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Telomere length as a biomarker of aging and diseases

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Abstract

As research related to healthspan and lifespan has become a hot topic, the necessity for a reliable and practical biomarker of aging (BoA), which can provide information about mortality and morbidity risk, along with remaining life expectancy, has increased. The chromosome terminus non-coding protective structure that prevents genomic instability is called a telomere. The continual shortening of telomeres, which affects their structure as well as function, is a hallmark of agedness. The aforementioned process is a potential cause of age-related diseases (ARDs), leading to a bad prognosis and a low survival rate, which compromise health and longevity. Hence, studies scrutinizing the BoAs often include telomere length (TL) as a prospective candidate. The results of these studies suggest that TL measurement can only provide an approximate appraisal of the aging rate, and its implementation into clinical practice and routine use as a BoA has many limitations and challenges. Nevertheless, measuring TL while determining other biomarkers can be used to assess biological age. This review focuses on the importance of telomeres in health, senescence, and diseases, as well as on summarizing the results and conclusions of previous studies evaluating TL as a potential BoA.

Keywords: telomere length, biomarker of aging, telomerase, age-related diseases

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Introduction

Over the last few decades, the life expectancy of human beings has increased globally, which is not always in positive correlation with their healthspan and productivity (1). This is due to the fact that aging is the leading cause of most pathological conditions that compromise healthspan and promote age-related diseases (ARDs), which constitute a constant and growing burden on healthcare systems around the world (2). The aging process is modulated by many genetic and non-genetic determinants, and it can be defined by chronological and biological age (3). Individuals of the same age show differences in many aspects of health status, implying that chronological age, i.e., the number of years that have passed since birth, does not reflect the functional individual status in the best way, which was the main reason for the development of the concept of biomarkers of aging (BoAs) (4). A BoA is a measure of biological age that is better at predicting the functional status of healthy individuals than chronological age, either alone or as part of a multivariate composite, and it can be a very useful tool for identifying those at risk for ARDs (5). Over the last few decades, a lot of effort has been made to identify a reliable, precise, and robust biomarker or group of BoAs (6). To be both accurate and useful, a true BoA must meet the following criteria specified by the American Federation for Aging Research (AFAR) in 2016: 1) it must be a better predictor of life expectancy than chronological age, 2) it must be capable of monitoring aging mechanisms and differentiating them from disease processes, 3) it must be non-invasive and able to be tested repeatedly, 4) it must be validated in humans after being tested on laboratory animals. While there are several potential BoAs, none has yet satisfied all the above criteria and proved to be a reliable indicator of the aging process. BoAs must be able to distinguish between the aging and disease processes, which is a difficult task and raises the question of whether the same BoA can be used for both. As a marker of the aging process, which is a risk factor for ARDs, a potential BoA should be able to predict the onset of ARDs and, furthermore, to distinguish them. It could be a biomarker that could be monitored in patients, especially with the aim of assessing the effectiveness of a therapy, so it could be a useful tool even in the assessment of the disease stage. Additional characteristics of a novel BoA include: easy measurability, accessibility, ability to identify underlying mechanisms that influence lifespan and healthspan, and other relevant features (7). A potential BoA should be assessed during pharmaceutical or non-pharmaceutical interventions aimed at delaying the onset or progression of ARDs. Blood biomarkers with diverse abilities, in spite of some weaknesses, are increasingly being used nowadays since they provide additional information that aids in better predicting biological age (8).

Telomeres are nucleoprotein chromosome terminus non-coding structures, formed by repetitive sequences TTAGGG (3). These structures are of critical importance for genomic integrity and stability, as well as preservation of the information contained in the genome (9). Each division of somatic cells causes telomere attrition until their critically short length triggers senescence and/or apoptosis (10). The attrition of these structures is controlled by telomerase, which synthesizes the lost sequences. Telomere

length (TL) may be a unique biological clock that can determine the biological age of an individual (11). Genetic mutations that impair telomere homeostasis cause premature aging with various manifestations called telomere syndromes, telomeropathies, telomere-driven diseases, or telomere biology disorders (TBDs) (12). Based on the fact that the attrition of telomeres is an age-related process, the idea that TL may be used as a BoA arose. TL is suitable as a monitoring biomarker during intervention studies aimed at delaying the onset or the progression of ARDs, and it has predictive potential for disease severity and mortality (13). Although TL satisfies the AFAR's criteria 3 and 4, the concurrence with criteria 1 and 2 is debatable (14). The correlation between TL and the onset of various ARDs, such as cardiovascular diseases (CVDs), cancer, dementia, and others, has been found (8). Because there is a lot of inconsistency in the findings, the nature of these connections and putative molecular processes behind the age-related telomere shortening phenomena are yet unclear (15). Different methods of TL measurement, variations among investigated populations, and other factors may contribute to this inconsistency. However, it is contentious whether the precision and reliability of TL measurement satisfy the criteria for usage as an assessment tool of biological aging (14). It is still unclear whether telomeric aging is an indicator of stress or a biological clock-like process (16). Notwithstanding this ambiguity, TL is one of the most considered BoAs, as well as a prospective individual biomarker in precision medicine (17). This review summarizes the literature on this topic and discusses the potential use of TL as a BoA for telomere-driven diseases.

Telomeres

The shielding role of nucleoprotein non-coding caps termed telomeres was discovered by Nobel Prize laureates Müller and McClintock many years ago (18, 19). These specialized structures in humans comprise thousands of repetitions of the TTAGGG hexanucleotide bound by shelterin, a protective six-protein complex, forming a 3D structure. This complex is implicated in chromatin remodeling and telomere structure shaping, preventing chromosomal end-to-end fusions and telomere fragility, which makes it vital for the protective features of these structures (20). Telomeres are composed of a G-rich, single-stranded section at the 3′-OH end of the leading strand as a result of incomplete DNA synthesis, which causes telomere attrition not only from damage but also with every cell division (15). The complex 3D telomere structure prevents fallacious identification of telomeric sites as DNA damage and its reparation by DNA damage repair (DDR) machinery (21). Telomere dysfunction activates the DDR pathway, causing cells to enter senescence (22–24). The previously mentioned shelterin complex is constituted of several telomere-specific proteins: telomeric repeat-binding factor 1 (TRF1), telomeric repeat-binding factor 2 (TRF2), protection of telomeres protein 1 (POT1), which localizes the telomeric sequence, repressor/activator protein 1 (RAP1), TRF1-interacting nuclear protein 2 (TIN2), and protein associated with POT1 (TPP1), which prevents activation of DDR pathways (10, 25). Telomeric regions of DNA are hidden inside the T-loop-D-loop structure that protect telomeres from premature

degradation. At the end of the telomere loop known as the T-loop, which comprises double-stranded DNA twisted around, the single-stranded section inserts back into the double-stranded DNA and forms the D-loop, i.e., displacement loop, evading the identification of telomeric sites as double-strand breaks (22, 26). The T-loop cannot be formed when TL comes to the critical limit, which leads to the appearance of a DDR signal. Consequently, cells stop proliferating and progressively enter senescence to avoid the destruction of the genome (15). In each somatic cell division cycle, a segment of telomere nucleotides is cleaved, and the telomere shortens by 50-200 bp, which would result in the wastage of genetic information from coding DNA in the absence of telomeres (27). Telomere shortening has the effect of limiting the number of divisions that somatic cells can undergo before their TL falls below the critical threshold, causing them to lose their protective features (23, 24, 28). When cells reach a threshold TL of about 4 kbp, they can no longer proliferate and enter senescence or apoptosis. As a result, telomere shortening reduces the lifespan of cells and acts as a tumor suppressor. Telomere erosion is the underlying mechanism of aging and can contribute to the development of ARDs. Hence, TL can be thought of as a "molecular clock of aging" (29, 30). Oxidative stress may directly damage suitable G-rich telomere sections, causing the cell to enter senescence (31, 32). Considering this, telomere-induced senescence has recently been identified as a key aging mechanism (33). There are multiple mechanisms for TL shortening, and oxidative stress-induced is one of them (34). It can be deduced that TL is used as a cumulative measure of cellular division and age, and multiple meta-analyses examine the relationship between those two variables (35, 36). Additionally, many studies have shown a relationship between TL and specific age-related disease processes, which can vary during the lifespan (7). Peripheral blood leukocyte telomere length (LTL) decreases by 30–35 bp per year (8), reaching approximately 5 kbp in adults older than 60 years (37). Hence, longer TL is beneficial for healthy aging (38). When compared to a younger control group, TL values dropped to around 3.5 kbp in centenarians and then remained constant, even lengthened in supercentenarians (39). Long telomeres are likely to be the key component for exceptional longevity and a low risk of ARDs and TBDs (39). The functional integrity of telomeres, which is regulated by cell multiplication, oxidative stress, and DNA repair mechanisms, is strongly linked to the immune cell lifespan. Telomeres can be lengthened by lymphocytes through the action of telomerase. LTL may be particularly relevant to the immune system, in which leukocytes play a key role (4), so dysfunctional telomeres could be a trigger of immunosenescence (40,41) and lead to higher mortality from immune-mediated inflammatory diseases in those with severely decreased TL (40). In the same manner, decreased LTL has been linked to CVD pathogenesis (41, 42). The measurement of TL from peripheral blood leukocytes has many advantages, since blood is a biological material that is easy to collect and suitable for routine laboratory practice, and leukocytes are readily available and convenient to handle and isolate from whole blood. Whether peripheral blood LTL adequately reflects TL in other tissues and serves as a useful parametar in ARDs diagnostics, however, remains insufficiently clarified.

Telomerase

As previously explained, telomeres naturally shorten with each cell cycle, either because of an end-replication problem or damage, and telomerase plays an important role in retrieving the lost DNA segments and preserving genetic information. Adult stem and germ cells, fetal tissues, and certain malignant cells evade telomere shortening by activating this enzyme (43). Telomerase activity in somatic cells is very low or non-existent, and their TL diminishes as replication occurs (9). Telomerase is a ribonucleoprotein complex that may prolong telomeres by synthesizing telomeric DNA (44). In humans, this enzyme is composed of a human telomerase reverse transcriptase (hTERT), a telomerase RNA component (TERC), also known as human telomerase RNA (hTR), and an important auxiliary protein termed dyskerin (8). The nucleotide bases are added individually in the right order to recover lost telomeric DNA. Telomerase is active throughout early embryonic development and maintains proper telomere extension, but it becomes inactive after birth. Alternative splicing is one of the mechanisms involved in telomerase suppression during the embryonic and neonatal periods (28, 45). Most human cell types are immortalized as a result of TL maintenance. Telomeres lengthened in a telomerase-independent way in some cancer cells can be explained by the ALT (alternative lengthening of telomeres) pathway.

Telomere erosion and the associated pathogenic processes are caused by the fact that most human somatic cells have limited or undetectable telomerase activity (6). On the other hand, a group of malignant cells have different mechanisms for maintaining TL, most likely involving genetic recombination (46), as well as reactivation of the telomerase silencer gene. This leads to incessant and unrestrained telomere extension (47). Despite the fact that telomerase overexpression is found in approximately 90% of human tumors, the use of telomerase activators in the treatment of telomerase-dependent diseases remains controversial (48, 49).

Telomere length determinants

The average LTL in humans is 11 kbp at birth and drops to below 4 kbp in the elderly (8). The rate of telomere attrition can vary with each cell division, and it is regulated by telomerase activity and telomere trimming mechanisms (15). Multiple data suggest that environmental and lifestyle factors might have a major impact on TL during the lifespan (Figure 1). Environmental variables one is exposed to in adulthood have been demonstrated to have long-term effects on TL. TL can be affected by various non-modifiable and modifiable factors, such as gender, chronic stress, physical activity, smoking, body mass index, alcohol consumption, antioxidants, vitamins, minerals, exposure to heavy metals and other toxic substances, socioeconomic status, etc (40,50–55). Gender is a non-modifiable determinant of TL since females have longer telomeres than males owing to the influence of estrogen, which stimulates the activity of telomerase (56). An additional well-known determinant that affects TL is psychological stress, which reduces telomerase activity and increases the formation of reactive oxygen species (57,58). When compared to women with modest stress levels, highly stressed

women had reduced telomerase activity and a higher level of oxidative stress (57–59). Nutritional habits can also influence TL (51,60,61). TL is positively associated with the proper intake of micronutrients such as vitamins A, D, E, B vitamins (B3, B9, B12) and ascorbic acid (52,62). Vitamins' effects on telomere stability can be explained via their antioxidative potential and DNA damage evasion. Additional TL modulators, including nutrients like Zn, Mg, and Fe, as well as omega-3 fatty acids, polyphenols, and curcumin are associated with longer TL via the enhancement of telomerase activity and DNA methylation, or the decrease of oxidative stress (15). Regular physical exercise, in combination to a balanced diet, aids in the maintenance of TL by lowering the level of oxidative stress and inflammation. Regular exercise routine has also been proven to stimulate telomerase (15,63,64). For example, moderate and high-intensity activity during a three-month lifestyle intervention leads to the lengthening of LTL, as well as stimulation of telomerase (58). Smoking and alcohol consumption are two other lifestyle variables that supposedly have an impact on TL. So far, however, there is little data supporting a hypothesis of alcohol-related telomere attrition (65). A recent meta-analysis found that ever-smokers have considerably shorter telomeres compared to non-smokers (66). Altogether, there is strong evidence that a healthy lifestyle helps to preserve telomeres. Genetic determinants can also be a very important modulator of TL. Even though DNA regions related to the maintenance of telomeric sequences are hereditable, variable local gene expression across different cell types results in inter-individual variation of TL (67–70). Testis, for example, have longer telomeres and increased telomerase expression, whereas cells with a higher turnover rate, such as blood or endothelial cells, have shorter telomeres (71). Extrinsic variables may also influence TL and attrition, as seen in the differences in TL across twins and family members (70,72). However, the results have not always been consistent among studies, which might be due to changes in methodology and sample size. A single determination of a TL may not accurately reflect the changes of this parameter throughout a lifetime (4). As a result, all metrics should be measured longitudinally. Finally, a better understanding of the maintenance of TL will likely lead to the discovery and implementation of novel therapeutic options aimed at reversing the harmful effects of physiological and oxidative stress on telomeres and thereby possibly extending the human lifespan (73).

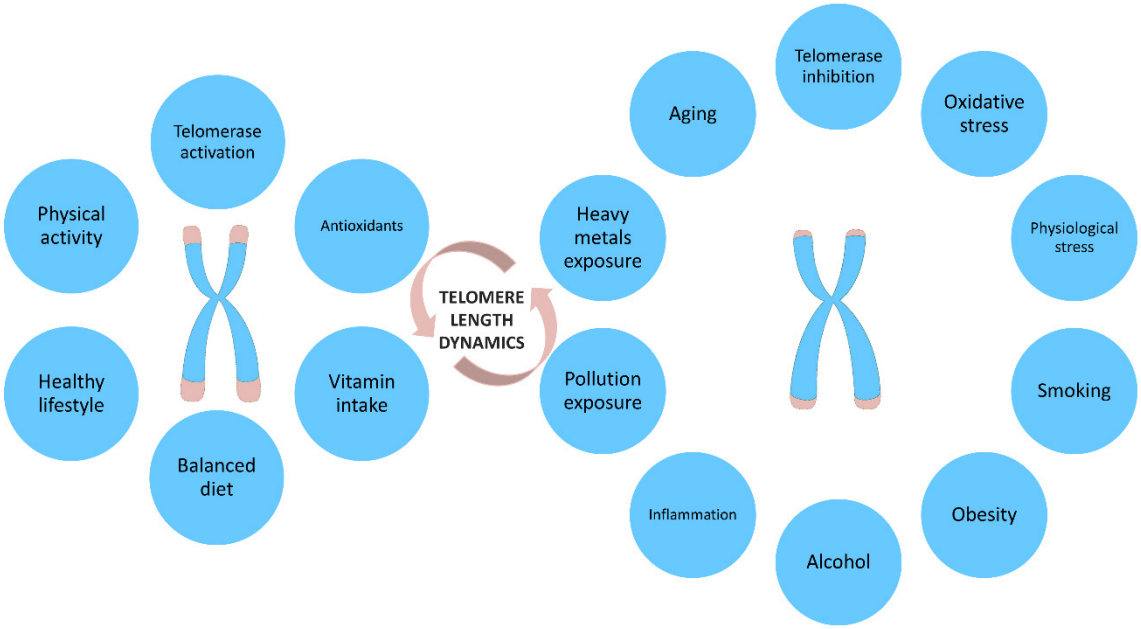

Figure 1. Telomere length determinants
Slika 1. Faktori koji utiču na dužinu telomera

Telomeres and age-related diseases

Aging is characterized by slow and gradual changes in an organism that result in a decreased ability to react and respond to extrinsic or intrinsic determinants over time (74). Aging is a significant risk factor for numerous diseases and mortality. Several potential BoAs with predictive ability have been found throughout the last few decades (75). Shortening the TL is considered to be a crucial step in ARDs development (76). The course of aging and life expectancy may be "programmed" early in the development and can be linked to telomere biology, according to a recent hypothesis (6). Early exposure variables determine TL dynamics, according to the "fetal programming of telomere biology" concept (77), and can lead to accelerated organismal aging in case of increased oxidative stress exposure accompanied by inflammation. It is assumed that telomere extension may increase the incidence of diseases associated with a higher rate of cellular proliferation, such as cancer, while eroded telomeres may increase the risk of CVDs (78). TL has been linked to the incidence and mortality rate, as well as course of ARDs, including CVDs in general (79), atherosclerosis (78), arterial hypertension (80), stroke (81), type 2 diabetes mellitus (T2DM), cancer, Alzheimer's disease, as well as idiopathic pulmonary fibrosis (IPF), and liver disease (82). Other health conditions, addictions, and intoxications, obesity (83), inflammatory, and oxidative processes, all show the same telomere shortening. Medications, such as immunosuppressive agents, proton pump inhibitors, and insulin, have been shown to shorten telomeres (84–86). On the contrary, some interventions are being tested to prevent telomere attrition and treat telomere-driven

diseases, such as antioxidants, non-acarbose antidiabetic agents (T2DM), and lithium (bipolar disorder) (82). However, this impact may not be desirable in malignant cells (87,88). So far, there is no underlying mechanism that completely explains the genesis and causes of telomere attrition in these diseases (89).

Cardiovascular diseases

CVDs, as a group of ARDs, are a global issue, particularly in developing countries, representing the major cause of death, whose prevalence and frequency increase with advancing age. TERT expression and telomerase activity in cardiomyocytes have prompted the hypothesis that telomeres are particularly important for cardiovascular aging (90–92). Several studies have examined the implication of telomere-telomerase system in CVDs during the last two decades, with mixed results. The majority of them used LTL as a surrogate endpoint for TL in other tissues. Those with high telomere erosion rate had an increased risk of CVD, myocardial infarction, heart failure, and stroke, according to many prospective cohort studies (40,93–96). The LTL predictive ability of myocardial infarction and stroke among 800 subjects who took part in the Bruneck trial has been proven (97). In comparison to the control group, CAD (coronary artery disease) patients showed increased telomerase activity and shorter TL, and TL and telomerase activity were used to distinguish STEMI patients and controls (98). The correlation between attrited telomeres and atherosclerosis is due to a greater telomere erosion rate in early life (11). TL appears to be associated with an increased incidence of ischemic, atherothrombotic, and hemorrhagic stroke (99–103). It has been discovered that TL is linked to post-stroke mortality (104). CVD is a complex disease with multiple risk factors and various pathophysiological mechanisms, such as inflammation, oxidative stress, and dyslipidemia (105,106). Given the numerous factors that influence TL, discrepancies in results are not surprising. A large Mendelian randomization (MR) study with over 261,000 individuals reveals a slight causal connection between increased LTL and decreased CVD risk, but increased malignancy risk. (107). Seven SNPs have also been discovered in GWAS studies to be responsible for interindividual variability in LTL and an elevated risk of CVD. Chronic inflammation intertwined with oxidative stress is an important variable of atherosclerosis and accelerate telomere erosion in endothelial cells, vascular smooth muscle cells (VSMCs), and blood leukocytes, resulting in premature cellular senescence (108), and severe form of CVD (15). Patients with acute coronary syndrome have very unstable atherosclerotic plaques due to shorter telomeres and consequently increased proinflammatory activity (109). Individuals with short telomeres experience a delay in re-endothelialization after arterial damage and stent placement (110). However, whether the telomere-telomerase system status plays a causative role in the development and progression of CVDs, or whether this link is only an epiphenomenon, is yet unknown.

Type 2 diabetes mellitus

In the past three decades, the prevalence of T2DM has risen dramatically. Several studies have shown that those with short telomeres are more likely to develop T2DM, to have a faster progression, and to be more prone to chronic complications (111–118). Furthermore, a recent meta-analysis revealed a significant relationship between TL and T2DM (119). According to autopsy research (120), T2DM patients' beta cells have shorter telomeres than those without diabetes. Current studies, on the other hand, are inconclusive and mostly observational. In a recent general population study including 3921 subjects (140), there was no link between LTL and patients' status and their metabolic control. During an 8.5-year follow-up period, no link between eroded telomeres and the onset of T2DM was found (121). The significant variation in study designs, as well as the participants' age, ethnicity, gender, and health condition, limits direct comparisons of different studies (15). As a result, the significance of telomere function in T2DM is unknown, and more data are needed to reveal a potential molecular link between TL and T2DM.

Cancer

Cancer is regarded as an ARD since the probability of its development increases with age. Numerous studies have researched whether TL is linked to cancer risk or prognosis (122). It is thought that critically low TL has an important role during malignant transformation and telomerase reactivation that enhances tumor invasion and metastasis by conferring immortality on the afflicted cells (123). Several pathways for telomerase reactivation have been postulated. Mutations in the TERT promotor region, as well as TERT gene amplification, can lead to enhanced TERT transcription in melanoma, hepatocellular carcinoma, glioblastoma, and urothelial cancer (124–127). In hepatocellular carcinoma, TERT expression could be increased because of viral enhancer components (128). Tumor cells can also evade telomere attrition by using homologous recombination pathways to prolong telomeres, which has been documented for neuroendocrine tumors and sarcomas (129). In breast and prostate cancer patients, short telomeres have also been associated with an advanced disease stage upon diagnosis, rapid disease progression, and poor survival (130). A low value of LTL was linked to a significantly increased incidence of malignancies and tumor-specific mortality (88,97). However, some studies found no significant link between LTL and the risk of malignant transformation (131), while others discovered that cancer patients had higher LTL than cancer-free participants (132). Two meta-analyses (133) confirmed these contradictory findings (134). Lung cancer patients had much shorter TL than healthy people, so it can be assumed that individuals with eroded telomeres are at a higher risk of developing this pathology, especially small cell carcinoma (135). Critically low TL has been linked to a high mortality rate in small cell lung cancer patients, predominantly at stage III or IV (136). These findings show that telomere shortening might be used as a biomarker for lung cancer susceptibility. TL is an independent prognostic marker in chronic lymphocytic leukemia (CLL) and eroded telomeres are linked with adverse outcomes,

which makes the telomere system important in CLL development, progression, and clonal evolution. Telomerase expression and activity are increased in the instances of short telomeres, which are linked to a poor prognosis (137). The mechanisms that lead to shelterin deregulation and TERT activation are poorly known. The activation of telomerase in cancer is of special relevance because it might be a target for innovative treatment methods in cancer patients. The fact that transformed malignant cells have eroded telomeres makes them more vulnerable to telomerase-targeting therapies (138). Telomere dynamics of transformed malignant cells is complex, and the importance of telomeres in the genesis and maintenance of malignant lesions is currently being studied. Short telomeres appear to enhance the chance of cancer development, whereas telomerase reactivation and intact telomeres appear to be critical for tumor growth and survival (15).

Osteoporosis and osteoarthritis

Bone cells, like many other tissues, show a reduction in TL with age. Furthermore, telomere dysfunction and osteoporosis are hallmarks of premature aging syndromes such as progeria (15). A comprehensive study of 2150 women aged 18 to 79 years revealed a substantial link between LTL and bone mineral density (139). Additionally, women with longer telomeres had a decreased probability of developing clinical osteoporosis. Several extensive studies, in contrast to the aforementioned, found no significant links between LTL, bone mineral density, and osteoporosis (140–142). The meta-analysis that included 678 osteoarthritis (OA) patients and 1457 healthy subjects (143) showed shorter TL in individuals with OA than in healthy controls. The findings imply that TL is linked to the etiology and development of OA, and more research in this area will aid in understanding the function of TL in OA pathology.

Neurodegenerative diseases

Telomere shortening associated with age has been linked to the malfunction of neurons and impairment of cognitive functions in the elderly, so it is expected that TL is linked to neurodegenerative diseases such as Alzheimer’s disease (AD) (15). This hypothesis has been confirmed by a recent meta-analysis, which has proven a substantial difference in LTL of Alzheimer's patients and healthy subjects (144). It’s still unclear whether reduced LTL in these patients is a manifestation of AD or an initiator of dementia formation and exacerbation. On the other hand, a review of eight studies found no significant variation in LTL between 956 individuals with Parkinson’s disease and 1284 healthy controls (8,144). Shortened TL, as a sign of premature biological aging, combined with several early-life variables, such as juvenile obesity, physical inactivity, and vitamin D defficiency, has been related to multiple sclerosis (MS) (145). Improved TL measuring approaches might contribute to a better understanding of the implication of TL in MS development and reveal new avenues for novel biomarkers and therapies in the future. TL has been linked to amyotrophic lateral sclerosis (ALS) in observational studies. High-quality genome-wide association studies (GWASs) have identified single-nucleotide polymorphisms (SNPs) for LTL (146).

Psychiatric disorders

56 studies involving 113,699 subjects with psychological distress have shown shorter TL in these patients compared with healthy individuals (147). Oxidative stress, intertwined with inflammation, is potentially an underlying biological mechanism that relates mental illnesses to telomere shortening.

Immune-mediated inflammatory diseases

Various immune-mediated inflammatory disorders (IMIDs), such as asthma, Crohn's disease, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and atopic dermatitis, have been demonstrated to be implicated in chronic inflammation, which can potentially be initialized by telomere disruption and short telomeres (148). In individuals with atopic dermatitis, there is an increase in telomerase activity (149). Recent meta-analyses verified the occurrence of decreased TL in rheumatoid arthritis patients (150,151). The expression and activity of telomerase have been found to be altered in these patients (152).

Interstitial lung diseases

Interstitial lung diseases (ILDs) reffer to a set of ailments characterized by pulmonary parenchymal fibrosis and/or inflammation. A variety of unusual telomerase gene mutations have been reported (50,153). Regardless of the underlying condition, fibrotic ILD patients with telomere gene mutations had a faster progression of disease (154). A number of patients with fibrotic ILDs had shorter TL compared to age-matched healthy individuals, and in IPF and fibrotic hypersensitivity pneumonitis, shorter TL has been associated with poor survival, regardless of disease severity (155). Patients with short telomeres have been shown to be more susceptible to immunosuppressant-induced adverse effects.

Covid-19

TL is a biomarker of interest even in the ongoing COVID-19 pandemic. Telomere attrition has been recommended as an indicator of disease severity in patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Tissues with critically short telomeres have a lower regeneration ability, which may impede their response to SARS-CoV-2 infection, especially in the elderly (156). TL might be assessed as a predictive biomarker in future trials with a larger number of patients, and it might help researchers better understand COVID-19 pathophysiology (157). Identification of high-risk patients and individualized treatment interventions can give additional insights into COVID-19 outbreak control (158).

Conclusion and future perspectives

Quantifying biological aging to provide representative lifespan or healthspan assessments is of growing importance (159). As the world's old population grows,

medical expenses for comorbidities are increasing, putting a strain on aging societies and healthcare systems. By changing the approach to this problem, it may be possible to treat multiple diseases by targeting "aging" itself (160).

So far, the research into BoAs has mainly been inconclusive and incomplete, and there is a general skepticism regarding the chances of meeting AFAR's strict requirements (161). A composite measure may be more relevant and applicable since a single BoA may not reflect the aging process completely and cannot be used to assess it. The discovery of the phenomena of age-associated telomere erosion has made TL one of the most promising BoAs. Der et al. investigated whether LTL fits the requirements for being regarded as a single BoA and whether it contributes to a composite biomarker panel. They created two composite scores, one including LTL and the other one without it. There was a little difference between them, but both composite scores were better in their prediction of health outcomes than chronological age (161). Composite BoAs have the potential to exceed age and should be investigated more in the future. Considering the entanglement of telomere dysfunction in disease onset, cellular vitality or activity, aging or longevity, measuring the LTL provides a clinical parameter that can be useful for diagnosis and prognosis (8,164–166), together with the evaluation of various therapies' efficiency, both conventional (167) and nonconventional (3). Because the level of telomere erosion is so important for the assessment of human health and course of the aging process, TL is by far the most researched biomarker of ARDs. As a result, various conclusions have been drawn about the relationship between TL, age, illness, stress, and a variety of other health outcomes. TL measurements can also be used as a precision medicine tool, assisting in the early detection of ARDs. Even though LTL measurement has been recommended as a predictor of the onset and progression of diseases, even death, in several studies, there is still a need for more data before its clinical application. The primary barriers to the extensive application of TL measurement are analytical challenges and pathophysiology features that are incompletely understood (8). The existing analytical methods are inadequately standardized and offer inconsistent results, thus limiting the comparability of the data. Harmonization of TL measurement amongst laboratories requires further work, including reference ranges stratified by age, gender and different cell types. This would allow researchers to compare the results from different studies and establish a gold standard for clinical testing (71). A variety of pre-analytical factors must also be taken into account. It is still unclear what the indications for LTL measurement are and which biological sample should be used for TL measurement. For the time being, TL will only be evaluated in research programs and clinical trials due to this issue. The fact that the average LTL measurement in peripheral blood may not adequately represent the TL in other cell types is a major drawback in clinical studies (15). Longitudinal monitoring of TL will be of particular importance in providing a dynamic picture of TL change over time (162). The link between telomere attrition and the aging process is shrouded in uncertainty, and the causal relationship is still insufficiently clarified. Hopefully, future advancements in these fields will considerably benefit society by lessening the demand for geriatric medical care.

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Dužina telomera kao biomarker starenja i bolesti

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Kratak sadržaj

Kako su istraživanja na temu starenja postala sve popularnija, javila se potreba za pouzdanim i praktičnim biomarkerom starenja, koji može pružiti informacije o riziku od mortaliteta i morbiditeta. Telomere su nekodirajući krajevi linearnih hromozoma koji održavaju njihovu stabilnost i integritet. Ćelijsko starenje i starenje organizma karakteriše progresivno skraćivanje telomera, što ugrožava njihovu strukturu i funkciju. Skraćivanje telomera je u vezi sa povećanom incidencom bolesti povezanih sa starenjem i lošom stopom preživljavanja, što ugrožava zdravlje i skraćuje životni vek. Stoga je dužina telomera dugo vremena prepoznata kao jedan od najboljih biomarkera starenja. Međutim, nedavna istraživanja ukazuju na to da dužina telomera može da pruži samo približnu procenu brzine starenja, pa je implementacija ovog biomarkera u kliničku praksu i rutinsku primenu praćena mnogim ograničenjima i izazovima. Uprkos tome, merenje dužine telomera, uz istovremeno određivanje drugih biomarkera, može poslužiti za procenu biološke starosti. Fokus ovog rada je na značaju telomera u ljudskom zdravlju, starenju i bolestima, kao i na sumiranju rezultata i zaključaka dosadašnjih studija koje su se bavile ispitivanjem dužine telomera kao potencijalnog kandidata za biomarker starenja.

Ključne reči: dužina telomera, biomarker starenja, telomeraza, bolesti povezane sa starenjem