JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 21, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.03.541

EDITORIAL COMMENT

Telomeres and Atherosclerosis

The Attrition of an Attractive Hypothesis*

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In this issue of the *Journal*, the paper by Fernández-Alvira et al. (1) is probably the (pen)ultimate nail in the coffin of the attractive hypothesis that cross-sectionally measured leukocyte telomere length (LTL) is causally involved in the development of atherosclerosis. In this study of 1,459 middle-aged cardiovascular disease (CVD)-free men and women, neither average LTL nor short telomere load was a significant independent predictor for the presence of subclinical atherosclerosis. These findings are in line with previously published reports from the Asklepios and Bruneck cohorts, which similarly did not find an association between average LTL and early atherosclerosis (2,3).

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Importantly, the current study extends these prior findings in 3 important ways. First, the phenotype of atherosclerotic burden is more extensive and, in all likelihood, also more precise than in previous studies. Subclinical atherosclerosis was evaluated by collating data from a coronary artery calcium scan, combined with 2-dimensional ultrasound of the infrarenal aorta and iliofemoral arteries and 3-dimensional ultrasound of the carotid and femoral arteries. Moving from binary "plaque presence" toward a more granular "plaque burden" is an important step forward. Second, LTL was measured with quantitative fluorescence in situ hybridization, instead of the previously used Southern blot (2) or quantitative polymerase chain reaction (3) techniques. Although quantitative fluorescence in situ hybridization is not necessarily more accurate, it was at least sufficiently sensitive to detect known associations among LTL and age, sex, and oxidized low-density lipoprotein serum levels in this cohort. Current results, therefore, pinpoint biology rather than methodology to explain the lack of a significant association between LTL and early atherosclerosis. Third, previous studies looked at average LTL and atherosclerosis. The findings from the PESA (Progression of Early Subclinical Atherosclerosis) study extended this by an insightful subanalysis investigating the association between atherosclerosis and the load of short LTL (<3 kb), which also proved negative.

To understand the wider relevance of this paper, it is not enough to merely look at what this paper adds to the field of telomere biology. The ultimate importance is closely related to understanding what makes the study of telomere biology potentially so attractive to a cardiologist.

The true driving force behind interest in telomere biology is the tantalizing promise of a biomarker that captures aging by integrating lifelong exposure to risk factors, including those that are known, unknown, and misunderstood, and thereby reflects the cumulative burden of subclinical damage. Such a biomarker should be far more informative in providing risk stratification and potential for therapeutic guidance than a biomarker that merely reflects a single point in time (4).

Both imaging-derived (intima-media thickness, plaques, and coronary calcium scores) and, even more so, biomechanics-derived time-integrative biomarkers (arterial stiffness, reflection magnitude, and pulse wave velocity) have, to a varying degree, proven additive value (5-8). Still, a time-integrative biomarker, obtainable from a simple blood draw (such as LTL), would be more easily applicable for prevention at the population level.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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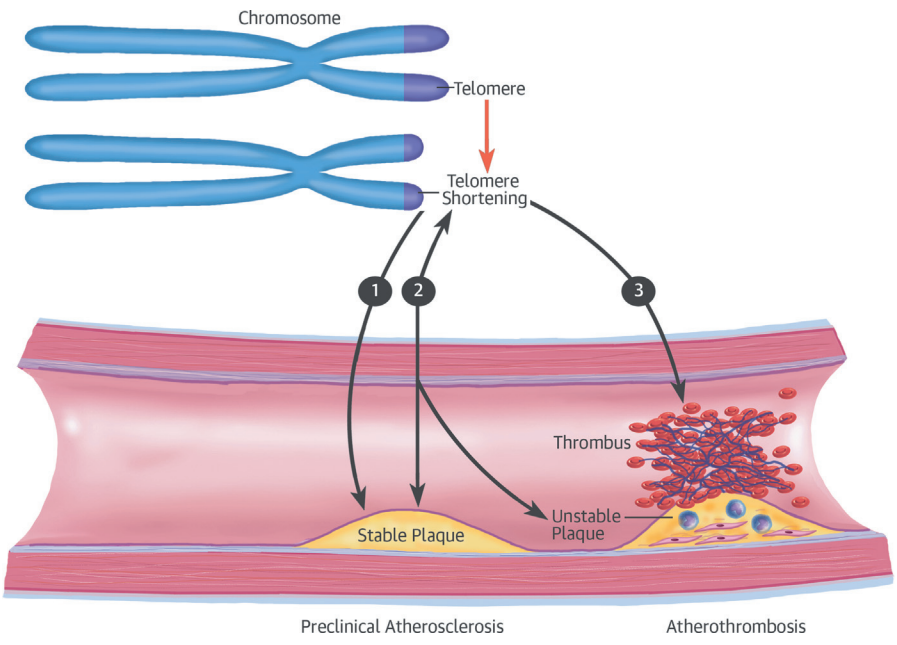
Telomeres are TTAGGG-hexamer repeat containing nucleoprotein complexes that protect the chromosomal termini by formation of a complex loop structure. A subject's telomere length is largely inherited (although only in part genetically) and is very similar between tissues. In somatic tissues, telomeres are characterized by age-dependent attrition due to cell division and oxidative stress, which may ultimately lead to replicative senescence (one of Nature's primary defense mechanisms against cancer development) (9,10).

Widespread interest in a potential link between telomeres and CVD was accelerated by the publication by Samani et al. (11) in 2001 showing shorter average LTL in subjects with advanced coronary artery disease compared with disease-free control subjects, a finding that was confirmed in a recent meta-analysis (12). Furthermore, results from genome-wide association and prospective studies suggest causality with CVD (13,14). A recurrent hypothesis therefore stated that inherited shorter telomeres result in early replicative senescence of vascular tissue, thereby inducing atherosclerosis and predestining subjects to future CVD. Yet, if LTL shortening is causally related to CVD through atherosclerosis initiation, it is highly paradoxical that findings from the PESA study and others show no association with early (pre-clinical) atherosclerosis (1,2).

Other potential causal and noncausal mechanisms linking telomeres to CVD have been postulated (**Figure 1**). One school of thought considers shorter telomeres as a pure epiphenomenon, the result of accelerated telomere shortening due to a cluster of shared risk factors also involved in atherogenesis, such as hypertension, oxidative stress, and inflammation (15–17). An extension of this hypothesis suggests that the resulting shorter telomeres may themselves have a causal effect in a much later stage of the atherosclerotic process (16), although it should be noted that the total burden of attrition on adult LTL is very limited compared with the overall effect of inheritance (18). As both atherosclerosis and LTL reflect cumulative exposure to partially shared risk factors over time, there is a high likelihood of a spurious association. This "associative bias" will be reinforced as longer timeframes and more advanced disease are considered and is likely to survive statistics adjusting for confounding risk

FIGURE 1 Main Hypotheses Linking Telomere Biology to Atherosclerotic Disease



Hypothesis 1: Shorter inherited telomeres result in early replicative senescence of vascular tissue, leading to accelerated atherosclerosis development. *Hypothesis 2:* The "common soil" of oxidative stress, aging, and inflammation cause both telomere attrition and atherosclerosis development. *Hypothesis 3:* Critically short telomeres induce hematopoietic stem cell senescence and fewer (and less functional) endothelial progenitor cells, leading to less effective repair mechanisms and destabilization of atherosclerotic plaques.

factors, which are usually measured at only 1 point in time.

A final alternative hypothesis assuming causality focuses on the transition from silent atherosclerosis to a cardiovascular event. For example, critically short telomeres could induce hematopoietic stem cell senescence and fewer (and/or less functional) circulating endothelial progenitor cells, which leads to less effective endothelial repair and subsequent destabilization of atherosclerotic lesions, triggering cardiovascular events (19). Interestingly, this hypothesis bridges the conflicting associations with late-stage diseases in the absence of an association with preclinical disease (16).

Taken together, current evidence suggests that although there is an association between LTL and atherothrombotic cardiovascular events, there is no association with pre-clinical atherosclerosis. The findings from the PESA study confirm and extend previous findings by adding both a very performant phenotyping of pre-clinical atherosclerosis at the population level and an alternative, yet innovative, methodology to study the more physiologically relevant short telomere load. Still, the potential of a potent "early vascular aging" biomarker available through a simple blood test is so alluring that research on telomere biology in the field of CVD is unlikely to end here.

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KEY WORDS aging, biomarkers, coronary artery disease, pre-clinical atherosclerosis, risk factors, telomere shortening