Telomere length: is the future in our "ends"?

Elisa Danese, Giuseppe Lippi

Section of Clinical Biochemistry, University of Verona, Verona, Italy

Correspondence to: Prof. Giuseppe Lippi. Section of Clinical Biochemistry, University Hospital of Verona, P.le LA Scuro 10, 37134 Verona, Italy. Email: giuseppe.lippi@univr.it.

Abstract: Telomeres, repetitive nucleotide sequences located at the end of each chromosome, play the important function of preserving chromosome stability and preventing molecular contact with neighboring chromosomes. Albeit the concept that telomere length may be a marker of health and disease seems hence counterintuitive, the translation of this clear-cut concept from the bench to the beside has appeared so far less straightforward. In particular, controversial evidence has emerged so far about the fact that telomere length may actually predict morbidity and mortality across many clinical settings. This uncertainty is actually due to a kaleidoscope of biological and technical factors, including preanalytical issues (e.g., sample matrix), poor standardization of techniques used for their assessment, and dependence of telomere structure upon genetics, epigenetics, environment and behavioral attitudes, which may be present at a variable extent in various physiological or pathological conditions. Therefore, although it is now undeniable that our future is largely in our "hands" (i.e., genotype, diet, exposure to environmental factors and so forth), larger and more solid evidence will be necessary before concluding that the future is also written in our (chromosome) "ends".

Keywords: Telomere length; chromosome; mortality; cancer

Submitted Jun 04, 2018. Accepted for publication Jun 12, 2018.
doi: 10.21037/atm.2018.06.24
View this article at: http://dx.doi.org/10.21037/atm.2018.06.24

Telomeres, whose name originates from the Greek words "telos" (i.e., "end") and "meros" (i.e., "part"), are made of repetitive nucleotide sequences (i.e., TTAGGG tandem repeats comprised between 5,000–15,000 base pair at birth) located at the end of the chromosomes, playing the important function of preserving chromosome stability and preventing molecular contact with neighboring chromosomes (1). Although the structure of telomeres was originally uncovered by Hermann Muller, nearly 80 years ago (2), it is only in recent times that their essential role in health and disease has been more clearly unraveled. Briefly, telomere integrity is dependent both on their length and on the catalytic activity of the enzyme telomerase. Telomeric DNA sequences undergo a progressive process of shortening during mitotic divisions, whilst disruption of telomere integrity may also occur as a consequence of many environmental factors impacting repair efficiency, until reaching a breaking point when both the aging-mediated or pathological repair of DNA will fail, thus leading to impairment of cell replicative potential and cell senescence (1).

Albeit the concept that telomere length may be a marker of health and disease seems at first glance counterintuitive, the translation of this clear-cut biological mechanism from the bench to the beside has appeared so far less straightforward.

Important insights on the role of telomeres in human biology have emerged from a very large study, recently published by the Telomeres Mendelian Randomization Collaboration (3). This Mendelian randomization study has collected data for 48 non-neoplastic diseases and 35 different types of malignancies, totaling 420,081 cases. Quite interestingly, telomere shortening was found to be directly associated with an enhanced risk of some types of cancers (i.e., glioma, neuroblastoma, ovarian, endometrial, lung, kidney, bladder, skin, testicular), but not with others (i.e., breast, prostate, colorectal, esophageal, pancreatic). Regarding other prevalent human disorders, no association was found between telomere shortening and some cardiovascular diseases (i.e., ischemic stroke,

heart failure) whilst, rather surprisingly, telomere length was negatively associated with the risk of acute coronary syndrome. A marginally statistically negative association was also found between telomere shortening and type 1 diabetes, interstitial lung disease and Alzheimer's disease. In another recent article, exploring whether or not telomere length may be considered a reliable biomarker of aging (4), Mather *et al.* concluded that the current strength of evidence is insufficient to define that telomere shortening will reliably predict function decline in aging individuals. More specifically, the association between telomere shortening and aging-related functional measures or mortality has remained mostly inconclusive. This evidence has been partially confirmed in another recent meta-analysis of two large prospective cohort studies, totaling 12,199 adults (5), which showed that telomere shortening was associated with a slightly enhanced risk (i.e., 23%) of all-cause death, but was not associated with both cardiovascular and cancer mortality.

The important findings emerged from these publications confirm that telomere length may not be ready for prime time for being used as a predictive, or even diagnostic or prognostic, biomarker. This is reasonably attributable to an ample series of biological and technical factors. Among the former, a litany of existing work supports the concept that telomere length is not directly influenced by the disease *per se*, but rather telomere shortening may occur as consequence of a complex and multifaceted interplay among several biological factors such as genetics, epigenetics, environment and behavioral attitudes, which may be present at a variable extent in various physiological or pathological conditions (6,7). Without further concrete evidence, it seems hence impossible to establish as yet whether telomere shortening may be an active player or a bystander in many human pathology. Regarding the techniques used for measuring telomere length, several methodological nuances characterizing the different assays explain the large variability of results emerged from the different published studies (8). Also differences in the nature of biological samples may contribute to this significant variability, since data generated on cells or genomic DNA are not directly comparable (9). Therefore, until a better standardization of biological matrices or methods can be reached, and a uniform means of reporting data is identified, data interpretation, or even generation of a trustworthy reference range, will remain rather problematic, thus further hampering the clinical usefulness of this measure.

As clinicians and biochemists, we will all agree that it would be extremely challenging to provide a reasonable answer to a patient asking "my telomeres are short: what can you do for me?". This is indeed the biggest and still unresolved question about telomere length. What we can perhaps argue is that telomere shortening does not provide an independent clinical insight on disease susceptibility or frailty, but is rather a still undefined accompanying phenomenon mirroring a worse status of health and wellbeing. Albeit it is now undeniable that our future is largely in our "hands" (i.e., genotype, diet, exposure to environmental factors and so forth), larger and more solid evidence will be necessary before concluding that the future is also written in our (chromosome) "ends".

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bojesen SE. Telomeres and human health. J Intern Med 2013;274:399-413.
2. Muller HJ. The remaking of chromosomes. Collecting Net 1938;13:181-98.
3. Haycock PC, Burgess S, Nounu A, et al. Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. JAMA Oncol 2017;3:636-51.
4. Mather KA, Jorm AF, Parslow RA, et al. Is telomere length a biomarker of aging? A review. J Gerontol A Biol Sci Med Sci 2011;66:202-13.
5. Mons U, Müezzinler A, Schöttker B, et al. Leukocyte Telomere Length and All-Cause, Cardiovascular Disease, and Cancer Mortality: Results From Individual-Participant-Data Meta-Analysis of 2 Large Prospective Cohort Studies. Am J Epidemiol 2017;185:1317-26.
6. Sanders JL, Newman AB. Telomere length in epidemiology: a biomarker of aging, age-related disease, both, or neither? Epidemiol Rev 2013;35:112-31.
7. Aubert G. Telomere dynamics and aging. Prog Mol Biol Transl Sci 2014;125:89-111.
8. Montpetit AJ, Alhareeri AA, Montpetit M, et al. Telomere

length: a review of methods for measurement. Nurs Res 2014;63:289-99.
9. Dlouha D, Maluskova J, Kralova Lesna I, et al. Comparison of the relative telomere length measured in leukocytes and eleven different human tissues. Physiol Res 2014;63 Suppl 3:S343-50.

Cite this article as: Danese E, Lippi G. Telomere length: is the future in our "ends"? Ann Transl Med 2018;6(13):280. doi: 10.21037/atm.2018.06.24

