Atherosclerosis 266 (2017) 41–47

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Leukocyte telomere length and cardiovascular disease in African Americans: The Jackson Heart Study

Stanford Mwasongwe [a, 1], Yan Gao [b, 1], Michael Griswold [c], James G. Wilson [b], Abraham Aviv [d], Alexander P. Reiner [e], Laura M. Raffield [f, *]

[a] Jackson Heart Study, School of Public Health, Jackson State University, Jackson, MS, USA
[b] Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA
[c] Department of Data Science, John D Bower School of Population Health, University of Mississippi Medical Center, Jackson, MS, USA
[d] Center of Human Development and Aging, New Jersey Medical School, Rutgers, Newark, NJ, USA
[e] Department of Epidemiology, University of Washington, Seattle, WA, USA
[f] Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

ARTICLE INFO

Article history:
Received 8 May 2017
Received in revised form
2 September 2017
Accepted 13 September 2017
Available online 15 September 2017

Keywords:
Coronary artery calcification
Telomeres
Coronary heart disease
Stroke
Mortality
Ankle-brachial index

ABSTRACT

Background and aims: In European descent populations, shorter leukocyte telomere length (LTL) has been associated with subclinical atherosclerosis, cardiovascular disease (CVD), and mortality, while longer LTL has been associated with greater left ventricular hypertrophy. We evaluated the relationship of LTL with subclinical cardiovascular disease indices and incident clinical events and mortality in African Americans (AAs).

Methods: Analyses were restricted to 2518 participants of the Jackson Heart Study (JHS) with LTL measured by Southern blot in baseline blood samples.

Results: Adjusting for established CVD risk factors, longer LTL was significantly associated with lower prevalence of coronary artery calcification (CAC) (odds ratio (OR) = 0.810) per 1 kb increase in LTL; (95% confidence interval [CI] 0.656, 0.9998), p=0.0498). Longer LTL was also associated with higher ankle brachial index (ABI) (β = 0.023; (95% CI 0.004, 0.042), p=0.017) when comparing the highest to the lowest LTL quartile. There were no significant associations between LTL and abdominal aortic calcification, carotid intima-media thickness, or left ventricular mass. After a median follow-up of 9 years, longer LTL was associated with lower risk of incident ischemic stroke (hazard ratio (HR) 0.69 (95% CI 0.48, 0.99), p=0.044) and total mortality (HR 0.81 (95% CI 0.67, 0.97), p=0.026) in age and sex adjusted models, but these associations were no longer significant in fully adjusted models.

Conclusions: Among a community-based cohort of AAs, longer LTL was nominally associated with lower odds of CAC and increased ABI, indicative of decreased prevalence of subclinical atherosclerosis and peripheral arterial disease. These findings do not offer strong support for LTL as an independent biomarker of CVD risk in AAs.

1. Introduction

Telomeres, the DNA-protein structures located at the end of chromosomes, progressively shorten with successive cell divisions. Telomere shortening eventually triggers replicative senescence in cultured somatic cells, and possibly tissue and organismal aging *in vivo*. Many studies have examined telomere length dynamics (telomere length and/or attrition) as a potential biomarker of biological aging and predictor of aging-related diseases [1]. Shorter leukocyte telomere length (LTL) has been associated with higher risk of mortality [2,3] and cardiovascular disease (CVD) events [3–5]. LTL is relatively stable during adulthood, suggesting that the links between LTL and health status may be established early in life [6]. Genetic risk scores of variants associated with shorter telomere length have been associated with increased risk of coronary artery disease events [7,8], suggesting a potential causative role for telomere length, as expressed in LTL, in CVD and other age-related diseases. Besides clinical CVD, associations have also been observed between shorter LTL and various subclinical indices of

* Corresponding author. Department of Genetics, University of North Carolina, 5100 Genetic Medicine Building, 120 Mason Farm Road, Chapel Hill, NC 27599, USA.
E-mail address: laura_raffield@unc.edu (L.M. Raffield).
[1] These authors contributed equally to this work as first authors.

https://doi.org/10.1016/j.atherosclerosis.2017.09.016
0021-9150/

atherosclerosis burden, such as coronary artery calcification (CAC) [9,10] and carotid intima-media thickness (cIMT) [11]. By contrast, longer LTL has been associated with greater left ventricular hypertrophy [12,13].

Along with chronologic age, various demographic and environmental factors such as smoking [3,14,15], male sex [3], younger paternal age at conception [16], lower socioeconomic status [17], sedentary lifestyle and higher body mass [14,15,18], and genetic factors [7,19,20] can contribute to variation in telomere length. Despite the higher rates of CVD and CVD mortality among African American (AA) compared to European American (EA) populations [21], AAs have been shown to have longer LTL compared to EAs [2,10,22]. AAs also display different patterns of subclinical vascular disease, including less atherosclerosis (as measured by coronary artery calcium) [23] but more LVH than EAs [24]. Despite these potentially important inter-ethnic differences in CVD risk and subclinical disease, data are limited on the connection between LTL and CVD in AAs; to our knowledge, no study has assessed associations of LTL with both multiple subclinical CVD measures and CVD events in this population. In two studies the associations of shorter LTL with subclinical atherosclerosis [10] or incident CVD and mortality risk [25] observed in EAs were not present in AAs.

To further address these questions, we examined the relationship of LTL with risk of CVD, assessed using subclinical indices (CAC, abdominal aortic calcification [AAC], cIMT, ankle-brachial index [ABI], left ventricular [LV] mass and LV mass index [LVMI]) and incident clinical events (coronary heart disease [CHD], stroke, and heart failure hospitalizations) and mortality in AAs from the Jackson Heart Study (JHS).

2. Materials and methods

2.1. Sample population and LTL measurements

The JHS is a prospective, community-based cohort designed to investigate risk factors for cardiovascular disease among AAs of the Jackson, Mississippi, metropolitan tri-county area (Hinds, Madison, and Rankin). The design and methods of this study have been previously described [26]. At baseline (September 2000–March 2004), a total of 5306 AAs ≥21 years of age were recruited to participate in the study from four pools: random sampling (17% of participants), volunteers (30%), participants in the Atherosclerosis Risk in Communities (ARIC) study (31%), and secondary family members (22%). After completing a baseline clinic visit (Exam 1), participants returned for two additional clinic visits, Exam 2 (October 2005–December 2008) and Exam 3 (February 2009–January 2013). All participants included in this analysis provided written, informed consent for use of genetic data, and all study protocols conform to the 1975 Declaration of Helsinki guidelines. The study was approved by the Institutional Review Boards of the participating institutions (University of Mississippi Medical Center, Jackson State University and Tougaloo College).

All participants were asked to provide blood samples at the baseline clinic visit. DNA was extracted from whole blood using Puregene reagents (Gentra System, Minneapolis, MN) [27]. LTL (in kilobases) was measured at the Center of Human Development and Aging at the New Jersey Medical School, Rutgers, using the Southern blot analysis method [28]. Quality control consisted of assessment of DNA integrity prior to LTL measurement. The average inter-assay coefficient of variation was 2.0%; for individual measures of LTL, the interclass correlation coefficient was 0.95. Of 2573 participants with genomic DNA, 2518 (61.0% female) had non-missing LTL values with adequate DNA content and were eligible for analysis. Participants with non-missing LTL values were slightly less likely to be female than the cohort as a whole (63.5% female, $p=0.001$), but did not differ significantly in age ($p=0.63$).

2.2. Covariates

Trained interviewers administered standard questionnaires to assess demographic characteristics (age, sex, and education), medical history, medication use, and lifestyle and health behavior (alcohol consumption, current smoking, and physical activity). Anthropometric measures and fasting blood and urine samples were collected following standardized procedures. Lipid profiles (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL]), and hemoglobin A1c (HbA1c) were assessed at the University of Minnesota, while blood cell traits (white blood cell [WBC], red blood cell [RBC] and platelet count), plasma glucose, and serum creatinine were measured at the University of MS Medical Center [27]. Prevalent diabetes was defined according to the American Diabetes Association (ADA) criteria as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, or self-reported use of a diabetes medication within 2 weeks prior to the clinic visit. Hypertension was defined as systolic blood pressure above 140 mmHg, diastolic blood pressure over 90 mmHg, or use of antihypertensive medications. Glomerular filtration rate (eGFR) was estimated from serum creatinine using the CKD-EPI equation [29]. Self-reported physical activity was assessed as a dichotomous measure using American Heart Association (AHA) criteria for ideal health; participants were grouped as having either poor health (no activity) or intermediate/ideal health (some reported physical activity) [30].

2.3. Subclinical cardiovascular disease

Computed tomography (CT), ultrasound, and echocardiographic imaging data collection, reading, and quality control in JHS have been previously described [26,27,31]. Using B-mode ultrasonography, cIMT was quantified as the maximum likelihood estimate of average right and left common carotid far intima-media thickness [32]. For the present study, LVM was calculated using the American Society of Echocardiography corrected formula by Devereux et al. [33]. LVM was divided by height in meters to the exponential of 2.7 to normalize heart to body size while LVMI was calculated as LVM/body surface area. Using Doppler ultrasound, JHS staff measured systolic blood pressure (mmHg) at the posterior tibial artery in the leg and the brachial artery in the arm. Ankle brachial index (ABI) was defined as the ratio of systolic blood pressure (SBP) of the posterior tibial artery to that of the brachial artery [34]. Individuals with an ABI>1.4 (n = 84) were excluded.

Cardiovascular imaging for coronary and aortic calcification was conducted at Exam 2 (median interval between Exam 1 and 2: 4.5 years; interquartile range 4.3–5.0 years). CT of the heart and lower abdomen was performed using a Lightspeed 16 Pro 16-channel multidetector system equipped with cardiac gating (GE Healthcare, Milwaukee, WI). Quality control and image analysis were performed at the JHS core reading center at Wake Forest University School of Medicine. CT scans of the coronary arteries were based on standard protocols developed for the MESA and CARDIA studies [35]. CAC and AAC were measured in CT images by trained and experienced technologists. The Agatston score [36], modified to account for slice thickness, was used to quantify calcified artery plaque, computed by multiplying the area of each lesion by a weighted attenuation score (in Hounsfield units) on a TeraRecon Aquarius Workstation. Reproducibility of CAC and AAC was 0.99. Presence of CAC or AAC was defined as Agatston score >0.

2.4. Incident cardiovascular disease and mortality

Evaluation of adjudicated incident CHD, stroke, and HF events