



Vitamins and Minerals Influence Telomere Length - An Integrative Approach

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ABSTRACT:

The protective covering of chromosome ends is called telomers, which is a DNA-protein complex that imparts two adjacent to adhere. The process of successive cell division causes the reduction of telomeric DNA and beyond a threshold limit a cell undergoes a phase of cessation of division which corresponds to cellular senescence. Thus, it becomes an indicator of biological ageing and henceforth several gerontological studies have been proposed to establish a correlation between telomere length and age-related diseases like Parkinsonism, Alzheimer's disease, and cancer. Since micronutrients are the beads of the foundation of life on the earth, their effect is pleiotropic. Several micronutrients including vitamins are proven to be involved in the regulation of cellular progression, ROS production, inflammation, DNA-structural modelling, etc. Keeping the proven links in context, this review aims to summarise, vitamins and other micronutrients play a crucial role in maintaining telomere length and hence the probability of health span might be altered.

1. Introduction

Telomeres, which are protein and DNA-associated tandem replications of the arrangement TTAGGG, guard the ends of human chromosomes. Chromosome ends cannot fuse together due to the presence of telomeres, which also inhibits DNA repair proteins from identifying the ends of the chromosomes as double-strand breaks. An RNA primer is used as an initiator by DNA polymerase enzyme as it duplicates the DNA terminus of linear chromosomes in the 5' to 3' orientation. After DNA replication, this RNA primer is eliminated, and the ends of the telomeric DNA are lost¹⁻². telomerase increases the length of telomeres in cancer, stem, and germ cells by attaching the telomeric sequence to the ends of newly synthesized DNA³. In active T-lymphocytes, telomerase activity is also present⁴, even though this does not maintain the length of the telomeres in T-lymphocytes. Instead, it might help moderately make up for the loss of telomere during the division of cells⁵. Almost all the somatic cells lacking the enzyme telomerase experience repeated cell divisions that shorten telomeric repeats till

it reaches a threshold extent, at which senescence occurs in a cell⁶.

Methylation of histone protein and DNA molecule controls the epigenetic telomere length regulation. The heterochromatin marks in telomeric and sub-telomeric areas are expressed by methylation of DNA and also similar outcome has been seen in lysine's trimethylation in histones 3 (H3-lysine 9) and 4 (H4-lysine 20)^{7,8}. Average telomere length decreases as a result of histone methyltransferase and DNA methyltransferase deficiency⁹. Telomerase enzyme expression is unaffected by the damage of histone methylation or DNA which is triggered by deficiency of methyltransferase. Telomere length is likely regulated by telomere elongating proteins' access to telomeric areas, which is likely regulated by methylation of both telomeric and sub-telomeric areas. Gender also affects telomere length; female telomeres are longer than male telomeres¹⁰.

The size of telomeres decreases with age-related conditions like stress, infections, and chronic illnesses¹¹. Telomeric repeats are lost as a result of accelerated cell



division during infection and illness, which is accompanied by inflammation. Telomere length and the inflammatory marker C-reactive protein plasma concentration are inversely associated¹². Anti-inflammatory medication can mitigate the telomere shortening caused by inflammation¹³. Oxidative stress is a side effect of inflammation. Minimal oxidative stress can lead to DNA oxidative base changes and single-strand breaks¹⁴. The arrangement of G-rich telomeres is more vulnerable to oxidative impairment, which causes this sort of damage to accumulate in telomeres¹⁵. Telomeres shrink as a result of the less effective repair of damage to telomeric DNA relative to coding sections of the genome¹⁶. The chromosomes become vulnerable to fusion with the ends of other chromosome and to double-strand breaks as a result of the repeats' attrition, losing their protective function, which affects the genomic stability¹⁷. Telomeres that are too short lose their epigenetic markings and are vulnerable to recombination¹⁸. Telomeric recombination is also more common in telomeres that are elongated and absent the typical histone methylation or DNA markers¹⁹.

Larger telomeres experience recombination more often than shorter telomeres¹⁹. Parkinson's, Alzheimer's, cardiovascular disease, cancer, and other age-related diseases are connected to telomere disruption²⁰.

2. Nutrition and the length of telomeres

2.1 Folate and its impact on health:

Studies in both genders have shown a connection between telomere length and folate levels. It is crucial for preserving the DNA methylation and integrity, which affect the length of the telomere. Methylene-tetrahydrofolate (THF) is utilized to produce purines and pyrimidine thymidylate. Homocysteine (Hcy) is methylated by methyl-THF into methionine, which is a forerunner to S-adenosylmethionine (SAM), which is a common methyl donor for genetic methylation processes, such as those involved in DNA methylation.

Low levels of folate availability cause uracil to be falsely incorporated into DNA instead of thymidine because as folate is necessary providing precursors for thymidylate synthesis²². DNA strand breaks occur when excision repair enzymes remove these uracil nucleotides²². Telomeric DNA damage can result from thymidine is exchanged by uracil in the presence of a folate deficit.

Low folate nutritional status likely leads to short telomeres, presumably due to DNA damage²¹. A lack of folate would lead to an imbalance in the cell's nucleotide pools. Telomere shortening can result from this imbalance, A process not related to DNA damage caused by uracil misincorporation, which can destabilize replication forks²³.

Folate availability affects DNA methylation because it contributes to the production of the methyl donor SAM. Hypomethylation of the genome is linked to low folate status²⁴, and folate supplement can change methylation of DNA and alter the epigenetically regulated genes expression²⁵. Epigenetically telomere length is regulated, but when histone methylation and DNA are removed, length of telomere is unregulated and they lengthen beyond the limit¹³. Men's telomere length was shown to be longer when their folate status was extremely low²¹, probably as a result of DNA hypomethylation but Similar outcomes were not seen in women²¹. The effect of nutrition on telomere length may vary depending on gender.

2.2 Vitamin A

The length of telomere is favourably correlated with dietary consumption of beta-carotene and vitamin A in women who is not on multivitamin supplement²⁶. Immune response benefits from vitamin A.

Vitamin A deficiency makes people more vulnerable to infections²⁷ that might cause telomere erosion. Supplementing with vitamin A enhance the anti-inflammatory cytokine such as interleukin-10 and reduces the level of pro-inflammatory cytokine levels tumour necrosis factor alpha in participants with vitamin A deficiency²⁷. Supplementing with vitamin A beyond the dietary requirement, as in the case of individuals who take multivitamins, does not appear to have a dose-dependent effect on telomere length²⁶.

2.3 Vitamin D

A study done by Richards et al., revealed a favourable relationship among serum vitamin D levels and telomere length in the peripheral leukocytes of women²⁸. The substance that is physiologically active have Immunosuppressive properties are seen in vitamin D (1,25 dihydroxy vitamin D₃)²⁹. The inverse relationship shows that the vitamin D levels and inflammatory CRP³⁰ marker and telomere length have a negative



relationship¹². Expression of the proliferation factor is decreased by the cell culture media. Granulocyte-macrophage colony-stimulating factor is an essential factor for the growth of all hematopoietic cells³¹ decreases lymphocyte production³². Additionally, Vitamin D's anti-inflammatory and antiproliferative properties help regulate the expression of inflammatory mediators such as interleukin and interferon gamma 2. By preventing excessive cell division, vitamin D may slow the reduction of telomere length³³.

2.4 Vitamin C and E

Vitamins C and E are widely recognized for their antioxidant properties³⁴. Getting enough these vitamins through food or supplements in a study was linked to larger telomeres, a dose-dependent manner in females²⁶. Shortening of telomeres occurs as you get older as well as a reduction in the activity of telomerase in cell cultures the addition of may be used to slow down ageing and lengthen life physiological levels of vitamin E or C in the culture³⁵⁻³⁷ medium Vitamin E (6-O-phosphorylated) in cells after treatment -Tocopherol), there was a decrease in the ROS as a result of the vitamin³⁷ is scavenging.

This procedure might prevent the telomere length from being shortened by oxidative damage to telomeric DNA. A similar ROS scavenging process may possibly be the cause of vitamin C's beneficial effect on telomere length^{35,36}.

2.5 Vitamin B12:

Homocysteine is methylated via a vitamin B12-dependent mechanism to create methionine, the precursor of SAM. Even though vitamin B12 is essential for methylation activities and for generating methyl groups, telomere length has not been associated with either vitamin B12 intake or plasma levels^{21,26}. However, women who supplement with vitamin B12 had lengthier telomeres compared to those who do not²⁶. More amounts of vitamin B12 are accessible in vitamin B12 pills compared to meals or multivitamin supplements because they may hold >400 times the everyday necessary amount of vitamin. Due to its potent antioxidant capabilities, vitamin B12 protects glutathione, which neutralizes oxygen radicals (ROS) in the body^{38,39}, hence reduction of oxidative stress. Additionally, nitric oxide synthase can be inhibited⁴⁰ and inflammation may be decreased by supraphysiological

levels of vitamin B12 obtained through supplements. The larger telomeres in individuals who take vitamin B12-rich supplements may be attributed to the reduction in inflammation and oxidative stress caused by the higher vitamin B12 dosage.

3. Minerals and their impact on telomere length:

3.1 Magnesium:

Several enzymes, which is responsible for RNA production, DNA repair, and replication of DNA require magnesium to function catalytically⁴¹. It has been demonstrated that dietary magnesium consumption is favourably correlated with women's telomere length²⁶. A chronic magnesium deficiency in rats and cells produced in culture causes shorter telomeres^{42,43}. A component that contributes to telomere attrition, oxidative stress, increases together with this decrease in telomere length during magnesium shortage⁴².

Elevated levels of the inflammatory marker CRP are also associated with low serum magnesium levels⁴³. Another hypothesis is that genomic integrity is negatively impacted by magnesium ions' decreased availability. The effectiveness and fidelity of DNA polymerase depend on magnesium ion binding^{44,45}. In addition, magnesium is required for endonucleases to operate properly and maintain the structure of chromosomes by interacting with nucleotide phosphate during DNA base excision repair⁴⁶. Magnesium deficiency impairs the body's ability to repair DNA⁴⁷ and causes abnormalities in chromosomes^{48,50}. Therefore, it is hypothesized that, including its potential functions in inflammation and oxidative stress, magnesium impacts the integrity of DNA and restoration in order to affect telomere length.

3.2 Zinc:

RNA polymerases, reverse transcriptase's, and DNA polymerases are three examples of zinc-dependent enzymes found in cells. A reverse transcriptase called telomerase becomes more active when more zinc is added to the medium used for cell culture⁵¹. When poly (ADP-ribose) polymerase is activated at DNA damage sites, it can repair the damaged DNA⁵². DNA damage has been demonstrated to occur in people when dietary zinc levels are low⁵³. Elderly patients have lower quantities of intracellular zinc and metallothionein, a protein that binds zinc, which is associated with a greater percentage of cells with shortened telomeres and a drop in the length



of telomeres⁵⁴. Chromosome abnormalities, such as fusion between chromosomes, are brought on by maternal diets low in zinc in rats' offspring⁵⁵. One of the causes of chromosomal fusion is attrition of the telomere cap, which may be brought on by DNA damage from zinc shortage.

In the case of oxidative stress, zinc also serves as protection⁵⁶. It is known that a lack of zinc in the diet contributes to oxidative damage⁵⁷. Zinc directly neutralizes free radicals or ROS has not yet been established. Zinc supplements can lessen inflammation and oxidative stress^{58,59}. It is believed that zinc competes with prooxidant metals like iron for binding to cysteine, thereby reducing free radicals. In bodily systems, zinc binding helps protect sulfhydryl groups from oxidation⁶⁰. Infection is an additional aspect that contributes to telomere attrition by increasing cell turnover, and Zinc supplementation lowers the risk of infection⁶¹. Therefore, it is conceivable that telomerase activity caused by zinc could affect telomere length.

3.3 Iron:

Iron supplements are linked to shorter telomeres⁶², compared to other nutrients. Inducing the production of hydroxyl free radicals is one of the prooxidant properties of iron⁶³. Free radical elimination in faeces is increased in healthy people who take an iron supplement⁶⁴.

It is possible that iron's capacity to produce free radicals and the resulting oxidative stress contributes to the shortening of telomeres seen in those who take iron supplements⁶². Telomere length is not adversely affected by iron consumption from the food and multivitamins, which can be less iron-rich than iron supplements²⁶.

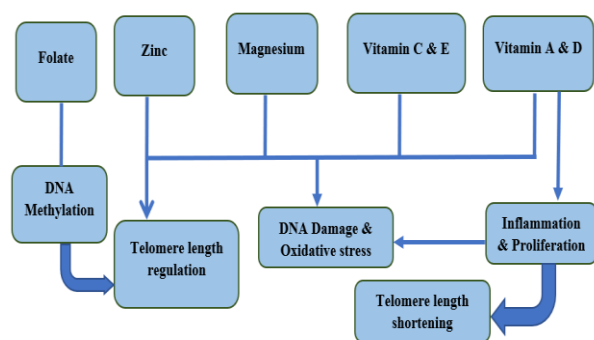


Figure 1 The numerous ways through which nutrients affect telomere length reflect their involvement in cellular processes.

4. Conclusion:

Telomere length serves as a biological ageing marker. Each time a cell divides, the telomeric length at the ends vanishes because DNA polymerase only replicates linear chromosomes partially.

Telomere dysfunction has been associated with numerous age-related disorders in both humans and animal models, diet affects telomere length and telomeric repeat attrition (Fig. 1). The processes by which various nutrients influence telomere length includes inflammation, oxidative stress, DNA methylation and telomerase activity, which adds telomeric repeats, are all factors in DNA repair and chromosome maintenance (Fig. 1). Inflammatory mechanisms that accelerate cell turnover lead to increased cell divisions, which in turn hasten the depletion of telomeric repeats. Telomeres shorten due to damage to telomeric DNA caused by oxidative stress or a deficiency in nucleotide precursors. The erosion of telomeres can be slowed down by anti-inflammatory and antioxidant foods. Nutrients may also influence the regulation of telomere length. For example, folate may affect this regulation through nicotinamide may play a function in the epigenetic state of DNA and histones by acting as a substrate for proteins posttranslational modification that are linked with telomeres. Based on existing knowledge, several processes by how nutrients affect telomere length have been postulated in this study. However, additional mechanistic studies are needed to gain a complete understanding of these processes.

CONFLICT OF INTEREST

No conflicts of interest are declared.

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Table 1 Table containing different study findings.

<u>AUTHORS</u>	<u>ORIGIN</u>	<u>RESEARCH DESIGN</u>	<u>TARGET POPULATION</u>	<u>MAJOR FINDINGS</u>
BLOUNT BC ET AL	USA	Follow-up study	Splenectomized healthy human volunteers.	Folate deficiency in humans causes a significant accumulation of uracil in DNA and leads to chromosome breakage, both of which can be effectively reduced with supplementation.
FRISO S ET AL	USA	Comparative study	Unrelated, age- and sex-matched subject.	Folate deficiency induces hypomethylation within critical regions of the p53 gene.
INGROSSO D ET AL	Italy	Cross-sectional	Men with hyperhomocysteinaemia and uraemia	Hyperhomocysteinaemia disrupts the epigenetic regulation of gene expression, but this can be restored with folate treatment.
AUKRUST P ET AL	Norway	Interventional study.	Common variable immunodeficiency (CVI) patients.	Vitamin A supplementation may play a role in CVI by potentially boosting immunoglobulin production and reducing inflammatory responses.
MORA JR ET AL	USA	Review		1,25(OH) ₂ D ₃ can enhance CCR10 expression on human T cells and ASCs6,39 while inhibiting the expression of receptors responsible for skin and gut homing.
FURUMOTO K ET AL	USA	Interventional study	Cell-line model	The age-related shortening of telomeres can be slowed down by reducing intracellular oxidative stress and/or maintaining telomerase activity, both of which are facilitated by high levels of vitamin C.
TANUKA Y ET AL	Japan	Interventional study	Cell-line	Telomeric DNA retention, along with sustained telomerase activity, has been linked to cellular longevity and may be promoted by reduced oxidative stress in a hydrophobic environment, a condition more effectively supported by tocopherol than ascorbate.
LING CT ET AL	USA	Comparative study	Animal model	This study indicates that vitamin B12 may act catalytically in maintaining sulfhydryl compounds in the reduced state.
MARTIN H ET AL	France	Comparative study	Animal model	Telomere shortening was measured in rat livers, and was decreased in old animals, as compared to young animals
SONG Y ET AL	USA	Follow-up	Americans	The findings indicate a connection between zinc deficiency, DNA integrity, oxidative stress, and DNA repair, highlighting zinc's role in preserving DNA integrity.
AVIV A ET AL	USA	Cross-sectional study	Cell line model	Leukocyte telomere length is influenced by the telomere length of hematopoietic stem cells at birth and its progressive shortening with age throughout an individual's life.