevity. Although exercise does not inhibit the aging process, it weakens many of the harmful systemic and cellular effects. Looking at the big picture, the safest and most effective path should be based on physical exercise, and the elderly community should be encouraged to engage in the continuous and regular practice of physical activity. Exercise can have drug-like effects and has the great advantage of being a non-pharmacological, non-toxic, low-cost and universally applicable therapy.

Further interventional studies are needed to confirm the specific effects of various training doses and intensities on TeLe, particularly those with long-term exercise. Many of the studies included highlight the positive effects of PA on telomere dynamics, but there is a lack of consensus on the type of exercise and the most beneficial training modality (intensity, duration and frequency). Inactivity is a major risk factor for cardiovascular disease and lots of other chronic conditions, independent of physical exercise. In particular, the reduction of sedentary behavior has a profound and positive effect on the maintenance and/or increase of TeLe. There is convincing evidence that lifelong elite or experts' athletes will have increased TeLe compared to inactive controls. Although dozens of studies highlight the beneficial role of PA on telomere dynamics and aging, the molecular events in TeLe preservation and/or elongation remain poorly understood. In addition to

further understanding telomere biology and potential damaging events at the molecular level tissue and cell type differences must also be taken into consideration in TeLe and telomerase assays. Future studies should provide more detailed information on participants' fitness level, as well as training modality characteristics, for standardization and comparison, to draw more definitive conclusions.

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Conflicts of interest.

The authors have any conflicts of interest to declare.

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