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SCIENTIFIC OPINION LETTER

Telomere length: what it could tell us?

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Human telomeres are tandem repeats of DNA (5'-TTAGGG-3') and a complex of associated proteins, called shelterin (e.g. telomeric repeat factors 1 and 2, TRF1 and TRF2) (1). This complex structure is responsible for protecting the chromosome end from nucleolytic degradation, chromosome end-to-end fusion and breakage-fusion-bridge-cycle (2). Due to the semiconservative replication of the DNA, in each cell division, a small portion of the DNA at 5' end chromosome is not replicated (3). Due to its high guanine content, telomeric DNA is highly susceptible to accumulation of oxidative stress induction of 8-oxo-guanine which is not efficiently repaired and may lead to reduced binding of TRF1 and TRF2 causing telomere dysfunction (4, 5). Furthermore, random accumulation of single-strand breaks resulting from hydroxyl radical attack on the DNA backbone all along the telomere and in subtelomeric regions leads to accelerated telomere shortening or complete loss of telomeres, respectively (6). Therefore, in normal somatic tissues, telomeres shorten and/or become dysfunctional with age (6), and this process can be accelerated by poor lifestyle and diet (7, 8), as well as by exposure to environmental and occupational factors (9). Both extremely short and long telomeres have been associated with neurodegenerative and cardiovascular diseases, cancer risk (10), and with some polymorphisms (11).

Telomeres have become an important issue in relation to healthy aging because their dysfunction leads to genomic instability, triggering senescence and accelerating age-related diseases (12, 13). What is known, so far, is that a diet rich in folate, omega-3 fatty acids, vitamin D, cereal fiber and use of multivitamins can help to maintain stable and functional telomeres. On the other hand, the intake of polyunsaturated fatty acids, processed meat and high homocysteine plasma levels, a metabolic indicator of folate deficiency, are associated with shorter telomeres (for a review, see reference 8). Results show that obesity can also be related to shorter telomeres (14), which is plausible because excessive accumulation of adipose tissue and associated metabolic imbalances, increases oxidative stress and can deregulate inflammatory cytokines.

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Chronic heart failure and coronary artery disease are strongly associated with inflammation and, as anticipated, have been linked with telomere shortening as well (10). There is growing evidence that telomere stability can be affected by occupational and environmental exposures, since some of these factors have been correlated with chronic diseases and inflammation. The environmental and occupational exposures linked to shorter telomeres include polycyclic aromatic hydrocarbons (PAHs), benzene and toluene, particulate matter and lead long-term exposure (for a review, see reference 9). PAHs are known for generating DNA adducts and, therefore, genomic instability. Lead induces double-strand breaks in DNA, particularly on the telomere lagging strand (for a review, see reference 9). Not all the mechanisms of action of these chemicals are already elucidated, but in almost all cases, the induction of oxidative stress and reactive oxygen species appears to be involved. Moreover, telomere shortening is a risk factor for several kinds of cancers (15). As previously stated, longer telomeres can also represent a health problem. For example, a recent study showed that folate deficiency leads to longer but dysfunctional telomeres associated with increased chromosomal instability possibly as a result of DNA hypomethylation (16). Persistent organic pollutants were associated with telomere elongation, but the mechanism is still unknown. Increased telomerase activity and, therefore, longer telomeres were observed in exposure to arsenic (for a review, see reference 9). Telomere dynamics also seems to be associated with psychological and psychosocial effects. Some authors observed that telomere shortening was associated with childhood chronic or serious illness, besides adverse lifetime events, as anxiety disorder and childhood maltreatment, resulting in shorter telomeres at adult life (7, 17). These results may indicate that childhood adversities might have a considerable impact on well being in later life. Higher stress levels in relation to psychosocial effects and higher average levels of depressive symptoms were observed in caregivers of Alzheimer's patients, and shortened telomeres were found (for a review see reference 7).

Finally, telomeric DNA is relatively less capable of repair, resulting in accelerated telomere shortening during the cell cycle and replicative senescence (12). It is recognized that diet plays an important role on telomere maintenance, and

personalised nutrition for DNA damage prevention is a growing and prospective science field (8). A proper diet combined with exercise appears to prevent genomic instability, possibly by providing an appropriate intake of antioxidants and reduced level of inflammation (8, 14, 16, 18). Prevention of exposure to environmental and occupational hazards as well as psychological stressors may further reduce the risk of telomere instability and further senescence (7, 9). Currently, we are in a Pandora's box of difficult questions about the real relationship between telomeres, diseases and a healthy life. Worldwide projects are being developed to help us to establish causality in the future and some of the huge questions about telomeres have begun to be answered. Although there are insufficient evidences to relate telomeres, disease and/or a certainty of aging, given the evidence that is provided here, optimizing nutritional and lifestyle factors could be a functional strategy for a healthy genome maintenance.

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