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Review

Telomeres and lifestyle factors: Roles in cellular aging

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ABSTRACT

Recent research has demonstrated that telomere maintenance might be a key integrating point for the cumulative effects of genetic, environmental and lifestyle factors on aging and aging-related diseases. It is timely to 'take stock' of where this work has led the field. This review summarizes studies that have examined associations between lifestyle factors and telomere length and telomerase activity. In most of the studies described in this chapter, telomere length was measured in leukocytes (LTL) or peripheral blood mononuclear cells (PBMCs), taken from blood draws from the study subjects. Much of this chapter focuses on psychological stress, a widespread factor often intimately tied in with lifestyle or behavioral factors that in turn are related to risks of clinical diseases. Together, these findings suggest that cellular aging is linked to a range of influences, with an individual's life events and lifestyle parameters playing significant roles. Lastly, we propose possible biochemical mechanisms that mediate these associations and discuss future directions.

Contents

1. Perceived stress and adverse life events

Severe or chronic psychological stress is known to accelerate biological aging, as defined in broad sense, although the mechanisms by which this occurs have been elusive. A 2004 study by Epel et al. first reported a novel correlation between short telomere length, low telomerase activity and perceived chronic psychological stress in mothers, some who had a healthy child and some who were caregivers of chronically sick children [1]. Those who scored high on a 10-item questionnaire assessing their perceived stress level in the past month had shorter telomere length and lower basal telomerase activity in their peripheral blood mononuclear cells (PBMCs). Although the finding was based on cross-sectional analysis, and therefore was not able to establish a cause-effect relationship, the authors found that years of caregiving were inversely related to telomere length, suggesting that the cumulative burden of psychological stress in caregiving may have caused the shorter telomeres observed. This finding was replicated in a different group of caregivers, spouses of Alzheimer's patients [2]. In this study, caregivers had significantly shorter telomere lengths in PBMCs as well as in T lymphocytes and monocytes. Caregiving is a prototypical example of chronic life stress, since it is typically full time, demanding, and continues for years. There are many other indices of chronic life stress, and here we review studies including low socio-economic status (SES), exposure to intimate partner violence, and childhood trauma.

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Several studies have examined the relationship between adverse socio-economic status and telomere length, but the results so far have been mixed. In one study, 1552 female twins aged 18–75 were compared for their leukocyte telomere length, and it was significantly shorter in lower SES groups. The mean difference in terminal restriction fragment length (TRFL) between non-manual (high SES) and manual SES (low SES) groups was 127 base pairs (bp) (approximating 3–5 years of accelerated shortening), after adjusting for body mass index, smoking and exercise [3]. A recent study of the Whitehall cohorts found a positive correlation between telomere length and educational attainment, but not current socioeconomic status [4]. However, Adams et al. [5] investigated the association between telomere length and life-course socio-economic status at age 50 in 318 participants in the Newcastle Thousand Families study and did not see correlations between telomere length and multiple measures of socio-economic position. Two other studies – 1542 men in the West of Scotland Coronary Prevention Study and 624 individuals in the National Long Term Care Survey (NTLCS) – also failed to detect a correlation between telomere length and socio-economic status [6,7]. Moreover, a survey of 958 men and 978 women aged 65 years and over living in Hong Kong showed that – in men only – after adjustment for age and other confounding factors, a higher ranking in community standing was associated with shorter telomere length [8], which is the opposite direction of the findings reported by Cherkas et al. and Steptoe et al.

Several distinct differences exist between these different reports. First, a larger sample size of 1552 twins in the Twins UK study compared to the 318 participants in Newcastle study and 624 participants National Long Term Care Survey. Given that the Twins UK study found a relative small difference of 127 bp between the low and high SES with a marginal statistical significance of $p < 0.047$, it is probable that Newcastle study and National Long Term Care Survey did not have enough statistical power to capture the small effect even if such a difference existed. The age, sex and racial compositions of each cohort may also play an important role as these factors are all known to be associated with telomere length [9–11]. Finally, different socio-economic status markers were used to assess socio-economic status and this may determine whether an association can be found.

Exposure to severe psychological trauma, early or late in life, may have lasting effects on hematopoietic stem cell integrity and thus on circulating leukocyte telomere length. Women who had previously experienced inter-partner violence (at least one year before the PBMCs were collected for telomere length measurements) had significantly shorter mean telomere length compared to controls. Length of time in the abusive relationship and having children were associated with telomere shortness after controlling for age and body mass index, suggesting that the stress caused by inter-partner violence and raising children in the abusive relationship causes accelerated telomere shortening [12].

Several studies show associations between childhood trauma and telomere length. Tyrka and colleagues [13] evaluated the effects of childhood adversity in a community-based sample of 31 men and women with and without a history of childhood maltreatment, and with no current depression. Participants reporting a history of maltreatment (mostly neglect rather than abuse) had significantly shorter telomeres than those who did not report such maltreatment independent of the effects of age, gender, smoking, body mass index (BMI), or other demographic factors known to be associated with shortened telomeres. Likewise, Kananen and colleagues [14] also reported that childhood adversity was associated with telomere shortening in adults in the Health 2000 Survey in Finland. Kiecolt-Glaser et al. reported that in 132 healthy older adults including 58 dementia family caregivers and 74 noncaregivers, the presence of multiple childhood adverse events was related to shorter telomeres after controlling for age, caregiving status, gender, body mass index, exercise, and sleep [15]. In a recent study of young to middle-aged adults with post-traumatic stress (PTSD), those with PTSD had shorter LTL. Early exposure to adverse events may have accounted for the difference in LTL between those with PTSD and controls; all those exposed to multiple events and types of trauma in childhood were in the PTSD group and had shorter leukocyte telomere length than those without such exposure [16]. The findings between short telomeres and childhood adverse event were replicated in a large study of ethnically homogenous population of 4441 women of the UK EPIC-Norfolk study [17]. However, one study reported a null finding between physical and/or sexual abuse in childhood and telomere length [18]. Here, like the findings for socio-economic status, the specific measurement tool used for assessing childhood trauma may be an important determinant of whether an association with telomere shortness is found. Those reported an association used a broad range of measurements including physical, sexual, emotional abuse, physical and emotional neglect [13,15,16]. Kananen et al. used a series of 11 questions about the subject's childhood social environment, which has an even broader scope that includes the financial situation of the family, physical and mental health of parents as well as the child, and the conflicts within the family and in school. It should be noted that the most significant childhood adversity in the Kananen et al. study was the person's own chronic or serious illness during childhood. Therefore, it is possible that physiological, rather than psychological adverse events in childhood are associated with shorter telomere length.

2. Stress and stress-related psychiatric conditions

Depression and post-traumatic stress disorder (PTSD) are closely linked to, and attributable to, exposure to chronic or severe psychological stress (reviewed by [19]. Several reports have found shorter telomere length in patients with mood disorders including major depressive disorder, and bipolar depressive disorder with and without anxiety [20–22]. In a small study, Wolkowitz et al. found only marginally shorter telomeres in individuals with major clinical depression compared with controls [23]. However, a significant inverse relationship was observed between telomere length and total cumulative lifetime duration of depression. This result suggests that telomere shortening may progress with longer exposure to depression. Interestingly, the major depression subjects in the Simon et al. studies had on average 31.8 ± 11.2 years of disease history, while patients in Wolkowitz's study had a shorter average disease duration (13.0 ± 11.2 years). It is possible that the lack of association between depression and short telomere length in the Wolkowitz study was due to the short disease duration in some subjects. Childhood trauma appears to set one up for both vulnerability to stress related mental health conditions, like PTSD and depression, but also for short TL. It is also likely that early trauma and later life PTSD and MDD may interact to contribute to accelerated cell aging.

3. Telomere length and temperament

Damjanovic et al., when examining LTL in older caregivers, found that simply being a caregiver was related to shorter LTL and our recent study on dementia caregivers replicates this finding (O'Donovan et al., under review). However, many studies of stressor exposure find that it is individual differences, such as perception of stress, or personality, that are linked to stress-related physiology. For example, Epel et al.'s 2004 study first demonstrated that level of perceived stress, as opposed to the inherently stressful caregiving situation itself, was correlated with shorter telomere length,