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REVIEWS: CURRENT TOPICS

Diet, nutrition and telomere length☆

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Abstract

The ends of human chromosomes are protected by DNA–protein complexes termed telomeres, which prevent the chromosomes from fusing with each other and from being recognized as a double-strand break by DNA repair proteins. Due to the incomplete replication of linear chromosomes by DNA polymerase, telomeric DNA shortens with repeated cell divisions until the telomeres reach a critical length, at which point the cells enter senescence. Telomere length is an indicator of biological aging, and dysfunction of telomeres is linked to age-related pathologies like cardiovascular disease, Parkinson disease, Alzheimer disease and cancer. Telomere length has been shown to be positively associated with nutritional status in human and animal studies. Various nutrients influence telomere length potentially through mechanisms that reflect their role in cellular functions including inflammation, oxidative stress, DNA integrity, DNA methylation and activity of telomerase, the enzyme that adds the telomeric repeats to the ends of the newly synthesized DNA.

Keywords: Telomere length; Nutrition; Diet; Vitamins; DNA damage; DNA methylation

1. Introduction

The ends of human chromosomes are protected by telomeres, which consist of tandem repeats of the DNA sequence TTAGGG and associated proteins. The presence of telomeres prevents the ends of chromosomes from fusing with each other and from being recognized as a double-strand break by DNA repair proteins. During the replication of linear chromosome, the enzyme DNA polymerase replicates the DNA termini in 5′ to 3′ direction using an RNA primer for initiation. When this RNA primer is removed after DNA replication, telomeric DNA sequence is lost from the ends [1–4]. In germ cells, stem cells and many cancer cells, the reverse transcriptase enzyme telomerase adds telomeric sequence to the ends of the newly synthesized DNA, maintaining the telomere length [5,6]. When cells are not undergoing division and DNA replication, the complex of proteins associated with telomere repeats termed shelterin prevents unwanted lengthening of telomeres by restricting access to telomerase [7]. Telomerase activity is also present in activated T-lymphocytes [8,9], although this does not result in maintenance of telomere length in T-lymphocytes but may partially compensate for loss of telomere repeats during cell division [10]. In most somatic cells which lack telomerase, telomeric repeats shorten with repeated cell divisions until the telomeres reach a critical length, at which point the cells enter senescence [11].

Telomere length is epigenetically regulated by DNA and histone methylation. Telomeric and subtelomeric regions have heterochromatin marks characterised by DNA methylation and trimethylation of lysines in histone 3 (H3-lysine 9) and histone 4 (H4-lysine 20) [12,13]. Deficiency in the DNA methyltransferases DNMT1 or both DNMT3a and DNMT3b, or the histone methyltransferases Suv39 or Suv4-20h, results in longer than normal telomeres that lack the epigenetic marks [12–14]. The loss of DNA or histone methylation due to the methyltransferase deficiency does not change the expression of telomerase enzyme. The methylation status of telomeric and subtelomeric regions regulates telomere length probably by controlling the access of telomere elongating proteins to telomeric regions [12–14]. Telomere length is also influenced by gender; telomeres in women are longer when compared to those in men [15–17].

Telomere length shortens with normal aging, life stress, infection and chronic diseases [3,18–20]. Inflammation and accompanying proliferation of cells during infection and diseases result in loss of telomeric repeats due to increased cell division. Plasma concentration of the inflammatory marker C-reactive protein (CRP) is negatively correlated to telomere length [21]. Use of anti-inflammatory drugs can reduce the shortening of telomere length that follows inflammation [22]. Inflammation also results in oxidative stress. Chronic low-level oxidative stress can cause oxidative base modifications and single-strand breaks in DNA [23]. This type of damage accumulates in telomeres since the G-rich telomeric sequence is more sensitive to damage from oxidation [24]. Damage to telomeric DNA is repaired less efficiently compared to the coding regions of the genome and thus results in shortening of telomeres [25]. Loss of protective

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function of the telomeres due to attrition of the repeats makes the chromosomes susceptible to fusion with other chromosome ends and double-strand breaks, resulting in chromosomal rearrangements which affect genomic stability [26]. Critically short telomeres lose their epigenetic marks and are prone to recombinations [27]. Elongated telomeres that lack the normal DNA or histone methylation marks also result in increased telomeric recombinations [13,14,28]. Although it is the structure of chromatin rather than the telomere length that is the determinant of recombination, longer telomeres undergo recombination more frequently than the shorter ones [28]. Telomere dysfunction is linked to the development of age-related pathologies including Parkinson disease, Alzheimer disease, cardiovascular disease and cancer [29–33].

Of interest to nutritionists, telomere length has been shown to be associated with nutritional status in human and animal studies. Healthy lifestyles and diets are positively correlated with telomere length. Changes in diet and lifestyle can modulate telomerase activity in peripheral blood mononuclear cells [34], though it is not clear if this translates in to changes in telomere length. This review summarizes the current knowledge on nutrition and telomere length and proposes mechanisms by which various nutrients may influence telomere length.

2. Vitamins and telomere length

2.1. Folate

Association between plasma concentration of the B vitamin folate and telomere length has been reported in men and women [35,36]. Folate plays an important role in maintenance of DNA integrity and DNA methylation, both of which influence telomere length. Methylene-tetrahydrofolate (THF) is used for the synthesis of the pyrimidine thymidylate and of purines, thus providing precursors for DNA synthesis. Methyl-THF provides methyl groups for the methylation of homocysteine (Hcy) to methionine, the precursor of *S*-adenosylmethionine (SAM). SAM is the universal methyl donor for biological methylation reactions including those of DNA and histones.

Since folate provides precursors for thymidylate synthesis, low folate availability induces misincorporation of uracil in place of thymidine in DNA [37]. When these uracil bases are removed by excision repair enzymes, strand breaks are formed in DNA [37]. The thymidine in the telomeric sequence may be replaced by uracil under folate deficiency, leading to telomeric DNA damage. Accordingly, low nutritional status of folate results in short telomeres possibly due to DNA damage [35,36]. Folate deficiency would result in imbalance of nucleotide pools in the cell. This imbalance can destabilize replication forks and cause shortening of telomeres in a process that is independent of DNA damage due to uracil misincorporation [38].

Folate availability also influences DNA methylation due to its role in generating the methyl donor SAM. Low folate status is associated with genomic DNA hypomethylation [39], and folate supplementation can modify DNA methylation as well as modulate the expression of epigenetically regulated genes [40]. When there is loss of DNA and histone methylation, epigenetic regulation of telomere length is lost, and telomeres become more elongated than normal [12–14]. Longer telomeres were observed under very low folate status in men [36] possibly due to the DNA hypomethylation. Similar results were not observed in a population that was predominantly female [35]. It is possible that the effect of nutrients on telomere length is influenced by gender.

Polymorphisms in the genes involved in folate pathway affect DNA integrity and methylation. The enzyme methylene tetrahydrofolate reductase (MTHFR) converts methylene-THF to methyl-THF. The C677T polymorphism of the MTHFR gene that substitutes a valine for alanine results in decreased enzyme activity [41] and thus reduced availability of methyl-THF for methionine synthesis. This polymorphism is linked to genomic DNA hypomethylation under low folate status [39]. In individuals homozygous for the T allele, there is a trend for longer telomeres under low folate status when compared to the heterozygotes or the CC homozygotes [36], suggesting loss of epigenetic regulation due to DNA hypomethylation. Loss of epigenetic status of the unusually long telomeres makes them susceptible to recombinations [14]. Chromosome rearrangements as indicated by nucleoplasmic bridges have been reported under low folate conditions in cell culture [42,43]. Telomere-dysfunction-induced genomic instability could be one of the mechanisms by which folate affects the risk for diseases.

Impairment of remethylation of Hcy to methionine due to inadequate levels of folate will result in elevated Hcy concentrations [44]. Thus, plasma total Hcy (tHcy) functions as a marker of folate status. Increase in plasma tHcy is linked to decrease in telomere length [35,45], except under high tHcy concentration, where longer telomeres were observed possibly due to loss of epigenetic regulation resulting from DNA hypomethylation [36].

2.2. Vitamin B12

Methylation of homocysteine to form methionine, the precursor of SAM, is catalyzed in a vitamin-B12-dependent reaction. Despite the role of vitamin B12 in generation of methyl groups for methylation reactions, plasma concentration of vitamin B12 or intake of vitamin B12 has not shown an association with telomere length [36,46]. But women who use vitamin B12 supplements have longer telomeres than nonusers [46]. Higher doses of vitamin B12 beyond that is available through food or multivitamin supplements are provided by vitamin B12 supplements, which may contain more than 400-fold the recommended daily allowance of the vitamin. Vitamin B12 has strong antioxidant properties and has the effect of sparing the reactive oxygen species (ROS) scavenger glutathione [47,48], thus reducing oxidative stress. In addition, supraphysiological doses of vitamin B12 derived from supplements can inhibit nitric oxide synthase [49] and potentially reduce inflammation. The reduced oxidative stress and inflammation due to the high dose of vitamin B12 may explain the longer telomeres in individuals who use vitamin B12 supplements.

2.3. Nicotinamide

Treatment of human fibroblasts with nicotinamide diminishes telomere attrition while increasing their replicative capacity in culture [50]. Nicotinamide adenine dinucleotide is the precursor for poly(ADP-ribose) synthesis onto acceptor proteins by poly(ADP-ribose) polymerases (PARPs) [51,52]. The addition of negatively charged ADP-ribose polymers by PARP modulates the function of the acceptor proteins, which are mostly proteins involved in nucleic acid metabolism, DNA repair and chromosome integrity maintenance [53–58]. In response to DNA damage, activity of PARPs and synthesis of poly(ADP-ribose) increase with corresponding utilization of nicotinamide adenine dinucleotide [55,59,60]. Incidence of micronuclei in lymphocytes, which is an indicator of genomic instability, is inversely related to the dietary intake of nicotinamide [61]. Nicotinamide also has the potential to influence telomere length due to the role of PARPs in telomere elongation. Telomere length is positively regulated by the PARPs tankyrase 1 and 2, by ADP-ribosylation of telomere repeat binding factor-1 which is a negative regulator of telomere elongation [54,58]. While ADP-ribosylation of telomere repeat binding factor-2 does not modulate telomere length or telomerase activity, it is important for the maintenance of telomere integrity [62]. In cell culture studies where addition of nicotinamide reduced telomere attrition, production of ROS was also reduced probably by influencing cellular factors that are involved in ROS production since

nicotinamide itself does not exhibit any antioxidant properties [50]. Thus, nicotinamide could influence telomere length through multiple mechanisms involving DNA stability and regulation of telomere length via PARPs.

2.4. Vitamin A

Telomere length is positively associated with dietary intake of vitamin A and β-carotene in women who do not take multivitamins [46]. Vitamin A plays an important role in immune response [63]). Deficiency of vitamin A predisposes individuals to infections [64] that can lead to telomere attrition. In subjects with deficiency of vitamin A, supplementation with the vitamin reduced the plasma concentration of the inflammatory cytokine tumor necrosis factor alpha and increased the concentration of the anti-inflammatory cytokine interleukin-10 [64]. Supplementation with vitamin A beyond the dietary requirement, as might be the case in individuals who take multivitamins, does not appear have a dose-dependent effect on telomere length [46].

2.5. Vitamin D

Richards et al. [65] reported a positive association between the concentration of vitamin D in serum and telomere length in peripheral leukocytes in women. The biologically active form of vitamin D, 1α,25 dihydroxyvitamin D3, possesses immunosuppressive properties [63]. This is reflected in the inverse relationship between plasma concentration of vitamin D and the inflammatory marker CRP [66]. Telomere length is negatively correlated to plasma concentration of CRP [21]. Addition of 1α,25 dihydroxyvitamin D3 to the cell culture medium reduces expression of the proliferation factor granulocyte–macrocyte colony stimulating factor that is important for the proliferation of all lineages of hematopoietic cells [67] and hence reduces proliferation of lymphocytes [68]. In addition, vitamin D also reduces the expression of inflammation mediators interleukin-2 [69] and interferon gamma [70]. These anti-inflammatory and antiproliferative properties of vitamins D limit the turnover of cells, thus potentially reducing their telomere length attrition.

2.6. Vitamins C and E

Antioxidant properties of vitamin C and E are widely acknowledged [71]. Intake of vitamin C and E either from diet or from multivitamins is positively associated with longer telomeres in a dose-dependent manner in women [46]. Age-dependent shortening of telomeres as well as decrease in telomerase activity in cell cultures can be slowed down and life span can be increased by addition of physiological concentrations of vitamin C or vitamin E to the culture medium [72–74]. In cells treated with vitamin E (6-*O*-phosphorylated form of α-tocopherol), there was a reduction in the ROS due to scavenging by the vitamin [74]. This process may limit oxidative damage to telomeric DNA that would otherwise cause shortening of telomere length. The positive effect of vitamin C on telomere length could also be due to a similar ROS scavenging mechanism [72,73].

3. Minerals and telomere length

3.1. Magnesium

Magnesium is required for catalytic activity of a wide array of enzymes including those involved in DNA replication, DNA repair and RNA synthesis [75]. Dietary magnesium intake has been shown to be positively related to telomere length in women [46]. Long-term magnesium deficiency leads to shorter telomeres in rats and cells grown in culture [76,77]. This decrease in telomere length during magnesium deficiency is also accompanied by an increase in oxidative stress [76], which is one of the factors that result in telomere attrition. Low serum magnesium concentration is also associated with high concentration of the inflammatory marker CRP [78]. Another possibility is that reduced availability of magnesium ions negatively influences genome integrity. Magnesium ion binding is necessary for efficiency and fidelity of DNA polymerase [79,80]. Furthermore, magnesium is necessary for the functioning of endonucleases involved in base excision repair of DNA and for maintaining chromosome structure by binding to the phosphate of nucleotides [75,81]. Insufficiency of magnesium reduces DNA repair capacity [82] and induces chromosomal abnormalities [83,84]. Hence, it is reasonable to hypothesize that magnesium influences telomere length by affecting DNA integrity and repair in addition to its potential role in oxidative stress and inflammation.

3.2. Zinc

Zinc-dependent enzymes in the cell include DNA polymerases, RNA polymerases and reverse transcriptases [85–87]. Providing additional zinc in the cell culture medium increases activity of telomerase which is a reverse transcriptase [88]. Zinc is necessary for activation of poly(ADP-ribose) polymerase involved in DNA repair at DNA damage sites [89]. In humans, deficiency of dietary zinc has been shown to cause DNA damage [90]. In older subjects, percentage of cells with critically short telomeres and decrease in telomere length are associated with decrease in concentration of intracellular labile zinc and the zinc-binding protein metallothionein in peripheral blood mononuclear cells [91]. Maternal diet deficient in zinc causes chromosomal abnormalities including fusion between chromosomes in the offspring of rats [83]. One of the reasons for fusion between chromosomes is the loss of telomere cap by attrition, which in this case could be due to DNA damage arising from zinc deficiency.

Zinc also has a protective role in oxidative stress [92]. While a direct role for zinc in removing ROS or free radicals has not been proven, it has been shown that dietary zinc deficiency is associated with oxidative damage [93]. Supplementation with zinc can reduce oxidative stress and inflammation [94,95]. In purified systems, zinc binding decreases the susceptibility of sulfhydryl groups to oxidation [96], and zinc has been proposed to compete with prooxidant metals like iron for binding to cysteine, thus preventing formation of free radicals [92,97]. Zinc supplementation also reduces the incidence of infection, [94,98], which is another factor that leads to telomere attrition by higher turnover of cells. Thus, it is possible that zinc may affect telomere length by influencing telomerase activity, DNA integrity, oxidative stress and susceptibility to infection.

3.3. Iron

In contrast to the effect of other nutrients, use of iron supplements is associated with shorter telomeres [46,99]. Iron is a prooxidant that can bind to cysteine residues of proteins and result in formation of hydroxyl free radicals [97]. Iron supplement intake has been shown to increase free radical excretion in feces in healthy individuals [100]. The shorter telomeres observed in iron supplement users could be due the free radical generating capacity of iron and resultant oxidative stress [99]. Iron intake from diet or multivitamins which may contain less iron than iron supplements is not negatively associated with telomere length [46].

4. Other bioactive dietary components and telomere length

4.1. Omega-3 fatty acids

Plasma concentration of marine omega-3 fatty acids docosahexanoic acid and eicosapentaenoic acid has been shown to be positively

associated with reduced attrition of telomere length in study subjects over a period of 5–8 years [101]. Individuals who had higher baseline omega-3 fatty acid concentration showed the maximum effect of omega-3 fatty acids on telomere attrition. Omega-3 fatty acids concentration in plasma is associated with low proinflammatory markers and high anti-inflammatory markers [102]. In mice, diet enriched in marine omega-3 fatty acids enhanced the activities of antioxidant enzymes superoxide dismutase, catalase and glutathione peroxidase and increased life span [103,104]. The anti-inflammatory and antioxidant properties changes induced by omega-3 fatty acids decrease the cell turnover and oxidative DNA damage and thus may reduce telomere shortening.

4.2. Polyphenols

Polyphenols in grape seed and tea have been reported to have antioxidant and anti-inflammatory properties [105,106] . Tea consumption is negatively associated with biomarkers of inflammation [107]. Possibly due to this anti-inflammatory effect, habitual tea drinkers have longer telomeres in peripheral blood cells than those who drink tea less often [108]. In mice, administration of grape seed polyphenols through diet resulted in a trend for longer telomeres when compared to controls [109].

4.3. Curcumin

Another dietary component that possesses properties similar to polyphenols is curcumin, the active ingredient of the spice turmeric. Curcumin induces synthesis of the antioxidant glutathione and inhibits release of the chemokine interleukin-8 and activation of the nuclear transcription factor NF-kappa B that mediates inflammatory response [110]. Mice that were fed diets containing curcumin showed decreased DNA damage and a trend for longer telomeres when compared to animals that were fed a control diet [109].

5. Diet, lifestyle and telomere length

Since diet and lifestyle can influence inflammation, oxidative stress and psychological stress, all of which cause telomere attrition, they could also influence telomere length. A healthy lifestyle with a diet high in fruits and vegetables combined with exercise, lower body mass index and not smoking is associated with longer telomeres [22]. While multivitamin use has been associated with longer telomeres in women, when analyzed for individual vitamin intake, only vitamins C and E were associated with telomere length [46]. Most multivitamin users follow a healthy lifestyle, which is another factor that could influence their telomere length [99]. A small pilot study in men [34] showed that comprehensive changes in lifestyle including a change in diet to include more low-fat, unrefined plant-based food supplemented with omega-3 fatty acids (from fish oil), soy and vitamins C and E for a period of 3 months increased telomerase activity of peripheral blood mononuclear cells. Increase in telomerase activity was correlated to decrease in plasma concentration of low-density lipoprotein and decrease in psychological distress [34]. Telomere length was not measured in this study since the short duration of the study was not considered sufficient to show any changes in telomere length. Consumption of whole grains and other plant-based foods ameliorates inflammation [111]. Perhaps due to this reason, dietary fiber intake, specifically from cereals and whole grains, is positively associated with telomere length [112]. Intake of processed meat was inversely related to telomere length in a multiethnic cohort [113]. Processed meats by virtue of their high fat and protein content could be high in advanced glycation end products that induce inflammatory mediators [114] and are associated with inflammatory diseases like type-2 diabetes [113,115]. Many studies have shown that maternal diet exerts a strong influence on the health and disease risks of the adult offspring. Maternal diet low in proteins during gestation can lead to increased DNA damage and accelerated shortening of aortic telomere length of the offspring in rats [116].

6. Conclusions

Length of telomeres is an indicator of biological aging. Due to the incomplete replication of linear chromosomes by DNA polymerase, telomeric repeats at the ends are lost with each cell division. Dysfunction of telomeres is associated with the development of many age-related diseases. Telomere length and attrition of telomeric repeats are influenced by nutrition in human and animal models (Fig. 1). Various nutrients influence telomere length via mechanisms that reflect their role in cellular functions including DNA repair and

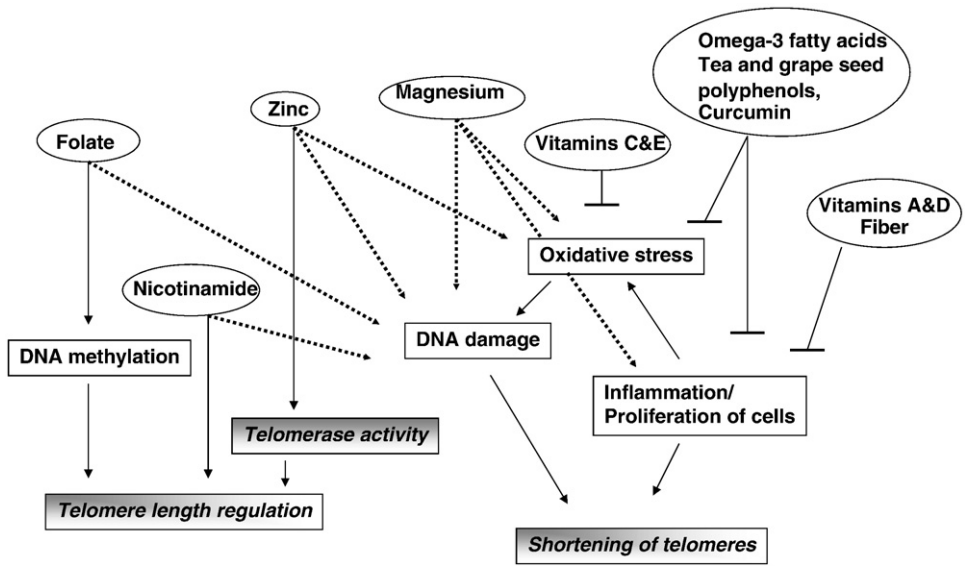

Fig. 1. Potential mechanisms behind the influence of nutrients on telomere length. Nutrients influence telomere length by various mechanisms that reflect their role in cellular functions. Dashed line indicates effect of deficiency of a nutrient.

chromosome maintenance, DNA methylation, inflammation, oxidative stress and activity of the enzyme telomerase that adds the telomeric repeats (Fig. 1). Inflammatory processes that lead to increased turnover of cells contribute to attrition of telomeric repeats by increasing cell divisions. Damage to telomeric DNA due to either oxidative stress or reduced availability of nucleotide precursors results in shorter telomeres. Anti-inflammatory and antioxidant nutrients can reduce erosion of telomeres. Nutrients also have the potential to influence regulation of telomere length, e.g., folate via its role in epigenetic status of DNA and histones, and nicotinamide through its role as a substrate for posttranslational modification of telomere associated proteins. The mechanisms behind the role of many of the nutrients in telomere length proposed in this review are based on current knowledge and need to be explored in mechanistic studies in the future.

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