Telomere shortening: a diagnostic tool and therapeutic target for cardiovascular disease?

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This editorial refers to ‘Rate of telomere shortening and cardiovascular damage: a longitudinal study in the British birth cohort’†, by S. Masi et al., on page 3296.

The high prevalence of cardiovascular disease and related mortality and functional decline resulting from increasing life expectancy highlights the need to understand how ageing influences vascular and cardiac function. Currently, ageing is viewed as a consequence of prolonged exposure to environmental and cardiovascular risk factors, during which accumulation of damage increases the risk of cardiovascular dysfunction and disease. However, the striking variability in the age of onset of manifestation of cardiovascular diseases and the large variability of cardiovascular phenotypes with ageing is inadequately explained by the traditional cardiovascular risk factors, but may be explained by variation in biological age.

Leucocyte telomere length (LTL) and telomerase activity are possible reliable markers of biological age, with shorter telomeres and reduced telomerase activity reflecting more advanced age. Telomeres are the TTAGGG nucleotide repeats at the ends of the DNA helix, protecting the end segment of the chromosome between cell divisions, and play an essential role in stabilizing the ends of chromosomes. With ageing and with every cell division, the telomere shortens in length. If the telomere becomes very short and the telomere maintenance system is failing, the cell stops dividing, leading to cellular senescence and cellular death.1 The initial LTL of a person is mainly determined by genetic factors. This is confirmed by a genome-wide meta-analysis identifying several loci associated with telomere length.2 Also, paternal age at birth is strongly related to LTL, independent of early life socio-economic status.3 A recent study has shown that the main determinant of age-related LTL shortening is LTL at birth.4 However, because of the sensitivity of the G triplets of the TTAGGG telomere repeats to the superoxide radical, it is plausible that oxidative stress is also an important factor involved in the age-related telomere shortening.5 Accordingly, oxidative stress has been postulated to cause endothelial and cardiovascular dysfunction through its effect on telomere length in the vessel wall. Telomere shortening in circulating leucocytes has been put forward as a biomarker of this process on the assumption that telomere shortening in circulating leucocytes reflects telomere shortening of the haematopoietic compartment. This is relevant since circulating progenitor cells and myeloid cells that are derived from this compartment are key for maintenance and remodelling of the vasculature.6

Evidence in support of the link between LTL and cardiovascular function includes clinical studies that related shorter telomere length to traditional cardiovascular risk factors and to an increased risk of cardiovascular disease.3,7,8 Also, a direct relationship between LTL and the presence of atherosclerotic plaques could be demonstrated.9 Consequently, telomere length and shortening might integrate the cumulative lifetime burden of genetic factors, oxidative stress, environmental stressors, and cardiovascular risk factors involved in the evolution of cardiovascular function and disease (Figure 1). However, until recently this hypothesis was mainly based on cross-sectional studies, and longitudinal studies investigating the relationship between telomere dynamics (shortening/lengthening) and cardiovascular function were non-existent.

Masi et al. are the first to present longitudinal data on the contribution of LTL dynamics to the age-related process of cardiovascular ageing.10 They found that over 10 years of follow-up, LTL shortening was related to subclinical measures of atherosclerosis independently of traditional cardiovascular risk factors. These results suggest that over and above chronological age and exposure to cardiovascular risk factors, a part of the vascular ageing process could be explained by mechanisms regulating the rate of progression of cellular ageing of leucocytes during their lifespan (Figure 1).

Obviously, telomere length or shortening represents only one of the multiple pathways contributing to genomic instability and cellular senescence, and epigenetic alterations and DNA repair capacity, for example, probably also play a role.11,12 However, as replicative senescence integrates the whole spectrum of cellular adaptation to environmental stress with a given genetic predisposition, it makes it very attractive to use LTL shortening as a proxy to identify those patients with a high risk of developing manifest cardiovascular disease. It also provokes the idea of monitoring telomere maintenance in leucocytes.

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as a possible way to measure efficacy of therapeutic cardiovascular strategies (Figure 1). This idea has been confirmed by an observational study showing that participants who stopped smoking had shorter baseline telomere length, although their annual attrition rate was comparable with that of those who never smoked. Furthermore, recent evidence has suggested that the anti-ageing effects of statins are linked to their ability to inhibit telomere shortening by reducing oxidative telomeric DNA damage either directly or indirectly. Other possible therapeutic strategies include nutritional interventions. Caloric restriction, which is considered among the most robust lifelong extending interventions, has been shown to delay the process of vascular ageing in mice possibly in part through telomere maintenance or elongation. In addition, omega 3 fatty acids and their dietary source, the Mediterranean diet, have been associated with reduced oxidative stress, LTL maintenance, and a slower rate of cellular ageing.

Given that ageing is a multifactorial and highly variable entity, the follow-up of LTL in a person provides a new dimension to cardiovascular ageing. Although critics argue the value of LTL measurements in the general population, the study by Masi et al. provides an important additional piece of evidence to previous association studies, and forms a basis to explore this concept further.  

Conflicts of interest: none declared.

References


