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Review Article

Telomere length as a marker of sleep loss and sleep disturbances: a potential link between sleep and cellular senescence

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ABSTRACT

The identification of biological markers that allow the early diagnosis, or even the prevention of age-related diseases, is an important goal that is being actively pursued in the research community. Sleep is one of the physiological processes that is most affected by aging, and there is a strong relationship between age-related sleep alterations and diseases. Changes in cellular senescence and the linked changes in telomere length might be potential markers of age-related sleep changes. In this review, we present some of the most recent evidence showing that telomere length has been associated with sleep loss and sleep disturbances in cross-sectional and case–control studies. We also present insights into the cellular senescence mechanisms relating to changes in telomere length, and we suggest that this field lacks basic and clinical research studies, especially long-term longitudinal studies, which may bring opportunities to sleep researchers to investigate this relationship in more depth.

1. Introduction

Population aging has led to an increase in the elderly population worldwide. Life expectancy is increasing by 1.6–2.3 years every decade [1,2], and although the fact that people are living for longer is to be welcomed, it has also increased the prevalence of age-related conditions and diseases. This is particularly important for the management of resources, as this part of the population usually requires a significant amount, especially with regard to health care and accessibility. The identification of factors that allow the early diagnosis and even prevention of age-related diseases could lead to older people having longer, healthier lives and save a considerable amount of health resources. It is for these reasons that this search is being so actively pursued in the research community. So far, a number of molecules and biological parameters, such as oxidative stress markers, protein modifications, hormonal deregulation, and inflammation, have been identified as possible markers that could be important in relation to age-related illness (for review, see Ref. [3]). However, markers of cellular senescence, such as telomere length (TL), are among the most studied parameters, mainly because they are thought to be regulated by many of the processes associated with aging in an organism [4].

Sleep is one of the physiological processes that is most affected by aging. Significant alterations in sleep patterns and the quantity and quality of sleep are found as people get older. The elderly population has been found to have a higher prevalence of sleep disturbances such as insomnia [5], obstructive sleep apnea syndrome (OSAS) [6], restless legs syndrome [7], rapid eye movement (REM) sleep behavior disorder [8], and overall sleep complaints [9]. These sleep alterations have been found by longitudinal studies to be associated with mortality and other age-related conditions and diseases [10,11]. As there is a coexistence of age-related sleep alterations, a higher prevalence of sleep disturbances and age-related diseases as well as significant variations in cellular senescence markers, we could suggest TL as a potential marker of age-related sleep changes.

It should be noted that only a few studies connecting sleep and TL have been published so far. Here, we present some of the most recent evidence showing that TL, especially mean leukocyte TL, has been associated with sleep loss and sleep disturbances in cross-sectional and case–control studies. We have conducted an integrative review aiming to examine studies that focused on TL and its relationship with sleep loss, sleep disturbances, and sleep-related traits. Through this literature search, we present insights into the cellular senescence mechanisms related to TL and we suggest that this field lacks basic and clinical research studies that would allow sleep researchers to investigate this relationship more thoroughly.

2. The molecular biology of telomeres

Telomeres are repeated and consecutive TTAGGG sequences at the end of each chromosome [12]. These functional elements of the genome are believed to protect the terminal region of chromosomes from degradation and erosion, and to be sensors activating cell senescence and/or apoptosis pathways, acting as an important

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tumor suppression mechanism [13]. During cellular division, there is an incomplete replication of these regions leading to a shortening of the telomeres after each cycle.

More specifically during DNA replication, the lagging strand synthesis results in short primer fragments. However, when replication reaches the end of the linear chromosome, there is no DNA template to synthesize the RNA primer necessary to initiate the last fragment. As a consequence, in every primer removal, a DNA segment is lost, promoting progressive telomere shortening. This process is known as the "end-replication problem," [14] and, as a result, the shortened telomere will cause destabilization of the chromosome. This state is very similar to DNA break, an unstable cellular state that can lead to senescence or apoptosis [12].

However, in tissues that require potential proliferative cells, such as in embryonic cells and stem cells, TL has to be maintained in order to keep chromosomal stability by protecting the ends from degradation. For this reason, an enzyme that elongates telomeric DNA, named telomerase, is present. This enzyme is a RNA protein complex that has reverse transcriptase activity. It contains two major components, the telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC), which serves as the RNA template for the synthesis and elongation of telomeres. Therefore, telomerase is an enzyme that stabilizes the length of the telomere in some specific cells by adding telomeric repeats, allowing chromosome stability [15]. Insufficient activity of telomerase results in telomere shortening after consecutive cycles of cellular division; consequently, this can cause the cell to enter a senescent state, which may be followed by apoptosis.

Short telomeres are commonly found in several pathological conditions as an indicator of disease onset and related outcomes. A number of recent studies have examined the association between telomere shortening and age-related diseases including cancer [16,17], cardiovascular disease [18], metabolic disease [19], chronic obstructive pulmonary disease [20], as well as adverse life conditions such as stress and unhealthy behaviors [21], and longevity [17]. However, topics related to sleep and sleep disorders have only recently gained attention. Sleep and circadian rhythms are conditions deeply affected by aging, and experimental evidence shows that sleep loss (sleep deprivation, sleep restrictions, and sleep fragmentation) is associated with an increase in oxidative damage [22,23], changes in transcriptional responses to cellular immunity, inflammatory responses, homeostatic imbalance [24], cellular stress and unfolded protein response [25], as well as with a number of important physiological process [26]. All these alterations are somewhat linked to the molecular mechanisms of aging, which lead us to hypothesize that telomere shortening might be a potential marker that connects the consequences of sleep loss to cellular senescence and, therefore, to aging.

3. Telomere as a biomarker of aging

Aging can be defined as a process that progressively transforms fit adults into less fit individuals, with an increasing probability of injury and illness and ultimately death [27]. Researchers therefore believe that it is extremely important to identify biomarkers of aging that not only reflect biological aging but also might identify the risk of age-related conditions and diseases [28].

In somatic cells, at each division, the TL gradually decreases due to the inability of the cell to completely replicate the ends of each chromosome [29]. Therefore, TL is an indicator of how many times a human cell has undergone cell division. By noticing that telomeres shorten with each division, TL could indicate a potential marker of the relationship between chronological age and biological aging. For that reason, the authors have suggested that TL could be a potential biomarker of the aging process [27]. The main biological pathways that might explain the link between TL and aging are the cellular senescence and the oxidative stress pathways [30]. However, it is possible that the shortening of telomeres systemically upregulates secretion of inflammatory factors that promote aging [27]. On the other hand, a recent study proposes that TL is in fact a marker of prospective mortality not only in middle age (30–80 years) but also at highly advanced age (≥90 years), regardless of immune-related markers [31]. Therefore, although the link between TL and aging is well known, a comprehensive understanding of the mechanisms remains to be elucidated.

4. Sleep and aging

In the broadest sense, sleep is a physiological process essential for the maintenance of life. Sleep can be characterized by a number of behavioral events such as specific posture and diminished response to stimuli that can be easily reversed. In addition, electrophysiological aspects can also be used to describe sleep, including brain oscillation patterns as well as synchronized and desynchronized electrical activity [32]. This state has a cyclic pattern, known as the sleep–wake cycle, with sleep alternating with wakefulness. Its importance in the maintenance of homeostasis is clearly shown in cases of sleep deprivation, and the consequent need for compensatory sleep [26].

Differences in the daily sleep–wake cycle are commonly observed in the elderly. Sleep quantity, quality, and the proportion of different sleep stages undergo specific changes with age, which include sleep fragmentation, earlier awakening, and reduced slow-wave sleep, when compared to young adults [33]. As pointed out in a review article by Roepke and Ancoli-Israel (2010), the most common subjective complaints of older adults regarding sleep problems are difficulty initiating and maintaining sleep, awakenings during the night, and decreased total sleep time [34].

The mechanisms that explain sleep alterations in the elderly are still not completely understood [35]. However, it has been established that sleep deprivation induces several behavioral, neurochemical, cellular, molecular, and metabolic changes [24]. Thus, one could propose that age-related changes in sleep quality and quantity might influence or be influenced by molecular components that could be detected as biomarkers of aging, such as TL. A number of studies evaluating this association between sleep and TL have been published, and in this article we present some of the most recent evidence describing this association between sleep loss and sleep disturbances and cellular senescence, measured by TL. As the selection criteria for inclusion in this review, we used the keywords "telomere" and "sleep" in the electronic database PubMed/Medline, and we searched for articles published or accepted for publication in English until November 2014. We also identified other potential published articles by cross-checking cited references. Table 1 summarizes the methodological aspects of the reviewed articles and Table 2 shows the sleep traits examined by each study, the main results, and the covariates used in multivariate analyses.

5. TL as a marker of sleep duration, quality, and disorders

5.1. Sleep duration, sleep quality, and TL

In the Nurses' Health Study, an investigation consisting of only female participants, Liang et al. observed a significant association between sleep duration and leukocyte TL in women under the age of 50 [45]. In this study, two major groups were compared: women with a sleep duration of ≤6 h and those who had ≥9 h of sleep per night. The results showed that women who slept ≤6 h had an equivalent to a 9-year telomere attrition, even after adjustment for age, body mass index (BMI), and smoking compared to the other group. However, this association was not significant in women aged

Table 1
Methodological considerations of the reviewed articles on the association between telomere length and sleep and sleep disturbances.

Reference	Type of Study	Domain	Sample characterisitcs	Method for TL measurement
Barceló et al. (2010) [36]	Case–control	OSAS and SDB	256 cases (51 ± 1 years, 17.2% female), 148 controls (47 ± 1 years, 27.2% female)	qPCR/peripheral leukocytes
Kim et al. (2010) [37]	Case–control		26 moderate-to-severe OSA (7.19 ± 1.83 years, 46.2% female), 85 mild OSA (7.79 ± 1.57, 36.5% female), 102 controls (7.71 ± 1.29 years, 45.1% female)	qPCR/peripheral leukocytes
Savolainen et al. (2014) [38]	Cohort		1948 participants (61.5 ± 2.9 years, 53.8%)	qPCR/peripheral leukocytes
Salihu et al. (2014) [39]	Cohort		67 participants (median age 25 years; 100% female)	qPCR/peripheral leukocytes
Garland et al. (2014) [40]	Case–control	Insomnia	70 cases (59.87 ± 9.57 years, 100% female), 70 controls (59 + 83 ± 9.40 years, 100% female), all breast cancer patients	Mean terminal restriction fragment/peripheral blood mononuclear cells
Prather et al. (2011) [41]	Cohort	Sleep quality and duration	245 participants (57.5 ± 4.4 years, 100% female)	qPCR/peripheral leukocytes
Jackowska et al. (2012) [42]	Cohort		434 participants (63.3 ± 5.6 years, 52.5% female)	qPCR/peripheral blood mononuclear cells
Lee et al. (2014) [43]	Cohort		283 participants (44.9 ± 8.4, 74% female), all HIV patients	qPCR/peripheral leukocytes
Cribbet et al. (2014) [44]	Cohort		154 participants (60.1 ± 6.76, 42.2% female)	qPCR/peripheral blood mononuclear cells
Liang et al. (2011) [45]	Cohort	Work schedule	4177 participants (44–69 years, 100% female)	qPCR/peripheral leukocytes
Parks et al. (2011) [46]	Cohort		647 participants (median age 53 years, 100% female)	qPCR/peripheral leukocytes

TL: telomere length; qPCR: quantitative polymerase chain reaction; OSAS: obstructive sleep apnea syndrome; SDB: sleep-disordered breathing.

Table 2
Summary of reviewed articles about the relationship between telomere length and sleep and sleep disorders.

Reference	Domain	Sleep traits	Main results	Covariates
Barceló et al. (2010) [36]	OSAS and SDB	OSAS	Shorter TL in patients with OSAS	Age, BMI, TC, TG, glucose, uric acid, smoking, hypertension
Kim et al. (2010) [37]		Pediatric OSAS	Longer TL in children with OSAS, positive correlation between TL and AHI	Age, sex, BMI, race
Savolainen et al. (2014) [38]		OSAS	Shorter TL in patients with OSAS	Age, sex, DNA concentration
Salihu et al. (2014) [39]		SDB in pregnancy	Shorter TL in fetuses born to mothers at high risk for SDB	Maternal age, gestational age, number of previous pregnancies, maternal BMI, birth weight, head circumference at birth, marital status, race/ethnicity, type of insurance, smoking status
Garland et al. (2014) [40]	Insomnia	Insomnia symptoms	Shorter TL in breast cancer survivors with severe insomnia symptoms, but not significant	Age and BMI
Prather et al. (2011) [41]	Sleep quality and duration	Sleep quality	Shorter TL in midlife women with poor sleep quality	Age, BMI, race, income
Jackowska et al. (2012) [42]		Sleep duration	Shorter TL in men reporting short sleep duration	Age, educational attainment, employment status, BMI, smoking, hostility, depressive symptoms
Lee et al. (2014) [43]		Sleep quality	Longer sleep duration preserved TL in adults with human immunodeficiency virus	age, sex, race, education, body mass index, metabolic hormones, depression, anxiety, sleep quality
Cribbet et al. (2014) [44]		Subjective sleep quality and sleep duration	Longer TL in older adults with adequate sleep duration	Age, sex, BMI, alcohol, smoking, exercise, HRT, use of medication for hypertension, cholesterol and diabetes
Liang et al. (2011) [45]	Work schedule	Rotating night shifts and sleep duration	Shorter TL in women <50 years old sleeping ≤6 h	Age, BMI, smoking
Parks et al. (2011) [46]		Work schedule	Shorter TL in full-time workers	Age, race, smoking, stress, BMI, sleep, physical activity, health status, CVD, diabetes, number of years worked, other demographic factors

OSAS: obstructive sleep apnea syndrome; AHI: apnea–hypopnea index; SDB: sleep-disordered breathing; TL: telomere length; BMI: body mass index; TC: total cholesterol; TG: triglycerides; CVD: cardiovascular disease; HRT: hormone replacement therapy.

over 50 [45]. Similar to what has been previously described, in older men (median age ~63 years), Jackowska et al. found significantly shorter telomeres among those who have shorter sleep duration when compared with those sleeping >7 h per night [42]. Although both findings suggests a relationship between TL and sleep duration in the same direction (shorter TL and shorter sleep duration), such an association might be dependent on age differently for men and women. On the other hand, Prather et al. found no association between sleep duration and sleep-onset latency with leukocyte TL in a sample of healthy women. However, the authors observed that this association might be relevant in patients who had chronic poor sleep quality [41].

More recently, Lee et al. studied a sample of men and women with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) to describe the relationship between TL and sleep duration and quality, measured objectively by actigraphy and subjectively by the Pittsburgh Sleep Quality Index (PSQI). In this report, longer sleep duration was a significant factor preserving TL. However, no relation was observed between the quality of sleep and telomere preservation after controlling for potential confounders [43]. A similar noteworthy study investigated whether subjective sleep quality and sleep duration were associated with TL in 154 healthy participants (age range 44–77 years), examined using the PSQI. It was reported that age was more related to TL in poor sleepers and that those with good sleep quality showed attenuation of the relationship between age and TL. Furthermore, adequate subjective sleep duration, defined as >7 h, was positively associated with TL in older adults (>60 years). However, no relationship was observed in middle-aged adults [44].

5.2. Insomnia symptoms and TL

A recent study conducted by Garland et al. evaluating for the first time the relationship between TL and insomnia, found that TL was positively skewed and shorter in breast cancer survivors with more severe insomnia symptoms when compared to age- and BMI-matched women without such symptoms; however, the difference was not significant [40]. Due to some limitations related to the study design and sample size acknowledged by the authors, this association deserves careful interpretation. Nevertheless, this report was useful for guiding new and more robust studies addressing the relationship between TL and insomnia.

5.3. Sleep-disordered breathing and TL

Telomeres shorten with cell division and from other processes such as high levels of oxidative stress and inflammation, conditions commonly observed with chronological aging [30]. Barceló et al. hypothesized that TL would be shortened in patients with OSAS as high levels of inflammation and oxidative stress also occur in this condition [36]. In this study, the TL of 256 patients with OSAS and 148 controls was compared to establish whether TL was related to the severity of OSAS and the presence of metabolic disorders and cardiovascular risk. The results showed significantly shorter telomeres in patients with OSAS than in controls, even after adjustments for potential confounders. However, the severity of OSAS did not show a relationship with TL [36]. Savolainen et al. investigated whether a history of OSAS or primary snoring had an association with leukocyte TL in later adulthood by evaluating 1948 participants from the Helsinki Birth Cohort Study (mean age of 61.5 years) [38]. It was found that participants with sleep apnea had shorter leukocyte TL than controls, whereas individuals with a history of primary snoring did not differ in leukocyte TL from controls, concluding that shorter leukocyte TL may be a specific risk factor for OSAS [38].

In a similar study, Kim et al. observed the relationship between TL and OSAS in children [37]. The study consisted of 213 children (mean age 7.7 ± 1.4 years) who were examined by objective sleep methods and underwent blood collection to measure TL. In contrast to what was expected, children with OSAS showed an increased TL [37]. To explain these findings, the authors propose the hypothesis that leukocyte TL is positively associated with left ventricular mass and wall thickness as found by Vasan et al. [47]. Thus, a longer leukocyte TL would be expected, taking into consideration evidence showing that OSAS induces increased activity and reactivity of the sympathetic nervous system, and that blood pressure elevations are OSAS severity dependent, especially in children with OSAS. Another hypothesis is that OSAS may induce early mobilization of mesenchymal stem cells, and that those cells stimulated by inflammatory mediators or hypoxia have a protective action, especially in children. Furthermore, proliferated lymphocytes can express telomerase. Considering that patients with OSAS exhibit lymphocytes in a highly activated state, telomerase could play an important role in the maintenance of TL in children with OSAS.

More recently, Salihu et al. investigated the impact of symptoms of maternal sleep-disordered breathing, on fetal TL measured from cord blood leukocytes [39]. The sleep outcomes were measured in pregnant women using the Berlin Questionnaire to characterize sleep apnea risk and the Epworth Sleepiness Scale to measure daytime sleepiness. The authors observed that fetuses born to mothers at higher risk of sleep apnea or habitual snorers had shorter fetal TL than their counterparts born to those at lower risk. These findings were able to support the hypothesis that maternal symptoms of SDB during pregnancy may be associated with shorter fetal TL [39].

5.4. Working schedule and TL

Particular working conditions, such as long hours, rotating shift work and night work, may be potential stressors, which lead to inadequate sleep and can be a risk factor for chronic disease. Parks et al. examined the association of employment and work schedule with TL [46]. Questionnaire data from 608 women aged 35–74 years in the Sister Study as well as TL measurements were investigated. The results showed that, compared with nonemployed women, those in regular long-term full-time work of approximately 40 h per week had a shorter TL. Contrary to expectations, no differences in TL were found for women who had a lifetime history of rotating shift work [46].

6. Concluding remarks and future perspectives

The aforementioned evidence indicates that short TL is a potential marker of sleep loss and sleep disturbances. However, it is important to point out that this relationship was not consistent in every reviewed study. The evaluated studies were highly heterogeneous in design (case–control vs. cross-sectional cohort studies), demographic characteristics (only men, only women, or both genders; only older adults vs. all age ranges), or health status (eg, HIV/AIDS and breast cancer survivors). In addition, there were only a few studies evaluating similar sleep outcomes (OSAS or sleep duration) and, in some cases, only one study per outcome (eg, insomnia symptoms and shift work). As another complicating factor, covariates used in multivariate models also differed across studies. Furthermore, even when the same outcome was measured, different approaches (ie, different questionnaires) were assessed. We also found a lack of studies with gold-standard objective sleep measurements, such as polysomnography and actigraphy, which would deeply improve the understanding of the relationship between TL and sleep.

Given the increased use of telomeres as a potential biomarker of certain conditions, multiple methods have been developed in order to access TL, which may affect the reproducibility of findings [48]. The traditional gold-standard method of measuring TL is the terminal restriction fragment method, where genomic DNA is digested using restriction enzymes followed by Southern blotting hybridization techniques. This method presents some limitations, as it requires large amounts of DNA, is labor intensive, and is unable to detect short telomeres that are present on a small number of chromosomes. Quantitative polymerase chain reaction (qPCR) methods try to overcome these problems. Although it is advantageous in some aspects as it is low cost, requires smaller amounts of DNA, and suitable for large epidemiological studies, qPCR results are highly variable, causing differential amplification efficiency or measurement variation between aliquots. Such differences in methodological aspects also have to be considered when assessing the association between sleep and TL [48], although most of the studies reviewed used qPCR as the TL measurement methods.

Taken together, these factors did now allow for a comprehensive systematic review of this topic. Nevertheless, the published literature suggests that there is a relationship between sleep duration, sleep quality or sleep disturbance, and shorter TL. Indeed, longitudinal studies evaluating the effect of baseline sleep disturbance on the rate of telomere shortening after specified years of follow-up are still warranted. In addition, experimentally controlled studies in animal models and in humans are still needed to verify the effect of chronic and acute sleep deprivation on TL. This emergent topic of research on the mechanisms that link sleep, sleep disorders, cellular senescence, and aging is expected to grow in the coming years, and be accompanied by the development of more accurate methods to measure TL.

Conflict of interest

The authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.02.519.

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