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REVIEW

The relationship between telomere length and aging-related diseases

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Abstract
The intensifying global phenomenon of an aging population has spurred a heightened emphasis on studies on aging and disorders associated with aging. Cellular senescence and aging are known to be caused by telomere shortening. Telomere length (TL) has emerged as a biomarker under intense scrutiny, and its widespread use in investigations of diseases tied to advancing age. This review summarizes the current knowledge of the association between telomeres and aging-related diseases, explores the important contribution of dysfunctional telomeres to the development and progression of these diseases, and aims to provide valuable insights for the development of novel therapeutic strategies.

Keywords Telomere length · Aging-related diseases · Biomarkers

Introduction

Telomeres—structure and function

Telomeres are nucleoprotein structures located at the ends of chromosomes and are composed of repetitive TTAGGG sequences [1]. They serve two essential functions: protecting chromosome termini and preventing the loss of genetic material during DNA replication. A critical component in telomere maintenance is the shelterin complex, which comprises six protein subunits—TRF1, TRF2, Tpp1, Pot1, TIN2, and Rap1 [2, 3]. This complex not only binds telomeric DNA but also facilitates its folding into a protective three-dimensional T-loop structure that safeguards the 3′–OH terminus [4]. Moreover, shelterin regulates telomerase activity at telomeres, maintaining length homeostasis and establishing the optimal telomere length [5]. Disruptions in the shelterin complex can lead to premature aging [6]. Despite shelterin's protection, approximately 50–200 base pairs of telomeric DNA are lost with each cell division. This attrition is inherent to DNA replication because DNA polymerase synthesizes DNA only in the 5′→3′ direction, rendering the complete replication of chromosome ends impossible [7, 8]. In this way, telomeres act as buffers that preserve the integrity of genetic information. Because telomere length reflects cellular replicative history, telomeres are often considered markers of aging—the "mitotic clock" of human biological age [9–12]. When telomeres shorten beyond a critical threshold, cells enter replicative senescence, eventually triggering apoptosis [13]. Telomerase, a ribonucleoprotein enzyme complex, counteracts telomere shortening by appending repetitive sequences to chromosome ends [3]. It consists of a catalytic subunit, telomerase reverse transcriptase (TERT), and an RNA template (TERC) that directs telomeric DNA synthesis [14]. While most somatic cells exhibit low or undetectable telomerase activity, certain cell types—such as germ cells, stem cells, and cancer cells—maintain high telomerase activity to support continuous proliferation [15].

Telomeres in aging

Cellular senescence is marked by a series of complex molecular changes that lead to the gradual decline of tissue

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function and increased susceptibility to disease and mortality. The characteristics of cellular aging can be categorized into several key areas: changes in cellular phenotypes (such as stem cell exhaustion and senescence), disruptions in signaling pathways (including nutrient sensing distortions and intercellular communication abnormalities), organelle damage (such as mitochondrial dysfunction and loss of protein homeostasis), and genomic instability (including telomere attrition and epigenetic dysregulation) [16]. The progressive loss of physiological integrity associated with aging impairs biological functions, making it increasingly difficult for organisms to maintain homeostasis. Aging is an inevitable and irreversible process linked to the gradual decline of cellular function. In 2013, López-Otín and colleagues identified nine fundamental hallmarks of aging [16]. Building on this framework, researchers discovered three additional markers in 2023, including telomere attrition [17]. Telomere shortening is recognized as a primary indicator of aging, closely tied to the Hayflick limit—the concept that cells have a finite number of divisions. When telomeres become critically short, cells enter a senescent state, losing their ability to divide normally, which ultimately contributes to cellular arrest and dysfunction. Animal studies support this, showing that mice with longer telomeres tend to have extended lifespans, whereas those with shorter telomeres exhibit premature aging and reduced longevity [18].

DNA polymerase is an enzyme that catalyzes DNA replication, which always proceeds in the 5′ → 3′ direction. However, this enzyme can only add nucleotides to the free 3′–OH end of an existing nucleotide chain. At the very beginning of a new DNA strand, there is no available 3′–OH group for DNA polymerase to extend. To initiate DNA synthesis, RNA primers, which provide the necessary 3′–OH group, are required. After replication, these primers are removed, and the resulting gaps are filled with DNA. However, at the 5′ end of each newly synthesized daughter strand, the region previously occupied by the primer remains unfilled due to the lack of a free 3′–OH group [19]. As a result, each round of replication leads to a gradual loss of DNA. Without telomeres, this progressive DNA loss during mitosis would eventually lead to the erosion of essential genetic material [7]. When telomeres shorten to a critical length of approximately 4 kbp, cells either enter senescence or undergo apoptosis, preventing further division.

Molecular mechanisms linking telomere dysfunction to disease pathogenesis

DNA damage response

Telomere length and DNA damage response (DDR) are deeply interconnected in the regulation of cellular aging [20]. When they become critically short, they lose their ability to maintain the protective T-loop structure, exposing chromosome ends and triggering DDR pathways [21]. A hallmark of DDR activation is the phosphorylation of histone H2AX, resulting in γH2AX, which serves as a marker for DNA double-strand breaks. Proteins such as 53BP1 and MDC1 are then recruited to these sites of damage. Central to this response are the kinases ATM (ataxia telangiectasia mutated) and ATR (ATM- and Rad3-related), which act as primary sensors of DNA damage. Upon activation, they phosphorylate downstream kinases like CHK2 and CHK1, respectively. This cascade amplifies the damage signal, leading to cell cycle arrest and facilitating DNA repair processes. However, if the damage is too severe or persistent, the DDR can lead to cellular senescence (a state of irreversible cell cycle arrest) or, in some cases, apoptosis (programmed cell death) [9]. Due to the irreparable nature of critically short telomeres, the DNA damage response remains continuously activated. This persistent signaling forces the cell cycle into a permanent arrest, ultimately contributing to cellular aging and apoptosis [20, 22, 23]. Although apoptosis helps remove severely damaged cells, excessive or inappropriate apoptosis can lead to disease development [23]. Apoptosis can lead to massive cell loss and a decline in organ function [24]. For example, excessive apoptosis of cardiomyocytes or neurons can directly result in heart failure or neurodegenerative diseases. Additionally, apoptosis can cause abnormal organ repair and fibrosis. If a large number of apoptotic cells are not cleared in a timely manner, they may induce neighboring stromal cells to secrete profibrotic factors (such as TGF-β), leading to compensatory fibrotic repair, which in turn causes organ hardening and functional impairment [25, 26].

However, this explanation relies solely on telomere shortening and fails to account for aging in undifferentiated or non-proliferating cells [23]. In non-proliferating cells, such as quiescent or terminally differentiated cells, telomere damage—rather than telomere shortening—is a key driver of DDR activation and age-related functional decline. Telomere-binding proteins play a crucial role in maintaining chromosome stability, but they also suppress DNA repair within the telomeric region, making it difficult to fix telomere-specific DNA damage (tDD) [27]. As a result, this unrepaired damage leads to persistent DDR signaling and the formation of telomere-associated foci (TAF). Experiments on mice have shown that as they age, the frequency of TAF increases in their intestines [20, 22, 27]. Notably, this process can occur even in non-proliferating cells with intact telomere length if they experience DNA damage. Consequently, the accumulation of telomere damage—regardless of whether telomeres have significantly shortened—can still drive cellular senescence and contribute to age-related dysfunction [28].

Oxidative stress

Telomeres are not only protective caps at the ends of chromosomes, but their damage plays a crucial role in exacerbating oxidative stress and triggering diseases [29]. When telomeres shorten or their structure is damaged, the function of the shelterin complex becomes disrupted, leading the cell to misrecognize telomeres as DNA breaks, thereby persistently activating the DDR [20, 30]. This, in turn, initiates the ATM/ATR signaling pathways and downstream effectors such as p53 and Chk1/Chk2 [20]. The prolonged activation of these damage signals drives cells into senescence or apoptosis while simultaneously inducing a pro-inflammatory response through the activation of transcription factors like NF-κB, further intensifying oxidative stress within the cell [31]. Meanwhile, telomere damage-induced cellular senescence is often accompanied by mitochondrial dysfunction, where impaired mitochondrial metabolism leads to electron leakage, resulting in the excessive production of reactive oxygen species (ROS) [32, 33]. The cellular senescence and oxidative stress environment induced by telomere damage not only reduce cellular regeneration and organ repair capacity, leading to tissue functional decline, but also compromise telomere protective functions, making chromosome ends more prone to fusion, breakage, and rearrangement [9]. Overall, telomere damage persistently activates DNA damage signaling, induces cellular senescence, and disrupts mitochondrial function, forming a positive feedback loop between ROS and telomere damage. This not only significantly exacerbates oxidative stress but also initiates and accelerates the onset and progression of various diseases through multiple molecular pathways.

Mitochondrial dysfunction

Telomere damage activates a persistent DDR, in which the activation of the p53 pathway plays a central role [20, 34]. In addition to regulating the cell cycle and inducing apoptosis, p53 downregulates key transcription factors involved in mitochondrial biogenesis and function, such as PGC-1α and PGC-1β [35]. PGC-1α/β are crucial for maintaining mitochondrial function and quantity, and when their expression is suppressed, mitochondrial renewal and repair capacity decline significantly, leading to mitochondrial dysfunction [34]. Dysfunctional mitochondria exhibit impaired energy production, resulting in ATP deficiency, which prevents cells from sustaining normal metabolic and physiological functions, ultimately driving them into apoptosis or senescence [36]. The loss of cellular function and increased cell death not only affect individual cells but also trigger chronic low-grade inflammation and cellular dysfunction at the tissue level, thereby compromising tissue repair and regeneration capacity. Over time, this persistent oxidative stress and energy-deficient environment create a foundation for the onset of various diseases. In the metabolic system, it disrupts insulin signaling, promoting the development of diabetes and other metabolic disorders [37]. And in the nervous system, mitochondrial dysfunction may accelerate neurodegenerative diseases such as Alzheimer's disease [37, 38]. Clinical and experimental evidence further supports this connection. A population study found that individuals with primary and secondary mitochondrial dysfunction had shorter telomeres compared to healthy controls [39]. Similarly, TERC-null mice exhibited mitochondrial dysfunction and a weakened antioxidant defense system [40]. Additionally, mitochondrial DNA (mtDNA) damage, particularly deletions, may contribute to mitochondrial dysfunction and excessive ROS production, further exacerbating telomere attrition [41].

Inflammation

Telomere damage not only triggers a persistent DDR within the cell but also induces cellular senescence, leading to the formation of the senescence-associated secretory phenotype (SASP), which in turn initiates a series of complex inflammatory responses in the body [20]. First, telomere dysfunction induces cellular senescence, which leads to increased synthesis and release of inflammatory molecules such as TNF-α and IL-6 [42]. These secreted factors not only exert autocrine effects within the cell, reinforcing senescence signaling, but also influence surrounding healthy cells through paracrine effects, exposing them to inflammatory stimuli and driving them into senescence or functional dysregulation [43]. Prolonged exposure to this inflammatory environment disrupts normal intercellular communication, induces tissue remodeling, damages the extracellular matrix, and gradually leads to pathological changes such as fibrosis and sclerosis [44]. In a mouse experiment, the reduction of the telomere protective protein Trf2 in endothelial cells of young mice resulted in telomere damage and cellular senescence, accompanied by enhanced inflammatory signaling and increased oxidative stress [45]. These changes led to endothelial dysfunction and impaired glucose tolerance [46]. Consequently, inflammation induced by telomere damage contributes to endothelial dysfunction and atherosclerosis in the cardiovascular system, accelerates neurodegenerative disease progression in the nervous system, and disrupts insulin signaling in the metabolic system, promoting diabetes and other metabolic disorders [47–49]. Additionally, studies indicate that YAP1 activation, through its interaction with transcription factors, regulates the expression of multiple genes involved in immune and inflammatory responses [43]. This activation may also influence the release of cytokines and inflammatory mediators such as IL-6, IL-8, and TNF-α [42], which further amplify inflammatory signaling and modulate immune functions.

Senescence-associated secretory phenotype

In senescent cells, the sustained activation of DDR maintains the expression of SASP. The activation of the ATM and p38 MAPK signaling pathways promotes the activation of NF-κB, which is a key transcription factor regulating SASP gene expression [31]. SASP includes the release of cytokines, chemokines, and proteases (such as IL-6, IL-8, TNF-α, and MMPs), which can reshape the surrounding tissue environment, promote chronic inflammation, and affect neighboring cells [23, 50]. Persistent local inflammation disrupts normal intercellular communication and balance, leading to extracellular matrix degradation and changes in the extracellular environment, which in turn promote pathological remodeling of tissue structure, such as loss of arterial endothelial function and liver fibrosis [51, 52]. Meanwhile, SASP leads to matrix remodeling, with proteases such as MMPs disrupting the integrity of the extracellular matrix, promoting pathological changes such as fibrosis and sclerosis [53]. Moreover, SASP factors can induce DNA damage in neighboring healthy cells, forming a positive feedback loop that further expands the damaged area [26].

In summary, telomere dysfunction accelerates disease progression in aging-related diseases primarily through mechanisms such as cellular senescence, genomic instability, and chronic inflammation.

Telomere and aging-related diseases

Metabolic diseases

Diabetes

Diabetes, encompassing type 1 and type 2 diabetes mellitus (T2DM) as well as gestational diabetes, is widespread on a global scale. The above text mentioned that telomere attrition and T2DM have a bidirectional causal relationship. Elevated oxidative stress in individuals with T2DM leads to increased DNA damage, particularly affecting telomeres. This accelerated shortening of telomeres can result in premature cellular senescence, contributing to the progression of T2DM [54]. Several cross-sectional studies have shown that patients with diabetes have shorter telomeres than those without diabetes, regardless of the type of diabetes [55]. In a population-based prospective study, researchers evaluated leucocyte relative telomere length (RTL) by quantitative polymerase chain reaction. They conducted repeat RTL measurements in 2005 ($n=558$) and 2010 ($n=479$), and found that low RTL was independently associated with the risk of incident T2DM [56]. Furthermore, a prospective study investigated 93 women with gestational diabetes and 186 non-diabetic women as a control group, and revealed no significant correlation between TL and gestational diabetes overall. However, in women under the age of 30, there was a certain association between TL and gestational diabetes, with a higher risk observed in those with shorter telomeres [57, 58]. Cross-sectional research findings vary, with some indicating that shorter TL is related to a twofold increased risk of gestational diabetes, while others found no connection [59]. In addition, impaired beta cell replication plays an important role in the occurrence and development of type 2 diabetes. Telomerase deficiency and consequent telomere shortening impair the replicative capacity of pancreatic β-cells [60]. This impairment leads to reduced insulin secretion and glucose intolerance [60]. Researchers built mouse models to study changes in pancreatic islet β-cell function. They discovered that in mice with type 2 diabetes, the distribution of β-cell subtypes shifted. Significantly, one subtype showed increased basal insulin secretion but a weakened response to glucose stimulation [61].

It is worth mentioning that diabetes treatment may affect TL. For instance, physical exercise, dietary control, medication, and other interventions can help alleviate oxidative stress and inflammatory conditions, consequently promoting the elongation of telomeres. This improvement in telomere length can enhance the condition and prognosis of individuals with diabetes. Silvia Canudas and colleagues conducted a systematic review of the relationship between the Mediterranean diet (MedDiet) and TL, involving 13,733 participants from five countries demonstrated a positive correlation between the MedDiet and TL [62].

Liver diseases

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver and can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, or even hepatocellular carcinoma (HCC). Research indicates a significant association between telomere length and the progression of NAFLD [63–65]. The TL likely a crucial factor in this complex connection, causing liver cells to become senescent, which in turn affects the overall health of the liver and contributes to the progression of NAFLD. The results of a controlled experimental investigation showed that the length of hepatocyte telomeres was shorter in individuals with NAFLD than in controls [66]. In a recent prospective study involving 467,848 participants from the UK Biobank, with a follow-up period of 12.83 years, 4809 patients with NAFLD were identified and TL exhibited a negative correlation with the incidence of NAFLD [65]. Moreover, a study revealed that individuals afflicted with NAFLD exhibited elongated telomeres compared to age-matched counterparts [67]. However, certain investigations have not confirmed an inverse relationship between the incidence of NAFLD and TL, which

may be attributed to differences in sample size and study methodologies [68]. In comparison with non-cirrhosis controls, cirrhosis patients display shorter telomeres and an increased occurrence of telomerase mutations. These mutations often trigger uncontrolled hepatocellular proliferation, predisposing these patients to the onset of hepatocellular carcinoma [69, 70]. Furthermore, telomerase-deficient mice exposed to chronic liver injury exhibit accelerated progression of liver fibrosis [71]. This suggests that telomere dysfunction may play a crucial role in the advancement of NAFLD to liver fibrosis and liver cancer.

Hyperuricemia and gout

Hyperuricemia and gout are becoming increasingly prevalent, with hyperuricemia being the primary risk factor for gout [72]. Uric acid affects cells in multiple ways, including promoting reactive ROS production, which contributes to inflammation at deposition sites within blood vessels and joints. A recent prospective study in China conducted a longitudinal analysis of 599 participants to investigate whether shorter telomeres could predict hyperuricemia. After adjusting for risk factors, the study followed 266 participants from June 2014 to December 2021 and found that shorter leukocyte TL was significantly associated with the development of hyperuricemia during the follow-up period (odds ratio [OR] 2.347; 95% confidence interval [CI] 1.123–4.906; $P = 0.023$) [73]. Similarly, a comparative study examining TL in 145 gout patients and 273 healthy individuals found that gout patients had shorter telomeres and experienced greater telomere erosion at all ages. Moreover, TL was negatively correlated with the frequency of gout attacks [74].

Cardiovascular diseases

Cardiovascular disease (CVD) is one of the leading causes of death worldwide, with a complex etiology influenced by both genetic and environmental factors. CVD encompasses a range of conditions affecting the heart and blood vessels, including heart disease, hypertension, myocardial infarction, and stroke. According to the World Health Organization, CVD accounts for approximately 17.9 million deaths annually, a number that continues to rise [75]. Major risk factors for CVD include physical inactivity, an unhealthy diet, smoking, and preexisting medical conditions [76]. Numerous studies have identified a strong association between TL and heart disease [77, 78]. The pathological progression of CVD is often accompanied by oxidative stress and chronic inflammation, both of which contribute to telomere shortening and dysfunction.

Cardiomyopathy

As the heart ages, myocardial hypertrophy and fibrosis lead to increased ventricular stiffness and impaired cardiac function [79]. A meta-analysis of 18,293 patients across 12 studies found that leukocyte telomere length (LTL) can serve as a predictor of atrial fibrillation [80]. Additionally, a study involving telomere gene testing identified genetic variants associated with shorter telomeres, which were linked to an increased risk of coronary artery disease in a cohort of 22,233 patients and 64,762 controls [81]. Telomere shortening also plays a role in cardiac aging. Myocardial hypertrophy and fibrosis are characteristic features of this process, and patients with genetic hypertrophic or dilated cardiomyopathy exhibit shorter myocardial cells compared to age-matched individuals [23]. A large independent cohort study further demonstrated a correlation between LTL and the severity of hypertrophic cardiomyopathy [82]. In a prospective population-based study, Willeit et al. assessed relative LTL using PCR in adults aged 45–84 years, comparing individuals without cardiovascular disease (CVD) to those with stable coronary artery disease (CAD). Their findings revealed that LTL in CAD patients was significantly shorter than in healthy individuals of the same age [83]. These findings suggest that cardiovascular diseases may influence telomere length, with conditions such as myocardial infarction and heart failure accelerating telomere shortening. This creates a vicious cycle that exacerbates cardiac damage and functional decline. Animal studies further support this connection. Two studies in mice revealed that their naturally long telomeres offer protection against heart disease. Researchers found that mice only developed heart conditions similar to those seen in humans after their telomeres were genetically shortened to human-like lengths [34, 84]. The research also suggests that shorter telomeres may impair heart function by disrupting mitochondrial activity. When mitochondria malfunction, as observed in dilated cardiomyopathy, the resulting energy deficiency can lead to severe heart failure [34, 84].

Atherosclerosis

Atherosclerosis is indeed a chronic and progressive arterial disease characterized by inflammatory changes within the arteries. These changes are typically associated with alterations in lipid metabolism and other metabolic factors. One study revealed that patients with atherosclerosis have shorter telomeres in circulating leukocytes compared to their healthy, age-matched counterparts [85]. Furthermore, vascular smooth muscle cells (VSMCs) in atherosclerotic plaques display a significantly shorter TL than unaffected VSMCs in the same individual [23]. A reduction in TL in the of VSMCs within atherosclerotic plaques correlates with the

severity of the disease. Additionally, VSMCs in atherosclerotic plaques exhibit oxidative DNA damage and express various markers of aging. Accelerated telomere attrition not only promotes atherosclerosis but also impairs vascular lesion repair, exacerbates endothelial damage, and enhances oxidative stress and inflammatory processes, thus accelerating telomere shortening-related atherosclerosis.

Hypertension

Hypertension is one of the most prevalent cardiovascular diseases, affecting individuals across all ethnicities worldwide. The relationship between TL and hypertension is thought to involve telomere shortening, which contributes to cellular aging and dysfunction, ultimately increasing the risk of hypertension [86]. Telomere dysfunction-induced cellular senescence in arterial walls may play a role in the pathogenesis of hypertension [87]. Research on spontaneously hypertensive rats (SHR) revealed that telomerase is selectively activated in the aorta, leading to alterations in telomere maintenance and the p53 checkpoint, which together promote VSMC proliferation. Inhibiting telomerase activity reduced VSMC proliferation and induced apoptosis in SHR, suggesting a potential therapeutic target for hypertension [88]. A case–control study involving 206 patients with essential hypertension (EH) and an equal number of sex-matched healthy controls found that EH patients had significantly shorter TL [89]. However, a genome-wide association study (GWAS) reported that longer TL was associated with a higher risk of hypertension—contradicting previous findings on coronary artery atherosclerosis, ischemic heart disease, myocardial infarction, and stroke [75]. These inconsistencies highlight the complex and still inconclusive relationship between TL and hypertension, underscoring the need for further research in this area.

Pulmonary diseases

Frequently encountered pulmonary diseases encompass idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), among other conditions. Numerous studies have suggested a significant correlation between pulmonary diseases and the aging process [90].

IPF

IPF is a progressive lung disease that primarily affects older individuals and ultimately leads to death. Its exact cause remains unknown [90]. The disease is characterized by excessive extracellular matrix deposition within the lung interstitium, resulting in abnormal scar formation and impaired lung function [91]. Telomere dysfunction plays a crucial role in IPF development. It accelerates fibrosis progression by inducing cellular senescence, particularly in alveolar epithelial cells, thereby reducing the lung's regenerative capacity. This process triggers inflammatory responses and compromises stem cell function, further contributing to disease onset and progression. In experimental studies, two independent mouse models—one with severe telomere shortening due to telomerase deficiency and another with TRF1 protein deletion in alveolar type II epithelial cells—both developed pulmonary fibrosis, highlighting the direct impact of telomere dysfunction on lung pathology [92]. Genetic studies provide further evidence of this association. Approximately 40% of familial IPF cases and 25% of sporadic IPF cases are linked to shorter telomeres, often due to mutations in TERT or TERC [91]. An analysis of 73 probands from the vanderbilt familial pulmonary fibrosis registry identified heterozygous mutations in these genes in six individuals [81]. Beyond familial cases, sporadic IPF patients also exhibit telomere shortening [93]. A study comparing TL in alveolar epithelial cells from individuals with normal lung function, sporadic IPF, and IPF with telomerase mutations found that both IPF groups had significantly shorter telomeres than healthy controls [94]. Additionally, large-scale genetic research has reinforced this link. A multigene risk score analysis involving 400,000 individuals and one million controls identified pulmonary fibrosis as the disease most strongly associated with short telomeres [95]. Moreover, shorter TL has been correlated with reduced time to allograft dysfunction following lung transplantation, underscoring its clinical significance [96].

Chronic obstructive pulmonary disease

COPD significantly heightens morbidity and death in elderly individuals [97]. COPD accelerates the aging of lungs, marked by inflammation and oxidative stress in lung tissue and airways, along with persistent restructuring of the smaller air passages, eventually resulting in emphysema [23]. Telomere shortening can result in the aging and functional decline in lung tissue, which in turn increases the likelihood of developing COPD in patients. Small airway epithelial cells from COPD patients exhibit increased levels of telomere-associated foci (TAFs) and senescence markers compared to healthy individuals [98]. Various studies have consistently shown that the TL in the blood or lung tissue of people with COPD is generally shorter than that in the blood or lung tissue of healthy individuals [98, 99]. In COPD, telomere shortening may indicate cellular aging processes, and aged pulmonary cells may impact the progression of airflow restriction. Moreover, the presence of COPD can impact the length of telomeres through the induction of systemic inflammation [100]. Research indicates that patients with COPD have higher levels of a wide range of inflammatory mediators in their lungs and blood [101]. Shortening of

telomeres leads to cellular aging and the release of inflammatory mediators, contributing to heightened incidence and severity of airway inflammation.

Bronchiectasis

Bronchiectasis is a chronic lung disease characterized by persistent inflammation and airway damage. Its development is closely linked to dysfunction and impaired repair capacity of airway epithelial cells [90]. These cells serve as the first line of defense against environmental insults and pathogens, maintaining airway integrity. Telomere attrition is thought to weaken their proliferative and reparative abilities, compromising the epithelial barrier. Histological analysis of lung tissue from affected individuals has shown shorter telomeres and increased expression of senescence markers [102]. Han et al. explored accelerated aging in bronchiectasis by examining aging-related markers in both systemic circulation and bronchial epithelium. Their findings indicate that individuals with bronchiectasis have shorter telomeres and lower levels of SIRT1 and Ku80 in peripheral blood compared to healthy controls [103].

Kidney diseases

The kidneys undergo both structural and functional alterations as they age. Various conditions such as acute kidney injury, glomerulonephritis, diabetic nephropathy, polycystic kidney disease, and chronic kidney disease (CKD) are linked to TL. TL is impacted by several variables, including oxidative stress and inflammation, which are commonly found in renal disorders.

Chronic kidney disease

Repetitive aging, stress-induced premature aging, and epigenetic abnormalities contribute to the development of CKD. Genetic damage and environmental stressors drive oxidative stress and chronic inflammation, leading to irreversible cell cycle arrest and increased secretion of the SASP [104]. Telomere shortening or damage can activate a persistent DDR, promoting cellular senescence [23]. In CKD, increased DNA damage has been observed, as evidenced by elevated DDR markers such as γH2AX in kidney tissues [105]. The disease is highly prevalent among the elderly, and numerous studies have linked shorter telomeres to CKD [106–108]. One study found that for every 0.1-unit decrease in relative TL, the risk of mortality increased by 14%, independent of age, sex, kidney function, and cardiovascular risk factors [107]. Another study of over 2,000 patients with type 2 diabetes mellitus (T2DM) showed that those with shorter leukocyte TL had a 1.9-fold higher risk of albuminuria progression after adjusting for established risk factors [109]. In CKD, premature cellular aging can result from chronic inflammation and metabolic abnormalities, contributing to telomere attrition. Additionally, telomere shortening has been associated with increased inflammation and oxidative stress in CKD [108]. Both factors are common in CKD patients, and researchers speculate that telomere attrition may play a role in disease onset by exacerbating these pathological processes [110].

Kidney fibrosis

Kidney fibrosis is a hallmark clinical feature observed in nearly all cases of CKD, yet its pathophysiology remains poorly understood. The development of renal fibrosis is influenced by multiple factors, including genetic predisposition, lifestyle choices, and environmental exposures. Cellular injury often serves as the initial trigger, activating a cascade of inflammatory responses and reparative processes that culminate in collagen deposition and fibroblast proliferation, ultimately forming fibrotic scar tissue [111]. Emerging evidence suggests a strong link between telomere shortening, telomere dysfunction, and renal fibrosis [23]. Saraswati et al. demonstrated that short telomeres in mice can exacerbate the epithelial-to-mesenchymal transition (EMT), increasing renal susceptibility to folate-induced fibrosis and accelerating fibrotic progression. Additionally, the absence of Trf1, a key component of the shelterin complex, was shown to induce kidney fibrosis. Telomerase-deficient mice with shortened telomeres also developed significant renal fibrosis and impaired kidney function following minimal folic acid exposure [112].

Neurodegenerative diseases

Studies suggest a discernible correlation between TL and neurodegenerative diseases. Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), among others, are a group of conditions characterized by the gradual dysfunction or death of neurons.

Alzheimer's disease

By 2050, AD, the most prevalent neurodegenerative disorder, is projected to affect over 100 million people worldwide, with the majority in low- and middle-income countries. Age is the primary risk factor for AD, with its impact becoming more pronounced as individuals grow older. Notably, research has demonstrated that shorter telomeres accelerate the natural aging process in humans [16]. A meta-analysis [113] of 13 studies comparing telomere length (TL) in 860 individuals with AD and 2022 controls revealed significant differences in TL between the groups. One study of 1983 participants aged 65 and older found that individuals with shorter telomeres had higher mortality rates and an increased

risk of developing AD during follow-up [114]. Moreover, a significant correlation was observed between white blood cell TL and hippocampal volume. In non-demented individuals carrying the APOE3/3 genotype, a genetic variant associated with AD susceptibility, a negative correlation was identified between white blood cell TL and hippocampal volume. Additionally, AD model mice exhibited shorter blood cell telomeres compared to wild-type mice, though no such difference was observed in hippocampal telomere length [115].

Parkinson's disease

PD, the second most prevalent neurodegenerative disorder after AD, is characterized by motor dysfunction resulting from neuronal loss in the substantia nigra and subsequent dopamine depletion in the striatum [116]. Telomere shortening in leukocytes and microglia may indirectly affect neuronal health by impairing immune cell function in the brain [117]. While no definitive population-based evidence currently establishes a direct link between PD and telomere shortening, ongoing research continues to explore this potential connection [118]. A meta-analysis of eight primary studies, including 956 individuals with PD and 1284 controls, found no statistically significant difference in TL between the two groups [119]. However, postmortem brain samples from PD patients have revealed the presence of senescent astrocytes [120]. Additionally, mice with critically short telomeres exhibited impaired neuromuscular coordination in performance tests [121]. These findings suggest a potential association between TL and PD, highlighting the need for further investigation into the biological mechanisms linking telomere dynamics and PD pathogenesis, which may inform future therapeutic strategies.

Skeletal disorders

Osteoporosis

Osteoporosis, characterized by reduced bone density and deterioration of bone microstructure [122], has been linked to the presence of senescent cells in the body [23]. Similar to many other tissues, telomeres in osteoblasts and mesenchymal stem cells (MSCs) shorten with age [7]. Telomere dysfunction and osteoporosis are also observed in premature aging syndromes, such as Werner syndrome and congenital keratinization disorders. An early cohort study by Valdes et al. examined LTL and its association with bone density in women, revealing an independent correlation between shorter LTL and decreased bone density, particularly in postmenopausal women aged 50 and above [123]. Additionally, aging is associated with increased levels of reactive oxygen species, which exacerbate oxidative stress, impair bone formation [124], and contribute to telomere shortening. However, some studies have found no significant association between leukocyte TL and osteoporosis. [125]. For instance, a health assessment study of 2750 community-dwelling elderly individuals reported no significant correlation between leukocyte TL, bone mineral density (BMD), bone loss, or fracture incidence [125]. In conclusion, further research is necessary to clarify the complex relationship between telomere length and osteoporosis.

Osteoarthritis

Osteoarthritis is defined by a decrease in bone mineral density and degeneration of bone tissue structure, leading to an increased likelihood of fractures [23]. In the context of osteoarthritis, several joint tissues, such as articular cartilage, synovium, and subchondral bone, exhibit increased numbers of senescent cells. These cells not only lose their ability to maintain tissue homeostasis but also secrete SASP factors that promote inflammation and matrix degradation, exacerbating joint degeneration [126]. Although age is recognized as a predictor of osteoarthritis, the precise underlying mechanism remains uncertain. Previous studies have revealed many aging markers in osteoarthritis [126]. Researchers found in a study on hand osteoarthritis and TLs that the shorter TL differed by approximately 11 years from those of normal people and was associated with the severity of the disease [127]. The damage and degradation of articular cartilage also correlate with TL shortening. In osteoarthritis, studies have found that many aging markers are deposited in chondrocytes [128]. Researchers showed that the shorter TL was associated with a higher degree of hand osteoarthritis and differed by approximately 11 years from that of normal individuals. There is a correlation between articular cartilage injury, deterioration, and TL shortening. A multitude of age markers have been found in chondrocytes linked to osteoarthritis. According to research, TL shortening may affect the ability of chondrocytes to divide and repair themselves. This could accelerate the deterioration of joint cartilage and increase the likelihood of osteoarthritis. After comparing the two populations, they also discovered more aging cells in the older population than in the younger group. Currently, researchers believe that extremely short telomeres provide a more accurate indicator of osteoarthritis damage than typical TL [129].

Discussion

In the past, scientists recognized telomeres as among the most accurate markers of aging, as aging diseases closely correlate with accelerated telomere shortening and telomere dysfunction [130]. Researchers discovered that during

aging, DNA damage-induced changes in the rate of replication forks, commonly referred to as replication stress, can lead to asymmetric fork progression, incomplete replication, fork collapse, and genomic instability, preferentially targets telomeres with G-repeat-rich. Notably, up to half of the foci observed in stress-induced aging were located on telomeres [22], as telomeres can form stable G-quadruplexes that impede the progression of replication forks. Therefore, repairing collapsed replication forks or inhibiting the formation of G-quadruplex structures by targeting them during replication stress may represent an effective strategy to delay telomere shortening and combat the progression of age-related diseases. TL shortening appears to be associated with oxidative stress, inflammatory responses, mitochondrial dysfunction, and other aging-related factors. This association primarily arises from the fact that chronic inflammation and oxidative stress can lead to guanine oxidation, which results in telomere shortening and instability. Consequently, these processes initiate aging and contribute to the associated degeneration observed in humans [30, 131]. In addition, lifestyle is also closely related to telomeres [132]. Diet, life stress, habits, etc., will affect telomeres. One study analyzing single-molecule telomere length and telomere fusion found that the frequency of short telomeres and telomere aberrant events increases with disease progression, and samples with short telomeres exhibit large-scale genomic rearrangements [22]. Telomeres impede the progression of replication forks, which can lead to stalling. When the replication fork becomes stalled, it may collapse, resulting in the formation of DNA double-strand breaks (DSBs). Telomere aberrant can occur during both classical and alternative non-homologous end-joining repair pathways that repair DSBs. Consequently, telomere shortening associated with aging may lead to telomere aberrant, further contributing to telomere dysfunction. In this context, the inhibition of DNA repair mechanisms may prevent the aberrations associated with short telomeres [22]. Moreover, telomeres protect the ends of linear eukaryotic chromosomes from being recognized as DNA double-strand breaks. Two major protein complexes are involved in the protection of telomeres: shelterin and CST; thus, the possibility of targeting protective proteins and CSTs through small-molecule inhibitors deserves further research and exploration [22]. However, the current study cannot determine whether telomere changes are the cause or result of aging [133]. Further research is needed to analyze its causality.

The epidemiological relationship between TL and disease and mortality is not always clear and can even be contradictory. Therefore, it is necessary to specify a standardized measurement standard to specify a standard TL reference range. When analyzing the data of different studies (Fig. 1 and Table 1), we noticed a lack of a unified and standardized reference range of TL for healthy people of different ages. We found significant differences in TL reported by different studies in healthy people. Some studies have shown that TL tends to decrease with age [13], while no obvious correlation was observed in other studies. This inconsistency in data may be partly due to the use of different measurement techniques, differences in sample sources, and limitations in study design. Considering the lack of a unified and standardized reference range of TL in healthy people at different ages, we believe that it is highly important to establish such a reference range. Firstly, this will help to assess the health status of individual TLs more accurately and better identify potential health risks, aiding in prevention of chronic diseases. Second, a unified reference range can promote comparisons and data sharing between different studies, thus promoting the progress of TL research. To establish a uniform reference range for TL, we recommend a multicenter, large sample prospective cohort study. Such a study can cover healthy people of different ages, genders, ethnicities, and geographical backgrounds to ensure the representativeness and universality of the reference range. In addition, standardized measurement techniques and analysis methods should be adopted to reduce measurement errors and uncertainty in the results.

Although the previous text did not mention cancer, cancer is closely related to telomeres and their associated factors [134]. When short telomeres induce the DDR, they can lead to chromosomal end-to-end fusions, breakages, and rearrangements, resulting in chromosomal instability [9, 20]. Chromosomal instability is one of the hallmarks of cancer [135]. Additionally, DDR promotes cellular senescence. Senescent cells secrete a variety of pro-inflammatory cytokines, growth factors, and proteases, collectively known as the SASP. For example, SASP factors can alter the tissue microenvironment, making it more conducive to cancer development [136]. These factors can stimulate nearby cells to proliferate more actively, enhance angiogenesis (the growth of new blood vessels), and create a permissive environment for cancer cells to thrive. Furthermore, if senescent cells are not cleared by the immune system, they can accumulate over time, exacerbating inflammation and further promoting cancer progression. Cancer cells typically exhibit uncontrolled cell proliferation and unlimited division capabilities, attributed in part to their aberrant regulation of telomerase. Previous research has highlighted the crucial and intricate roles of TERT and its various subtypes in telomerase activity [137]. A study investigated 14,830 samples, and among 6,835 cases of cancer, 73% expressed TERT [138]. While there is substantial evidence suggesting an association between TL and age-related diseases, establishing a causal relationship requires longitudinal studies and the evaluation of other markers of telomere biology to elucidate the role of telomeres and telomerase in cancer.

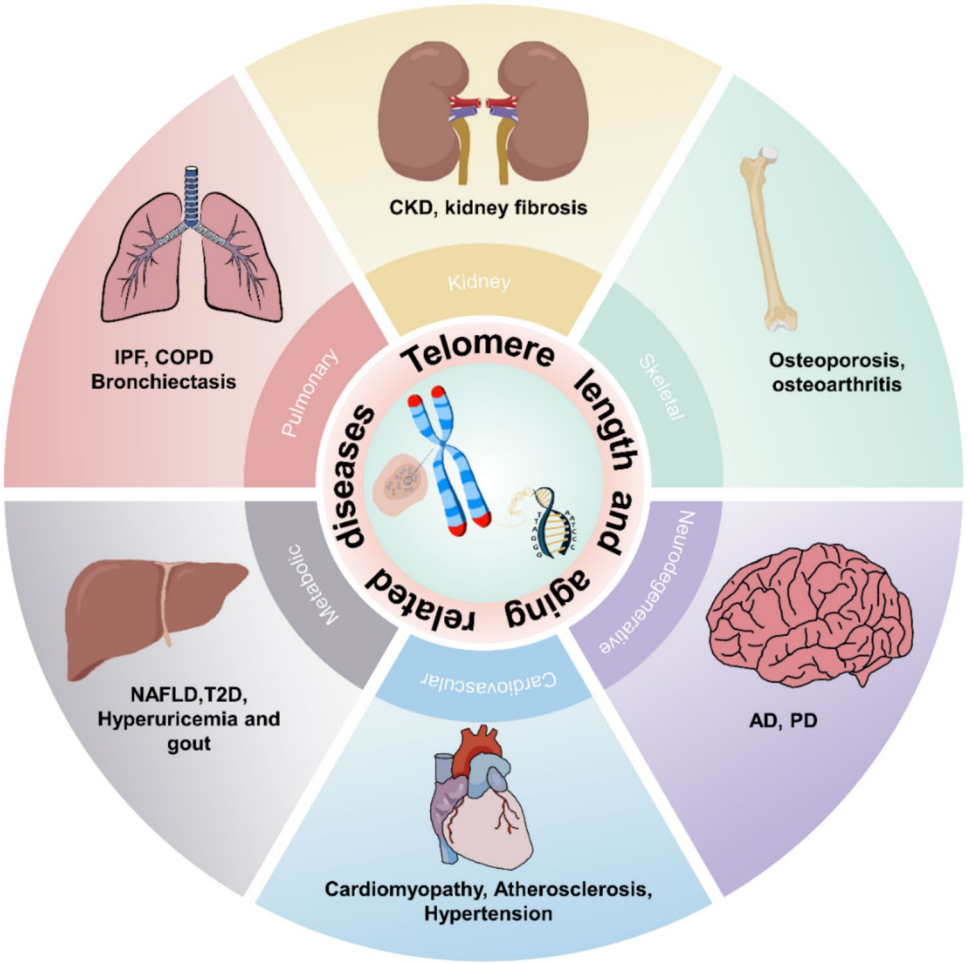

Fig. 1 Telomere length and aging-related diseases. A schematic overview of the aging-related diseases discussed in this Review, organized by organs or systems. AD, Alzheimer's disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; NAFLD, non-alcoholic fatty liver disease; PD, Parkinson's disease; T2D, type 2 diabetes

Although telomeres are widely recognized as one of the precise biomarkers of aging, the complexity and cost of TL measurement methods pose challenges that limit their application in clinical practice. However, with ongoing technological advancements, we anticipate that TL measurements could be more extensively utilized in clinical diagnostics and therapeutics.

Potential interventions

Telomeres, the protective caps at the ends of chromosomes, play a crucial role in maintaining genomic stability and cellular lifespan [1]. As cells divide, telomeres progressively shorten, eventually leading to cellular senescence or apoptosis. Interventions targeting telomere biology hold potential for addressing age-related diseases and extending healthy lifespan.

Strategies for telomerase activation

Small molecule activator

In recent years, certain small-molecule compounds have been found to have the potential to activate telomerase activity. For example, components extracted from traditional Chinese herbs (such as TA-65) have shown telomere-lengthening effects in both in vitro studies and animal models [157]. The primary mechanism of action involves upregulating the expression of TERT, thereby slowing telomere shortening and the process of cellular aging. It is important to note that while telomerase activation may help delay aging, its high activity in most cancer cells raises concerns about the potential risk of inducing abnormal cell proliferation with long-term use. Therefore, rigorous safety assessments should be conducted before clinical application [157].

Table 1 Associations between telomere length and aging-related diseases

Disease	Study type	Method	Expression of TL	Cases		Controls		References
				Type	No	Type	No	
T2DM	Meta-Analysis	q-PCR	T/S, short	without T2DM	606	N/A	N/A	[56]
T2DM	Observational	q-FISH	T/S, short	T2DM AND CVD	204	without T2DM and CVD/without T2DM but CVD	258/798	[139]
T2DM	MR	q-PCR	T/S, short	T2DM	569	without T2DM	448	[140]
T2DM	Randomized Controlled Trial	q-PCR	T/S, short	CHD and Mediterranean diet/CHD and low-fat diet	502/500	without CHD	462	[141]
T2DM	Observational	q-PCR	T/S, short	T2DM	930	without T2DM	867	[142]
GDM	Observational	q-PCR	T/S, short	GDM	93	without GDM	186	[57]
DN	Observational	Southern Blot	kb, short	T1DM	132	without DN	44	[143]
NAFLD	Observational	q-PCR	T/S, short	NAFLD	60	without NAFLD	23	[64]
NAFLD	Observational	q-FISH	T/S, short	NAFLD	70	without NAFLD	60	[66]
CLD	Observational	q-PCR	T/S, short	CLD	521	without CLD	600	[69]
Gout	Observational	q-PCR	T/S, short	GOUT	145	without Gout	273	[74]
Hyperuricemia	MR	q-PCR	T/S, short	Hyperuricemia	488/400	N/A	N/A	[144]
CAD	Observational	q-PCR	T/S, < Q1	CAD	566	N/A	N/A	[145]
CAD	MR	N/A	N/A	CAD	22,233	without CAD	64,762	[81]
CAD	Observational	Southern Blot	kb, short	CAD	484	without CAD	1058	[146]
HCM	Observational	q-PCR	T/S, short	HCM	56	without HCM	59	[82]
CVD	Observational	q-PCR	T/S, short	PAD and T2DM	241	without PAD but T2DM	249	[147]
CA	Observational	Southern Blot	kb, short	CA and hypertension	90	without Carotid plaque but hypertension	73	[148]
Hypertension	Observational	Southern Blot	kb, short	male with hypertension	120	female with hypertension	73	[149]
IPF	Observational	q-FISH	Kb, short	IIP	62	without IIP	400	[94]
IPF	Observational	q-PCR	Kb, short	Dallas IPF cohort/Chicago IPF cohort/San Francisco IPF cohort	149/139/54	Dallas Cohorts: without IPF	221	[150]
COPD	Meta-Analysis	N/A	N/A	COPD	934	without COPD	15,846	[99]
COPD	Observational	q-PCR	Kb, short	COPD and smoking	70	smoker without COPD	73	[151]
Bronchiectasis	Observational	q-PCR	T/S, short	Bronchiectasis	8	without Bronchiectasis	7	[102]
CKD	Randomized Controlled Trial	q-PCR	T/S, short	CKD and n-3 FA/CKD and CoQ/CKD and n-3 FA + CoQ	19/21/18	CKD and placebo	15	[152]
CKD	Observational	q-PCR	T/S, Q1-Q4	CKD	4955	N/A	N/A	[153]
AD	Observational	q-PCR	T/S, short	AD	32	Stable aMCI/Healthy people	13/20	[154]
AD	Observational	q-PCR	T/S, Q1-Q5	aMCI	137	without aMCI	137	[155]
PD	Observational	q-PCR	T/S, short	PD	168	without PD	30	[156]
OP	Observational	Southern Blot	kb, long	OP	2150	without OP	2150	[123]
OA	Observational	Southern Blot	kb, short	OA	160	without OA	926	[127]

AD: Alzheimer's disease; aMCI: Amnestic mild cognitive impairment; CA: Carotid atherosclerosis; CAD: Coronary artery disease; CKD: Chronic kidney disease; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; DN: Diabetic nephropathy; GDM: Gestational diabetes mellitus; HCM: Hypertrophic cardiomyopathy; IIP: Idiopathic interstitial pneumonias IPF: Idiopathic pulmonary fibrosis; NAFLD: Non-alcohol-related fatty liver disease; OA: Osteoarthritis; OP: Osteoporosis; PD: Parkinson's disease; T2DM: Type 2 diabetes mellitus

Gene therapy strategy

Gene therapy introduces the TERT gene into the body using viral vectors or other delivery systems, thereby directly enhancing intracellular telomerase activity [158]. A study by Bernardes de Jesus et al. in a mouse model demonstrated that this strategy not only extends telomeres but also improves tissue function, delays aging symptoms, and, to some extent, prolongs lifespan [159]. Moreover, the study did not identify significant cancer risks during the evaluation process. However, due to the inherent challenges of gene therapy, such as immune responses and long-term regulatory issues, further research is needed before its application in humans [159].

Strategies for lifestyle change

Balanced diet

A balanced diet (such as the Mediterranean diet) is rich in antioxidants, fiber, polyphenols, and omega-3 fatty acids, which help reduce oxidative stress and chronic inflammation in the body, thereby protecting telomeres from damage [160, 161]. Research has shown that a high antioxidant diet not only helps maintain telomere length, but is also associated with a reduced risk of cardiovascular disease, metabolic syndrome, and other conditions [162]. Therefore, a reasonable dietary structure is considered an important non-pharmacological intervention to delay cellular aging.

Moderate exercise

Regular and moderate exercise can improve cardiovascular health, regulate endocrine function, and reduce inflammation levels, thereby indirectly protecting telomeres [163]. During physical activity, the body releases various beneficial factors that enhance antioxidant defense and cellular repair capacity. Numerous epidemiological studies have shown that individuals with higher levels of physical activity generally have longer leukocyte telomeres, providing important evidence for the role of exercise interventions in anti-aging [164].

Stress management

Chronic psychological stress is considered one of the key external factors accelerating telomere shortening, primarily through the prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis [165, 166]. Under persistent stress, the body continuously secretes cortisol, a stress hormone that not only increases oxidative stress levels but also promotes the release of inflammatory factors, leading to negative effects on cells and accelerating telomere shortening [167]. To counter these adverse effects, various stress management strategies have been proposed and have shown potential in protecting telomeres. For example, mindfulness meditation helps individuals focus on the present moment, thereby reducing anxiety and emotional fluctuations [168]. Studies have shown that after a period of mindfulness training, participants experience significantly lower cortisol levels and improved inflammatory biomarkers [169]. Additionally, practicing yoga, which integrates physical postures, breath control, and meditation, can help alleviate both physical and psychological tension. Deep breathing exercises activate the parasympathetic nervous system, reducing heart rate and blood pressure, thereby mitigating stress responses. Lastly, maintaining good sleep quality is also crucial, as individuals with sufficient and high-quality sleep tend to exhibit lower stress levels and longer leukocyte telomeres [170].

Conclusions

We have outlined the connection between TL and aging-related disorders here. TL reduction is directly linked to the development and occurrence of many chronic diseases, including diabetes, cancer, and cardiovascular disease. This emphasizes how crucial TL is for preserving cellular health and function. Environmental factors such as stress, pollution, and poor lifestyles are linked to aberrant telomere shortening, providing additional evidence of the influence of lifestyle on cellular health. Therefore, an improved lifestyle may facilitate the maintenance of healthy TLs and lower the risk of disease. Despite numerous studies suggesting that TL is a prognostic indicator for aging-related disorders and mortality, clinical practice currently underutilizes its detection. Strengthening communication between the laboratory and clinical settings is essential for laying the groundwork for its clinical application.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Informed consent Not applicable.

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