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Original Study

Telomere Length and Frailty: The Helsinki Birth Cohort Study

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A B S T R A C T

Objectives: Telomere length is associated with aging-related pathologies. Although the association between telomere length and frailty has been studied previously, only a few studies assessing longitudinal changes in telomere length and frailty exist.
Design: Longitudinal cohort study.
Setting and participants: A subpopulation of the Helsinki Birth Cohort Study consisting of 1078 older adults aged 67 to 79 years born in Helsinki, Finland, between 1934 and 1944.
Measures: Relative leukocyte telomere length (LTL) was measured using quantitative real-time polymerase chain reaction at the average ages of 61 and 71 years, and at the latter the participants were assessed for frailty according to Fried criteria.
Results: The mean ± SD relative LTLs were 1.40 ± 0.29 (average age 61 years) and 0.86 ± 0.30 (average age 71 years) for the cohort. A trend of shorter mean relative LTL across frailty groups was observed at 61 years ($P = .016$) and at 71 years ($P = .057$). Relative LTL at age 61 years was significantly associated with frailty: per 1-unit increase in relative LTL, the corresponding relative risk ratio (RRR) of frailty was 0.28 (95% confidence interval [CI] 0.08–0.97), adjusting for several confounders. Also, LTL at age 71 years was associated with frailty (RRR 0.18, 95% CI 0.04–0.81) after adjustment for sex, age, and adult socioeconomic status, but further adjustment attenuated the association. No associations between telomere shortening and frailty were observed during the 10-year follow-up.
Conclusions: Shorter relative LTL was associated with frailty in cross-sectional and longitudinal analyses, but telomere shortening was not, suggesting that short LTL may be a biomarker of frailty.

Frailty, in which incomplete recovery from changes in health status occurs as the result of decreased capacity and function of several organ systems, is associated with adverse health outcomes, such as hospitalization and death.[1,2] Although the prevalence of frailty has been observed to increase from 3.2 % at age 65 to 70 years to 16.3% at age 80 to 84 years,[1] not all interindividual variation in frailty can be

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explained by chronological age alone.[3] To account for this variation, knowledge of the aging process has been applied to identify markers of biological aging.[4]

Telomeres consist of tandem DNA repeats located at the ends of eukaryotic chromosomes and function to maintain chromosomal integrity.[5] Progressive shortening of telomeres occurs at each somatic cell division, unless their length is maintained by the enzyme telomerase.[5] Because the number of cell divisions is expected to increase with age, shorter leukocyte telomere length (LTL) has been associated with aging-related markers of inflammation[6] and oxidative stress,[7] as well as pathologies including cardiovascular disease,[8] type 2 diabetes,[9] and dementia,[10] as critically short telomeres may compromise chromosomal stability and predispose the cell to senescence and apoptosis.[5] Furthermore, in some but not all studies, LTL has been found to predict all-cause mortality.[11,12] As a result, telomere length has been proposed to act as a marker for biological aging.[13]

Seven previous studies have failed at demonstrating associations between telomere length and frailty.[14–20] However, with the exception of a longitudinal study[15] on telomere length measured at one time point in relation to changes in frailty status in 2006 older Chinese adults, these previous studies have been cross-sectional in design. Our aim was to explore cross-sectional and longitudinal associations between LTL measured at 2 time points over a 10-year interval and frailty according to the criteria of Fried et al.[1] in a cohort of 1078 older individuals born in Helsinki, Finland, between 1934 and 1944.

Methods

Study Design

The present study is a substudy of the Helsinki Birth Cohort Study that includes a subpopulation of 8760 individuals who were all born in Helsinki between 1934 and 1944, had visited child welfare clinics at that time, and lived in Finland in 1971 when a unique personal identification number was assigned to all Finnish residents.[21] Random-number tables were used to select a subset of people who attended a clinical examination between 2001 and 2004. Of the 2902 invited subjects, 2003 were examined clinically. From this clinical study cohort, 1094 of the invited 1404 cohort members participated in a clinical follow-up between 2011 and 2013. Of these, 1078 individuals had information on frailty.[22] LTL was measured at the clinical examination (n = 1042) in 2001–2004 and at follow-up (n = 1061) in 2011–2013. A total of 1037 participants had both LTL measurements available, and for these participants telomere shortening was calculated.[23] The clinical study protocol was approved by the Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from each participant before initiating any study procedures.

DNA Extraction and Telomere Length

Relative LTL was measured twice: at the baseline clinical examination between 2001 and 2004 and at the 10-year follow-up between 2011 and 2014. In brief, DNA was extracted from peripheral whole blood using a commercially available kit and then assessed for purity and integrity using detailed methodology described previously.[23] Using slightly different methods, a real-time quantitative polymerase chain reaction (PCR) approach was applied at both time points to measure relative LTL. First in 2001–2004, the ratio of telomere DNA to hemoglobin beta single-copy gene signal intensities was used to determine relative LTL, as previously described.[24–26] Later in 2011–2014, relative LTL was measured using a multiplex quantitative real-time PCR method, described previously by Cawthon[27] and Guzzardi et al.[23] Four genomic DNA control samples were included in all plates to calibrate the plate effect and for monitoring the coefficient of variation (CV), which was 21.0% and 6.2% at the first and second time points, respectively. Telomere measurements are expressed as T/S ratios, which equals the ratio of telomere repeat copy number to single gene copies in experimental samples compared with a reference sample. Significant correlation was observed between the 2 relative LTL measurements ($r = 0.254$, $P < .001$). Telomere shortening during the 10-year period was calculated adjusting for the baseline relative LTL measurement (relative change in LTL = [(LTL at 71) − (LTL at 61)]/[LTL at 61] × 100) to avoid error due to different methodology used.

Frailty

Frailty was defined as the sum of 5 criteria, including weight loss, exhaustion, low physical activity, slowness, and weakness, at the clinical examination in 2011–2013.[1] A question from the Beck Depression Inventory[28] was used to assess recent weight loss. Those who reported losing at least 5 kg met the criterion. Exhaustion was assessed using the following question: “How many times during the last week have you felt unusually tired or weak?” The criterion was met if the response was “On 3 days or more.” The validated Kuopio Ischemic Heart Disease Risk Study (KIHD) questionnaire was used to evaluate leisure time physical activity (LTPA).[29] Those whose total LTPA time (including walking, resistance training, and gardening) was 1 hour or less per week met the criterion of low physical activity. In case of missing KIHD LTPA data (n = 37), physical activity was assessed using the question: “In total, how many hours a week do you do the following sports (walking, jogging, cycling, swimming, gymnastics, group exercise)?” The criterion was met if the total duration of physical activity was 1 hour or less per week. Slowness was assessed based on maximal walking speed over a 4.57-m distance. For walking speed, sex-specific cutoffs for medium height (for men ≤175.9 cm cutoff was 1.65 m/s and >175.9 cm 1.83 m/s, and for women ≤162.2 cm cutoff was 1.47 m/s and >162.2 cm 1.55 m/s) were used to identify the slowest 20% who met the criterion. Weakness was assessed by measuring isometric grip strength of the dominant hand with an adjustable dynamometer chair (Good Strength; Metitur Ltd, Jyväskylä, Finland). For grip strength, sex-specific quartiles of body mass index were used to identify the weakest 20% who met the criterion. Cohort members were classified as frail if they met 3 or more, prefrail if they met 1 or 2, and nonfrail if none of the criteria were met.

Covariates

Body composition was assessed in 2001–2004 using bioelectrical impedance by the InBody 3.0 8-polar tactile electrode system (Biospace Co. Ltd, Seoul, Korea). Segmental multifrequency analyses (5, 50, 250, and 500 kHz) were performed separately for each limb and trunk to estimate body fat percentage.[30,31] Smoking status (smoker, former smoker, never smoked) and self-reported diabetes and cardiovascular disease were assessed using questionnaires at the clinical examination. Data on adult socioeconomic status (SES), which was obtained from Statistics Finland, was coded based on occupational status attained at 5-year intervals between 1970 and 2000 as follows: upper and lower middle class, self-employed, and manual workers.

Statistics

Results for continuous variables are expressed as means and SDs and as proportions for dichotomous or categorical values. Significance between groups was evaluated using 1-way analysis of variance and cross tabulation, respectively for continuous and categorical values. Multinomial logistic regression analysis was used to study the association between telomere length and frailty. The analyses were first adjusted for age and sex and then additionally for adult SES, adult body fat percentage, smoking, and the prevalence of cardiovascular disease and diabetes. Because no significant interactions were