

# Telomere length: biological marker of cellular vitality, aging, and health-disease process

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## SUMMARY

The aging process occurs due to the decline of vital physiological functions and adaptability of the body, being influenced by genetics and lifestyle. With advances in genetics, biological aging can be calculated by telomere length. Telomeres are regions at the ends of chromosomes that play a role in the maintenance and integrity of DNA. With biological aging, telomere shortening occurs, causing cellular senescence. Several studies show that shorter telomeres are associated with acute and chronic diseases, stress, addictions, and intoxications. Even in the current COVID-19 pandemic, telomere shortening is proposed as a marker of severity in individuals infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On the other hand, healthy lifestyle habits increase telomere length and balance of various cellular functions, preventing diseases.

**KEYWORDS:** Telomere. Telomere shortening. Telomere homeostasis. Telomerase. Biomarkers. Aging. Cellular senescence. Chronic disease.

## INTRODUCTION

The irreversible aging process is marked by a decline in vital physiological functions and the adaptability of the body, being strongly influenced by genetics, environmental factors, and lifestyle. Currently, the aging process is divided into two main components, namely, chronological age and biological age, which may differ for the same individual. Biological aging can be calculated by telomere length (TL)<sup>1,2</sup> and DNA methylation levels (epigenetics)<sup>3,4</sup>.

Telomeres are noncoding regions of the genome, located at the ends of chromosomes (functioning as protective covers of chromosomes), which consist of long series of short and repeated sequences formed by nitrogen bases 5'-TTAGGG-3' and associated proteins, which play an important role in the maintenance and integrity of DNA. Telomere shortening may compromise the replicative potential of cells, contributing to the natural process of cellular senescence. To counteract this process, the telomerase enzyme promotes the maintenance of telomere length by synthesizing the repetitive sequences of lost telomeric DNA.

In 2009, Elizabeth H. Blackburn, Carol W. Greider, and Jack W. Szostak received the Nobel Prize in Physiology or Medicine for discovering the protective role of telomere and telomerase enzyme in chromosomes<sup>5-7</sup>. These extremely significant findings paved the way for researchers to further explore the role of telomere homeostasis in cell aging and chronic diseases in general.

## Mechanism of action of Telomeres

During cell division or duplication, cells are unable to replicate approximately 50 pairs of nitrogen bases from the ends of chromosomes, as conventional DNA polymerase cannot reproduce the 3' end of a linear molecule (end replication problem). This leads to progressive chromosome shortening along the divisions of a cell lineage, resulting in loss of replicative capacity and induction of cellular senescence. This mechanism of action is the main cause of cell aging and age-related chronic diseases<sup>8-10</sup>.

To avoid this progressive telomere shortening that occurs at each cell division and the loss of respective genetic information,

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periodically, the lost DNA segments are recovered by the action of a ribonucleoprotein enzyme complex called telomerase. This complex has a small RNA component that is a template for the synthesis of the repetitive sequences, which make up the telomere. In the recovery of lost telomeric DNA, nucleotide bases are added individually and in the correct sequence, and telomerase progresses discontinuously, i.e., the RNA mold is positioned on the initiator DNA, several nucleotides are added to it, and finally the enzyme translocates to restart the process<sup>10-12</sup>.

In neonatal period, telomerase activity is reduced or null, as evident from the absence in most somatic tissues of the body. Telomerase is active in early stages of human development (pluripotent embryonic cells), and throughout life, in blood stem cells, germ cells and cells of adult tissues undergoing continuous renewal, such as endometrial tissue<sup>13</sup>. Due to gradual loss of telomerase activity, in each cell division, the telomere terminals of these cells are shortened, reaching a minimum length that precludes cell division<sup>14</sup>.

On the other hand, 90% of cancerous somatic cells, which reach “immortality,” have high expressiveness of telomerase (increasing the telomere length). In these tumor cells, the reactivation of the telomerase silencer gene has been one of the mechanisms used to circumvent the natural system of cellular senescence and apoptosis, allowing cancer cells to promote continuous telomere elongation and replicate in an uncontrolled and uninterrupted manner<sup>15,16</sup>.

### Role of Telomeres in health disorders

Several studies show that shorter telomeres are associated with a number of chronic diseases: congenital dyskeratosis, aplastic anemia, idiopathic pulmonary fibrosis, and liver cirrhosis<sup>17</sup>; cardiovascular diseases in general<sup>18,19</sup>, such as atherosclerosis<sup>20</sup>, arterial hypertension<sup>21</sup>, and stroke<sup>22</sup>; diabetes mellitus type 2<sup>23-25</sup>; autoimmune diseases, such as systemic lupus erythematosus<sup>26</sup> and rheumatoid arthritis<sup>27</sup>; psychiatric diseases<sup>28</sup>; and dementia<sup>29,30</sup>, among other age-related diseases<sup>31</sup>.

In cancer, telomere sizes play a dual role as follows: telomere shortening can lead to the induction of chromosomal instability and the onset of tumor formation (precancerous lesion); on the other hand, initiated tumors need to reactivate telomerase to stabilize chromosomes and gain “immortal” growth capacity<sup>32,33</sup>.

The same telomere shortening is observed in other health disorders, addictions, and intoxications, namely: obesity<sup>34</sup>; inflammatory and oxidative processes<sup>35</sup>; smoking<sup>36</sup>, alcoholism<sup>37</sup> and drug dependence<sup>38</sup>; and exposure to pollutants and mineral particles<sup>39-41</sup>, among the others.

Even in acute diseases, such as the current coronavirus disease 2019 (COVID-19), telomere shortening is proposed as a marker of disease severity<sup>42,43</sup> identifying patients at risk of

higher morbidity and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Studies suggest that T-cell lymphopoiesis may be discontinued in the infected individuals with short telomeres<sup>44</sup>.

In cancer-surviving children, a study shows the decrease in telomere size associated with chronic health disorders as a result of the treatment received (radiotherapy and chemotherapy)<sup>45</sup>. Similarly, other treatments have demonstrated the same shortening effect on telomere (e.g., immunosuppressive drugs<sup>46</sup>, proton pump inhibitors<sup>47</sup>, and insulin<sup>48</sup>).

On the other hand, some therapies are being assessed to counteract telomere shortening and act on telomere diseases: sex hormones (aplastic anemia and idiopathic pulmonary fibrosis)<sup>17,49</sup>, antidiabetic agents without acarbose (type 2 diabetes)<sup>50</sup> and lithium (bipolar disorder)<sup>51</sup>, among the others. Similarly, natural compounds and their extracts have demonstrated to increase telomerase activation (*Astragalus membranaceus* or TA-65, *Centella asiatica*, *Euterpe oleracea*, oleanolic acid, maslinic acid, and multi-nutrient formulas)<sup>17,52,53</sup>, which may be indicated in the treatment of diseases related to telomere shortening.

Given that in most cancer cells telomerase activity is higher, different anti-cancer approaches have been designed in the search for telomerase inhibitors: small-molecule inhibitors, antisense oligonucleotides (imetelstat), G-quadruplex stabilizers, immunotherapy, gene therapy using telomerase promoter-driven expression of a suicide gene, and chemicals that block telomerase biogenesis<sup>17,54,55</sup>. Among the natural compounds, anthraquinone<sup>56</sup> and wogonin (extract from *Scutellaria baicalensis*)<sup>57</sup> appear as promising anti-tumor agents.

Analogous to physical disorders, traumatic social exposures or lifelong psychoemotional disorders, such as chronic stress and childhood traumas (abuse, violence, racism, bullying, low socioeconomic status, maternal depression, family disorder, and institutionalization, etc.), also cause a decrease in telomere length<sup>58-65</sup>.

Finally, in addition to natural and chronological aging, telomere shortening can be influenced by physical activity, body mass index, chronic inflammation, oxidative stress, hormone therapy, drugs, dietary antioxidants, and vitamins, among others. Studies show that individuals who follow a healthy lifestyle have longer telomeres<sup>66</sup>.

## CONCLUSION

Functioning as an important biomarker of cellular vitality or activity, longevity or aging, and the health–disease process, measuring the telomere length of leukocytes DNA extracted from peripheral blood<sup>67</sup> provides clinical and dynamic parameters of health and well-being and can be used as a diagnostic and prognostic method of the illness process<sup>31,68-70</sup>, as well as

measuring the efficacy and effectiveness of various therapies employed, conventional<sup>71</sup> or nonconventional (e.g., homeopathy<sup>72</sup>, acupuncture<sup>73</sup>, and meditation<sup>74</sup>).

According to vitalist medical rationalities<sup>75</sup>, such as homeopathy and acupuncture, cellular activity, physiological homeostasis, and the health–disease process would be related to vital force or chi (tsri), respectively; cellular senescence, physiological imbalance, and the disease manifestation would occur due to the disturbance of the body vitality. In order to approximate different rationalities, recent studies correlate the characteristics and properties of the homeopathic vital principle with those of the genome (exome *plus* epigenome), suggesting that the

genome would be the biological representation or substrate of the organic vital force, according to biomedical episteme<sup>76,77</sup>. In this context, the telomere length could be used as an important biomarker of the effectiveness of homeopathic treatment in maintaining vitality, physiological balance, and health.

Current knowledge about telomeres and telomerase reiterates the importance that should be devoted to healthy lifestyle and health-promoting measures, such as regular physical activity, balanced diet, body weight control, spiritual and contemplative activities, and integrative and complementary practices in health, that increase telomere length and balance of various cellular functions, preventing diseases, and other somatic and psychic disorders.

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