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Chapter 8

Telomere Length and Its Relation to Human Health

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Abstract

Telomeres are complex nucleotide sequences that cap the end of chromosomes from degradation, unwanted recombination-fusion, inappropriate activation of DNA damage response and play a critical role in cell division and chromosome stability. There is growing evidence that telomere stability can be affected by occupational and environmental exposure, as some of these factors have been correlated with increase in inflammation, oxidative stress, DNA damage, chromosome aberration, and epigenetic alterations. Both extremely short and long telomeres have been associated with neurodegenerative, cardiovascular diseases (CVD) and cancer risk. Occupational and environmental exposure to several synthetic and natural chemicals has been found to be associated with changes in telomere length, although the molecular mechanism is not fully understood. Telomeric DNA is relatively less capable of repair, resulting in accelerated shortening during the cell cycle and replicative senescence. It is recognized that diet plays an important role in telomere maintenance. Prevention of exposure to environmental and occupational hazards as well as psychological stressors can reduce the risk of telomere instability. This review provides a broad evaluation of the associated mechanism between human health and environmental and occupational exposure with telomere length, including recent findings and future perspectives.

Keywords: telomere length, biomarkers, human health, occupational exposure, environmental exposure

1. Introduction

The telomere structure is essential for maintaining chromosomal stability. It prevents the chromosome ends from being identified as damaged DNA and, therefore, nucleolytic degradation, chromosome end-to-end fusion, and break-fusion-bridge cycle (reviewed by Kahl et al. [1]). Human telomeres are nucleoprotein structures that consist of a repeat TTAGGG se-

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quence, located at the end of chromosomes. Along with its complementary sequence, AATCCC, telomeres form a t-loop structure at the terminal ends of chromosomes [2]. A single-strand 3′ G-rich overhang, several DNA-binding proteins and specific telomerase-binding proteins, named "shelterin" complex, also comprise telomeres. The shelterin complex is formed by six proteins: TRF1, TRF2, and POT1 that directly recognize TTAGGG repeats; and TIN2, TPP1, and Rap1 that interlink the first three proteins. Even though telomeres and double-strand breaks (DSBs) are processed in the same manner, the DNA repair system clearly distinguishes the telomere region from sites of damaged DNA because of shelterin [3]. Telomere length (TL) is balanced by telomerase, a riboenzyme that synthesizes telomeric DNA *de novo* using its own RNA component as template. Even in complex organisms, telomerase-dependent telomere elongation occurs, although it is difficult to access this *in vivo*, as this happens in leukocytes, which means moving cells [4]. Telomeres shorten in each cell division due to incomplete replication of the lagging strand, the so-called "end replication problem". In most normal somatic cells of human adults, telomere length decreases with age, suggesting that telomere attrition contributes to the organismal senescence by reducing cell proliferation. So far, it is not yet understood how telomere length is set in an organism [5], but it is known that they are dynamic structures, especially when examined during short periods [4]. Because of their close relationship to lifespan and cellular senescence, telomeres have been widely studied with regard to human health and the development of diseases. One of the topics most often associated with telomere length dysfunction is, for example, how human cancers are invariably related to activation of some mechanisms to maintain telomere length [6]. Telomerase is commonly expressed in human cancer cells, mainly in 85–90% of cancers. Recent studies suggest that telomerase is implicated in tumor progression in several manners, most of them unexpected and new to science [7]. Yet, some reports have shown the reactivation of telomerase, resulting in cell immortalization, without chromosome aberrations, tumorigenic parameters or oncogenic activation (reviewed by Cech [6]). Although normal cells have some active telomerase, telomere dynamics is still unclear with regard to several pathologies. Further, whether telomeres shorten or elongate in different human everyday life situations, and by which mechanism this occurs, are still under investigation. What is known is that telomere length is strongly influenced by many other factors such as genetics, diseases, occupational and environmental exposures, and diet (reviewed by Kahl et al. [1]). Optimum telomere function and length are important for cell proliferation and apoptosis. Critically short telomeres initiate senescence resulting either in apoptosis or cell cycle arrest, through proteins such as BUB1, CENP-E, CENP-A, Chk2, among others [8]. Therefore, it is relevant to identify yielding factors that are responsible for accelerated telomere shortening.

2. Earlier telomere shortening: why?

Due to its high content of guanine, telomeric DNA is highly susceptible to accumulation of oxidative stress through induction of a wide range of DNA lesions, including base modifications, such as 8-oxo-guanine and O^6-methylguanine. In the first case, guanine oxidation converts it into 8-oxo-7,8-dihydroguanine (8-oxo-G), a tautomeric form of guanine nucleotide. Thereby, 8-oxo-G erroneously pairs with adenine instead of cytosine, causing a mutation

through transversion G-C→T-A [9]. This damage is not easily repaired by DNA repair mechanism and may lead to reduction of TRF1 and TRF2 linking, generating telomeric dysfunction [10, 11]. Moreover, accumulation of single-strand breaks (SSBs), as a result of the hydroxyl radical attacks on the DNA strand throughout telomere and subtelomeric regions, leads to accelerated telomere shortening or to complete loss of telomeres [12]. Telomere integrity appears to be a critical element in chromosomal stability and telomere shortening, which is induced by an increase in oxidative stress and can also be influenced by DNA repair mechanisms and polymorphisms, epigenetic status, and lifestyle habits.

Reactive oxygen species (ROS) are generated in aerobic organisms by cellular metabolism and by exogenous sources such as ionizing radiations, UV radiation, redox cycling drugs, carcinogenic compounds, and environmental toxins. DNA lesions resulting from this type of damage are mutagenic and cytotoxic and, if not repaired, can cause genetic instability, cell proliferation problems, oxidative enzyme imbalance, cell death, apoptosis, and angiogenesis. Consequences of DNA damages depend on their severity and cell type. DNA effects may lead to the development of diseases, including carcinogenesis [13].

Living organisms evolved to possess DNA repair mechanisms to repair DNA damage and thus to protect the genetic stability for survival [13, 14]. Telomeric DNA is less capable of repair, resulting in accelerated telomere attrition during the cell cycle and replicative senescence [15]. Telomeres seem to be very sensitive for both single-strand breaks (SSBs) and double-strand breaks (DSBs). As a mechanism to prevent end-to-end fusions, telomeric repeats have been shown to inhibit non-homologous end joining (NHEJ) repair mechanism. NHEJ is a major pathway to repair DSBs and has been reported to be inhibited *in vitro* by TRF2, which could be a main contributor to a persistent DNA damage response (reviewed by Hewitt et al. [15]). Furthermore, ROS produce SSBs and in contrast to the majority of genomic DNA, telomeric DNA may be deficient in repairing this type of damage [16, 17]. Single-strand breaks caused by hydrogen peroxide and an alkylating agent in human fibroblasts took at least 19 days to be repaired in telomeres, but it was repaired in 24 h in the bulk of genome and minisatellite regions (reviewed by Coluzzi et al. [17]). Failure to repair DNA damage may lead to detrimental biological consequences for organisms.

Mutations and polymorphisms also occur in DNA repair genes adversely affecting DNA repair systems. An example of DNA damage influenced by repair polymorphisms was recently shown by Borghini et al. [18], in which authors demonstrated that individuals exposed to higher levels of arsenic combined with the hOGG1 allele were associated with significantly lower TL in leukocytes [18]. As OGG1 is a protein part of the base excision repair mechanism and catalyzes the excision of oxidized purines, mainly 8-oxo-dG [13], it is reasonable that it produce some effect on telomeres. Other authors showed that individuals with congenital heart disease had reduced TL when compared to controls, related to XRCC1 194Trp allele [19]. In addition to these polymorphisms, XRCC1 399Gln allele [20] and XRCC4-null cells [21] were already associated with telomere dynamics by different repair routes.

The instable condition of telomeres can lead to activation of molecular cascades evolved in response to cellular stress, such as p53 and p16INK4a pathways, resulting in some cases in apoptosis or cellular senescence [21]. Shorter telomeres in peripheral blood lymphocytes have

been shown to predict cancer risk [22, 23]. It is also relevant that p16 methylation is found in several types of cancer such as melanoma, oropharynx, and esophagus [24-26]. In addition, increasing evidence indicates that epigenetic modifications are important regulators of mammalian telomeres [27]. Epigenetic regulators, such as histone methyltransferases and DNA methyltransferases, correlate with loss of telomere-length control, thus telomere shortening affects the epigenetic status of telomeres and subtelomeres. It has been shown that such oxidative lesions interfere with the DNA's ability to function as a substrate for DNA methyltransferases, resulting in global hypomethylation [28]. Thus, genomic DNA, including the subtelomeric region, may become hypomethylated. Methylation in subtelomeric regions of the chromosomes is associated with telomere length and hence could be an important region for epigenetic regulation of the biology of telomere length maintenance [29]. A number of studies also indicate the posttranslational ubiquitination in TL proteins, albeit this modification effect on telomeres has not been directly demonstrated. The ubiquitinated telomere unbound form of TRF1 induces telomere elongation [30], while the *MKRN1* gene that encodes a portion of ubiquitin promotes the degradation of hTERT [31]. A progressive loss of DNA methylation in repetitive elements was recently shown [32], providing evidence that methylation can decrease over time as individuals age. Therefore, the association of aging with telomere epigenetic regulation is an important factor. Links between epigenetic status and telomere-length regulation provide important new avenues for understanding processes such as cancer development, which are characterized by telomere-length defects.

Several studies suggest that telomere dynamics can be challenged according to lifestyle factors. Recent studies showed that smokers had shortened telomere length when compared to never smokers [33, 34]. A cohort study found shorter telomeres for active smokers in a dose-dependent manner [34]. Other publications reported that smokers presented shorter telomere length, and irrespective of the number of cigarettes smoked per year, the lifetime accumulating exposure to smoking was more important to this outcome [35]. The main mechanisms related to reduction of telomere length by cigarette smoking are increased oxidative stress levels and inflammation [36]. Exercise and a balanced diet can also influence telomere maintenance, in a positive manner, attempting to support a healthier life.

3. Telomere length and human health

Aging starts even before birth, that is why is necessary not only to study telomere length at birth, as a prerequisite to understand its dynamics throughout life, but also to investigate several exposures, and genetic and epigenetic factors that may contribute to accelerate this process [37]. Aging is defined as the time-dependent event that results in a progressive functional decline that affects most living organisms. This process is the subject of several scientific studies, including mutagenesis, as the accumulation of DNA damage throughout life is a common denominator of aging [38].

Much attention has been given to the relationship of telomeres with human health in the last few decades. The natural telomere shortening can be accelerated by unhealthy lifestyle habits

and a poor diet [39, 40] and also due to occupational and environmental exposures [1, 41]. Exogenous physical, biological, and chemical stressors, such as environmental pollutants, medicines, chemotherapeutics, continuously challenge DNA stability. In addition, endogenous agents such as DNA replication errors, ROS, and spontaneous hydrolytic reactions can have the same effect on DNA. Different lesions arise from this damage and may include chromosomal aberrations, translocations, point mutations, gene disruption, and telomere shortening. There are various causes of ROS overexpression and exacerbated oxidative stress increases telomere shortening [9–12, 15–17]. One example is hyperglycemia, which increases ROS from the mitochondrial electron transport chain and increased glucose auto-oxidation, production of advanced glycation end-products, and activation of polyol pathway and kinase K pathway [42].

Critical telomere shortening induces cellular senescence or even the definitive inability of cells to divide. Telomere attrition in stem cells results in the depletion of their tissue and self-renewal ability. In both cases, telomere shortening can lead to different age-related pathologies [43]. The average difference of telomere length between proliferative and minimally proliferative tissues was constant in a study performed with patients whose ages ranged from 19 to 77 years old suggesting that the first 20 years are a crucial period in establishing some differences [44]. The telomere shortening in somatic cells results in changes on telomere structure that may induce replicate senescence depending on p53 and p16/retinoblastoma proteins [45].

A wide range of studies have shown that dysfunctional telomere length in biological human samples is usually related to increased risk of degenerative diseases of aging, diabetes, cardiovascular diseases (CVD), dementia, cognitive impairments, and cancer [46–51]. Ultimately, cancer and aging can be considered two different expressions of the same process: the accumulation of DNA damage. Specific location of shelterin complex is what lastly enables chromosome end protection. It is also known that within shelterin, certain components are responsible for preventing specific aspects of DNA damage repair mechanism [5]. The great challenge is to understand what signal triggers checkpoint activation at dysfunctional telomeres [5, 52].

Telomere length in pancreatic β-cells is reduced in individuals with type 2 diabetes mellitus (DM) [49] as a pathophysiology of diabetes shows an age-related aspect. The authors propose that shorter telomeres in type 2 DM could lead to an impaired ability for proliferation and insulin secretion, accelerating cell death. Obesity, which is also associated with shortened telomere length [53], is frequently associated with type 2 DM. In both cases, it is considered that excessive oxidative stress induces telomere damage, together with hyperglycemia in DM patients. In cancer biology, telomere dysfunction has been linked to tissue decrease on mitochondrial DNA copy number, while mitochondrial oxidative stress appears to be required to maintain cellular senescence [54]. A recent review suggests the hypothesis that heterogeneity of mitochondria uncoupling proteins may affect oxidative stress that imbalance telomere and cell cycle regulation, further diabetes risk and metabolic disease progression [55]. In diabetes mellitus, oxidative stress is higher in leukocytes, but also in pancreatic β-cells, which could result in shortening of β-cell telomeres, subsequently causing dysfunction of insulin secretion [49]. Results show that obesity can be associated with shortened telomeres [53], as

the excessive accumulation of adipose tissue and the associated metabolic imbalance increases oxidative stress and may deregulate inflammatory cytokines. Chronic heart failure and coronary disease are strongly associated with inflammatory processes, and as expected, have also been linked to telomere shortening [41].

Cardiovascular diseases (CVD) are the main reason for heart failure, the leading cause of mortality worldwide. Two different studies have shown that telomere biology plays a role in CVD [56, 57]. The first study found an association of risk factors for CVD and telomere length, mainly with interleukin-6, an inflammatory factor. Burnett-Hartman et al. [56] observed that two single nucleotide polymorphisms in *OBCF1* and *TERC* genes (both related to leukocyte telomere length) were similarly associated with CVD mortality in women. CVD is strongly linked to the inflammation process, which may lead to increased oxidative stress. In both cases, telomere attrition may be attributed to increased oxidative stress and inflammation [56, 57].

Telomeres are related to several other humans diseases in which some mutations of TERC are reported, such as dyskeratosis congenita, several hereditary, several hereditary syndromes of bone marrow failure, and idiopathic pulmonary fibrosis (reviewed by Armanios [58]). Although the presentation of these diseases is different, shortened telomeres are present in all patients with dyskeratosis congenita, in some with bone marrow failure syndromes, and in an unknown proportion of idiopathic pulmonary fibrosis patients [59]. Shortened telomeres were also observed in patients with aplastic anemia. Some studies suggest that baseline TL is associated with late events of hematologic relapse in aplastic anemia patients treated with immunosuppressant therapy [60]. Valdes et al. [61] showed that clinical osteoporosis is related to shorter telomeres in over 2000 women, in whom leukocyte telomere length was significantly correlated with bone mineral density. This result was corroborated by Tang et al. [62], who analyzed women and men regarding telomere length and bone marrow density, and a positive correlation was found for females. These studies even suggest that TL could be a new bone aging biomarker, but these conclusions should be carefully observed as other reports did not find the same correlations [63, 64]. Both short and long telomeres have been associated with neurodegenerative and cardiovascular diseases, cancer risk [46, 59], and some human polymorphisms [65]. Indeed, several loci were identified by linkage analysis of modulators supposedly linked to telomeres and through genome global association studies. *DDX11* [66], *SIRT1*, and *XRCC6* [67] genes, as chromosome 14 and loci 10q26.13 and 3p26.1 [68], seem to be involved in telomeric dynamics. Mostly, loci near the RNA component of telomerase (TERC) are more evident in studies that correlate genetic heritage and telomere length [59]. Some polymorphisms of *OBCF1* [56] and *MEN1* [65] genes, as the $^{-1327}$C/T hTERT polymorphism [69], were associated with critically shorter and longer telomeres. However, two studies showed a greater influence of environmental effect than the genetic one on telomere length (reviewed by Andrew et al. [68]).

Another study analyzed telomere length in white blood cells and buccal cells in patients with Alzheimer's disease (AD). The researchers observed reduced telomere length in both cell types for individuals with AD. More than that, telomeres with less than 115 kb per diploid genome in white blood cells showed an odds ratio of 10.8 for a diagnosis of AD, while telomeres shorter than 40 kb per diploid genome had an odds ratio of 4.6 for AD diagnosis [48]. In concordance

with this study, Hochstrasser et al. [70] also suggests that AD may contribute to telomere shortening. They found shorter telomeres on monocytes of AD patients compared to healthy subjects. In fact, a recent work found out that telomere length is significantly shorter in AD patients with alipoprotein E (ApoE) homozygote than in those with ApoE heterozygote and noncarriers. ApoE is a strong genetic risk factor for developing Alzheimer's, and seems to be associated with shorter TL when in homozygosis [71].

Telomere dynamic has been also correlated with psychological and psychosocial effects. Some authors observed telomere shortening associated with severe and/or chronic diseases in childhood, besides adverse events, such as anxiety disorders and mistreatment in childhood [39, 72]. Children aged 4-14 from over 80 neighborhoods in Louisiana, USA, were evaluated with regard to the influence of social stress on telomere length. Children living in highly disturbed neighborhoods showed shorter salivary telomere length when compared with less disturbed environments [73]. These data may indicate that childhood adversities have an impact on wellbeing throughout life. High levels of stress related to psychosocial facts and high levels of depressive symptoms were observed in caregivers of individuals with Alzheimer's, and shortened telomeres were associated with those stress factors (reviewed by Lin et al. [39]). A recent review of telomerase activity and its associations with psychological and mental factors observed a mixture of results, but some consistent findings reported decreased telomerase activity in individuals under chronic stress and increased telomerase activity in individuals with depressive disorders [74]. Oxidative stress has been suggested to play a role in the etiology of anxiety disorders and psychological distress, supporting the involvement of oxidative stress in the regulation of telomere length in psychological and psychosocial adverse effects.

Telomere shortening is a risk factor for several types of cancer [46]. A recent review investigated telomere length in several types of cancer in surrogate tissues and observed only longer telomeres in melanoma skin and hepatocellular carcinoma. No effect on telomere length was seen for colorectal, prostate, and endometrial cancers and squamous-cell carcinoma. For breast cancer, although longer and shorter telomeres were found in nine different studies, no effect on telomere length was prevalent among the findings. Two kinds of cancer were linked to both longer and shorter telomeres: lung and kidney [46]. Up to now, reduced telomere length has been prevalently found in patients with these cancers. As regards lung cancer, a study included 122 Chinese with clinical symptoms [22]. In general, telomere length was not associated with lung cancer. Nevertheless, three SNPs in telomere length maintenance genes were linked to risk of lung cancer. The *G* variant at *POT1* rs10244817 and the *A* variant of *TERT* rs2075786 were associated with decreased risk of developing lung cancer; while the *G* variant of *TERT* rs251796 was associated with increased risk. The *POT1* SNP interacted significantly with telomere length and lung cancer risk, showing the close relation between shelterin proteins and cancer [22]. In the review, for most types of cancers evaluated, only shorter telomeres were found: bladder, head/neck, ovarian, gastric, skin (basal cell carcinoma), osteosarcoma, and esophagus [46]. It is interesting to observe that for different types of skin cancer, the cancer etiology has a different telomere dynamic, which only shows that telomere dynamic is heterogeneous according to tissues and even with their differentiation process.

In another meta-analysis with regard to telomere length and cancer risk population studies, authors reviewed more than 50 publications [50]. Their results revealed heterogeneous association between different cancer types. In opposition to other reviews, they did not observe a significant association of short telomeres with the overall risk of cancer. Still, shorter telomeres were found associated with increased risk of gastrointestinal and head and neck cancers, similar to prior review [46]. Both are mainly cases of epithelial malignancies, which mostly appear to develop from morphologically defined precursor lesions termed intraepithelial neoplasia. The meta-analyses also revealed a significant dose-response association of gastrointestinal tumor and head and neck cancer with telomere length. The authors also highlight that telomere length is critically shortened in more than 90% of intraepithelial neoplasias. It is accepted that telomeres have different roles in different types of cancer, but again, this review indicates that short telomeres may be risk factors for tumors, especially of the digestive system [50]. A shorter TL in individuals with cancer when compared to healthy controls is biologically plausible. The accumulated mutations from critically shortened telomeres, genetic lesions, and inactivated tumor suppressor checkpoints may ultimately result in cancer [6, 7, 47, 52].

For many years, oncogenesis has been linked to telomerase activity in somatic cells [6, 7]. In fact, overexpression of telomerase is enough to neutralize the natural telomere shortening and to indefinitely extend the replicative lifespan of cultured cells when genomic instability is lacking, turning them into cancerous cells. The active telomerase complex may be more necessary to cancerous cells than to normal somatic cells due to its chromosomal aneuploidy and rapid cell division cycle [47, 75]. Thus, it seems conflicting that shortened telomeres are linked to several types of cancer. However, the mechanism of the shortened telomere relationship with cancer is through genomic instability. In the oncogenesis process, the inactivation of senescence pathways by some viral oncogenes, mutations on key-genes or chemical substances allows cells to bypass replicative checkpoints. This enables the propagation of cells with damaged telomere leading to end-to-end fusions and genome instability, and then to age-associated diseases, like cancer [43].

4. Occupational and environmental exposures

Different approaches are used to evaluate effects and risks of exposure to chemical, physical, and biological agents during routine work or where an individual lives. Biomarker is a general term for analysis of the interaction of a biological system and an environmental agent. There are three classes of biomarkers: (a) of exposure, that involve exogenous substances or their metabolites, or a product of interaction between a xenobiotic agent and some target cells or molecules; (b) of effect, that are biochemical, physiological or behavioral parameters, or other changes within the body and, depending upon the extent, they can be recognized in association with a disease or as a potential risk for the development of a disease; and (c) of susceptibility, that refers to the inherent or acquired ability of an organism to respond to changes in exposure to xenobiotic specific substances [76–78].

There is growing evidence that telomeric stability may be affected by environmental and/or occupational exposure, as some of those factors have been related to inflammation and chronic diseases. Occupational exposures related to shorter telomeres include polycyclic aromatic hydrocarbons (PAHs), benzene and toluene, particulate matter and long-term exposure to lead (reviewed by Zhang et al. [41]). PAHs are known for generating DNA adducts and, therefore, genomic instability. A recent study has shown the relationship between telomere shortening and pesticide use in workers associated with the agricultural industry [79]. Lead, in turn, induces double-strand breaks in DNA, particularly in lagging strands on telomeres (for a review, see [41]). Working as a hairdresser has been associated with increasing risk of cancer, due to cancer-related DNA alterations. Telomere length was shortened in a group of Sweden hairdressers [80]. The authors suggest that, as hairdressers are exposed to strong oxidative agents, it is likely that oxidative stress is the main reason for telomere shortening in these workers [80].

A study from our group observed shortening telomeres in individuals occupationally chronically exposed to low doses of pesticides at tobacco farms [33], in addition to various kinds of DNA damages already found in those individuals [81–84], corroborated by several other studies [85, 86]. Pesticides are known for inducing oxidative stress [33, 82, 87, 88], and although not all action mechanism of these chemicals are clear, induction of oxidative stress and of ROS seems to be involved. Senescent cells present 30% more modified guanines within their DNA and fourfold more free 8-oxo-dG basis, contributing to telomeric loss through oxidative stress [89]. Recently, our group was able to show two different pathways involving the ubiquitin proteasome system (UPS) by which pesticides and nicotine influence telomere length. Using System Biology approach tools, we evaluated proteins involved in telomere maintenance and their relation to pesticides used in tobacco crops at Brazil, including the natural pesticide of tobacco leaves, nicotine. In this interaction network of proteins related to telomere length and tobacco pesticides, it is important to highlight the ubiquitination bioprocess of proteins involved in some clusters of interaction [90]. The UPS is a highly conserved cell pathway that plays an important role in the selective degradation of proteins that are essential for several cell functions [91]. Some works have shown the role of ubiquitination in maintaining telomeric length [30, 31].

Longer telomeres may also reflect a health problem. Persistent organic pollutant (POPs) was associated with telomere elongation, but the mechanism remains unknown. Increasing telomerase activity and, therefore, longer telomeres were also observed in occupational exposure to arsenic [41]. The Agricultural Health Study (AHS) analyzed farmers with regard to telomere length and both cumulative and recent use of several pesticides [92]. Shorter telomeres were found associated with the lifetime use of two pesticides, and one with recent use, while only alachlor was significantly associated with longer telomeres for both cumulative and recent use [92]. The Chernobyl nuclear power plant accident forced workers to clean up the region. Some studies revealed high occurrence of age-associated degenerative diseases, cardiovascular disorders, and cancer among them (reviewed by Reste et al. [93]). However, when telomere length was analyzed, longer telomeres were found for the workers undertaking excavation and deactivation, and in workers with cancer. The authors suggest that the

exposure to ionizing radiation led to longer telomeres through telomerase activation, which could potentiate carcinogenesis [93]. Even so, it is possible to highlight that most occupational exposures induce telomere shortening.

Environmental factors can also trigger epigenetic changes [94], which can also be related to telomere maintenance [67, 95]. Previous studies suggested that DNA methylation plays an important role in maintaining genomic stability, and is highly sensitive to environmental exposure [96, 97]. The impact of adverse exposure on telomere shortening starts at a very early developmental stage. Environmental exposure to lead in children appears to be associated with shorter telomeres [98], as prenatal exposure to toxic agents also seems to be a predictor of telomere imbalance. Neonatal umbilical cord blood showed a positive association between shortened fetal telomere length and smoking during pregnancy [99]. Even with the concept that high variation in telomere length between individuals is already present before birth and could increase due to environmental exposure, 128 Indian newborns from high-level natural background radiation areas showed no evidence of telomere length attrition [100]. On the other hand, placental tissues of over 200 twins were evaluated with regard to telomere length [101]. The aim was to verify if maternal residential traffic exposure was associated with telomere length. Maternal residential proximity to a major road was linked to shortened placental telomere length, while maternal residence closer to more wooded sites increased placental telomere length by 3.6%. As traffic exposure is an important source of free radicals that are known for accelerating aging, the air pollution-related adverse outcomes started early in life [101].

A group of Italian pregnant women living close to waste landfill sites was analyzed with regard to telomere length to investigate if pollution, as an environmental stressor, could affect their health. The authors observed that pollution from illegal waste sites was significantly associated with shorter telomere length, higher oxidative stress levels, and lower telomerase activity, which are known factors of cellular senescence and aging-related meiotic dysfunction in women [102]. Even low levels of cadmium shortened buccal cell telomere length in adolescents environmentally exposed to this metal [103]. Arsenic exposure to drinking water increased telomere length in individuals from West Bengal, India. This effect was telomerase-dependent but did not exhibit an overexpression of alternative lengthening of telomere-associated proteins TRF1 and TRF2 [104]. Some environmental toxic metals can produce epigenetic changes, such as DNA methylation, loss of expression of tumor suppressor gene *p16*, among others [105], eventually leading to telomere dynamics alterations.

5. What can be done to help maintain telomere length?

Diet is known to play an important role in telomere maintenance and personalized nutrition is a growing and promising field to prevent DNA damage [40]. A proper diet combined with physical exercises seems to prevent genomic instability, possibly providing a proper intake of antioxidants and reduction of inflammation levels [40, 53, 106, 107]. Several intervention studies have been performed to challenge the common sense that telomeres only shorten

during a lifetime. According to literature, dietary patterns and individual micronutrients can influence telomere length and function. A recent review reported that individuals undergoing the following lifestyle interventions presented increased telomerase activity: practice of physical exercise, diet micronutrient supplementation, yoga, and mindfulness meditation [74].

Folate is an important vitamin required for DNA synthesis, one-carbon metabolism and repair. When there is folate deficiency, the incorporation of uracil instead of thymine in DNA is increased [108]. Plasma homocysteine concentration, which is increased when folate and vitamin B12 are deficient, seems to be inversely associated with telomere length. On the other hand, homocysteine and folate are inversely correlated [109]. Low levels of folate were associated with shorter telomeres in an older male cohort, although this effect was not observed either in female subjects or younger adults [108]. Another study showed that the MTHFR C677T polymorphism of the folate metabolism gene, which may raise plasma homocysteine, was weakly associated with increased telomere length at below-median folate levels [110]. A recent study showed that folate deficiency leads to long but dysfunctional telomeres, associated with increased chromosome instability, possible due to DNA hypomethylation [107]. Some molecular mechanisms have been proposed on how folate deficiency induces telomere shortening, such as (a) abnormal epigenetic state of subtelomeric DNA; (b) ineffective binding of shelterin complex proteins to telomeric DNA due to decrease affinity to uracil; (c) the increased excision of uracil in the telomere structure that generates abasic sites and DNA breaks. Therefore, folate status modifies telomere length by affecting DNA integrity and the epigenetic regulation of telomere length through DNA methylation [111].

As discussed earlier in this chapter, DNA damage in adulthood may originate in early life [98, 101], as lifelong dietary patterns are established in childhood. Yet, most studies with regard to telomere length in children are conducted on the effects of environmental exposure and socioeconomic and psychological status [72, 73, 98, 99, 101, 103]. A recently published study analyzed whether nutritional factors are associated with telomere length in children [112]. Between 2009 and 2011, 437 children aged 3, 6, and 9, were sampled and telomere length and micronutrient levels were measured. After adjustment for several parameters, telomere length was inversely associated with plasma levels of zinc. Also, children with the homozygous mutant genotype of the *RFC* G80A (rs1051266) polymorphism presented the shortest telomere. The RFC (reduced folate carrier) gene encodes for an enzyme required for bioavailability and metabolism of folate and vitamin B12. The chosen polymorphism is known to reduce the activity of the enzyme; indeed, the *RFC G80AA* genotype was associated with a 26 kb/diploid genome telomere loss when compared to the *RFC 80GG* genotype. Although the association between zinc levels and telomere length is still not clearly understood, the authors suggest that the inverse relationship between the two parameters may be a result of an increase in telomere sequence deletions by labile zinc induction of oxidative stress [112, 113].

High levels of plasma vitamin D were associated with longer telomeres in women, with evidence of a dose-response relationship [114]. Vitamin D is known for reducing inflammation and cell proliferation. Because both increased inflammation and enhanced cell proliferation accelerate telomere attrition [8, 56, 57], vitamin D seems to improve telomere biology through anti-inflammation and antiproliferative mechanisms [114]. Individuals treated daily with

vitamin preparations are characterized by 273 bp longer telomeres than those who are not treated [115]. Vitamins C and E have also shown associations with longer telomeres [115]. It is relevant that both ascorbic acid (vitamin C) and tocopherol (vitamin E) are recognized antioxidants [116–119] that can prevent ROS generation, therefore increasing oxidative stress. For patients with Alzheimer's disease, elevated oxidative stress levels were found, besides shorter telomeres [120]. When vitamin E was administered to these patients, although there was no significant difference in telomere length after 6 months, levels of oxidative stress were lower [120].

Iron is a biologically very important trace element for maintaining metabolic homeostasis and genome stability. Nevertheless, it is required in a relatively narrow range, otherwise iron becomes a high potential generator of ROS [121]. Iron catalyses the Fenton reaction by generating the 8-hydroxy-guanine adduct, one of the most common DNA oxidative damages [13], found also in telomeres [17]. Iron overload induces DNA hypermethylation and can shorten telomere length [122], although the relationship between iron status and telomere dynamics is not totally clear. Shortened telomeres were found in patients with primary hematochromatosis and in patients taking supplements containing iron [123]. In women using iron preparations, telomeres were shortened by 9% when compared to non-users [115].

A low fat diet has also been associated with improvements in telomere dynamics. Men with prostate cancer who changed their lifestyle to a low fat diet, increased activity and stress reduction, presented increased peripheral blood mononuclear cells telomerase activity [124]. Also, polyunsaturated fatty acid intake was inversely associated with telomere length after multivariate adjustment in a group of 2284 American women [125]. The practice of physical exercise is well known as an important resource for a healthier life. Considering its effect on telomere length, some studies have reported no effect at all. One study observed a significant moderating effect of vigorous physical activity in protecting telomeres against cellular stress in women [126]. Endurance exercises were also relevant for older athletes. When compared to individuals of the same age, but low levels of exercise, older athletes had longer telomere length. Yet, among younger athletes, this difference was not observed regardless of endurance or practicing lower levels of exercise [106]. This result suggests that the lifetime practice of exercises might help the slower shortening of telomere length.

6. Conclusion

The observed associations reported in this chapter between telomere length and the risk of many different diseases suggest that telomeres play a fundamental role in health both at cells and organism levels. **Figure 1** summarizes some aspects that could influence telomere length. Nevertheless, for several of those diseases it is not clear if telomere length is itself the cause or consequence. For many cancers, though, telomere length shortening seems to be a major cause for triggering oncogenesis through genomic instability. It is recognized that telomeres shorten with age, but also that other factors may accelerate this process, or even reverse it in an unhealthy manner. Both occupational and environmental exposure to toxic agents has been

shown to modify telomere dynamics. At the same time, telomere length has emerged as a biomarker for studies analyzing this kind of exposure. Interventions aimed at increasing telomere length proposing to reverse the ageing process or preventing diseases have obtained strong evidence but are not yet enough. On the other hand, it is clear that dietary factors are associated with telomere maintenance in humans. Considering molecular and cellular mechanisms by which telomere dynamics can be modified, it is evident that epigenetic status, mainly DNA methylation, and oxidative stress are strongly involved. Oxidative damage appears to be the main condition that can destabilize telomere dynamics. We still have a long way to go trying to figure out all the particularities of telomere maintenance. The current challenge for researchers is to include other markers and analysis beyond the telomere length to further understand its mechanism and elucidate telomere biology and its influence on human health.

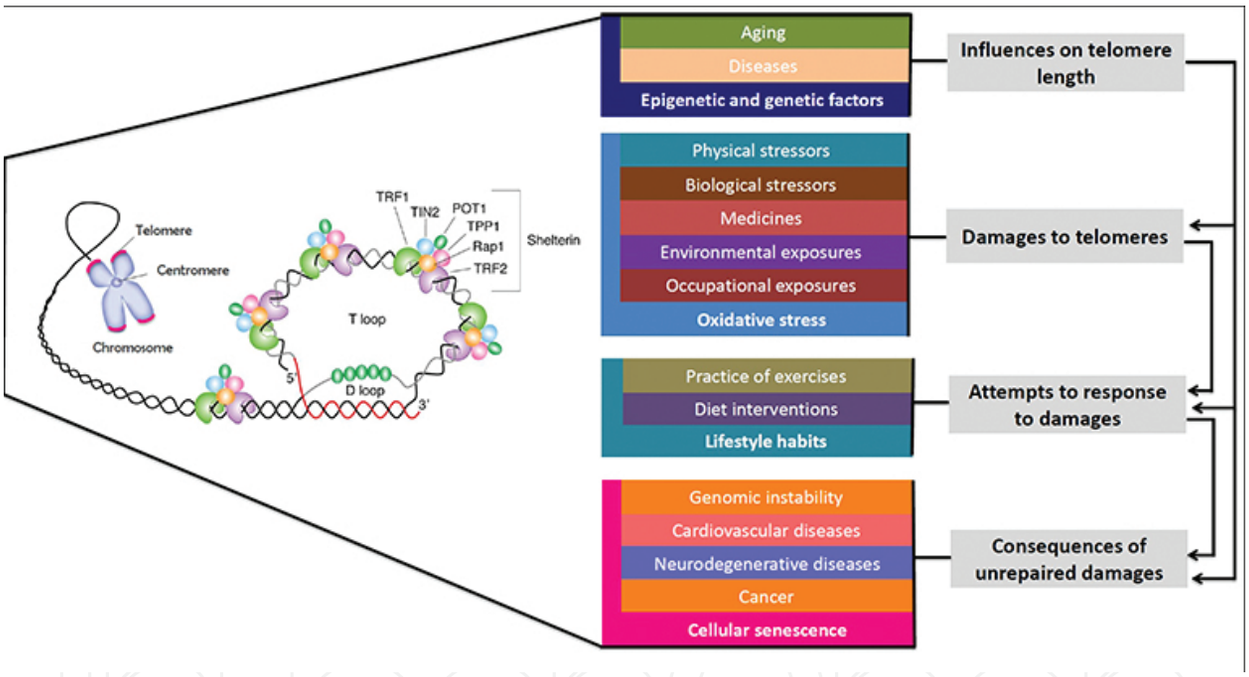


Figure 1. Graphical representation of factors that influence telomere length in different aspects.

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