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Association of Telomere Length With Myocardial Infarction: A Prospective Cohort From the Population Based HUNT 2 Study

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ABSTRACT

As possible markers of biological age, telomere length (TL) has been associated with age-related diseases such as myocardial infarction (MI) with conflicting findings. We sought to assess the relationship between TL and risk of future MI in 915 healthy participants (51.7% women) 65 years or older from a population-based prospective cohort (the HUNT 2 study, Norway). Mean TL was measured by quantitative PCR expressed as relative T (telomere repeat copy number) to S (single copy gene number) ratio, and log-transformed. During a mean follow up of 13.0 (SD, 3.2) years and 11,923 person–years, 82 participants were diagnosed with MI. We used Cox proportional hazard regressions to estimate hazard ratios (HR) and 95% confidence interval (CI). Relative TL was associated with age in women (P=0.01), but not in men (P=0.43). Using relative TL as a continuous variable, we observed a higher risk of MI in participants with longer telomeres with HRs of 2.46 (95% CI; 1.13 to 4.54) in men, and 2.93 (95% CI; 1.41 to 6.10) in women. Each 1-SD change in relative TL was associated with an HR of 1.54 (95% CI; 1.15 to 2.06) and 1.67 (95% CI; 1.18 to 2.37) in men and women, respectively. Compared with the bottom tertile of relative TL, HR of incident MI in top tertile was 2.71 (95% CI; 1.25 to 5.89) in men, and 3.65 (95% CI; 1.35 to 9.90) in women. Longer telomeres in healthy participants 65 years or older are associated with a high risk of incident MI. Future large scale prospective studies are needed to confirm these findings and explore the potential association between TL and MI.

Statement of Conflict of Interest: see page 654.

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Abbreviations and Acronyms
BMI = Body mass index
BP = Blood pressure
CI = Confidence interval
CVD = Cardiovascular disease
DM = Diabetes mellitus
HR = Hazard ratio
HUNT = The Nord-Trøndelag Health Study
MAP = Mean arterial pressure
MI = Myocardial infarction
PA = Physical activity
rHR = Resting heart rate
rTL = Relative telomere length
S = single copy gene number
T = Telomere repeat copy number
TL = Telomere length

Contents

Telomeres are associated with the aging process, and often explained as the biological footprint of age.[1] Telomere length (TL) decreases with age, and when too short, the cell can no longer maintain its function, and at a critical length undergoes apoptosis. Because of this, several age-related diseases have been hypothesized to have short telomeres as part of their aetiology.[2–6] One such disease is myocardial infarction (MI), which is arguably one of the greatest causes of death in modern times,[7] and for which age is a major determinant of risk.

The association between TL and future cardiovascular disease (CVD) events has been studied to some extent,[4,5,8] and was recently reviewed[9,10] concluding with an overall negative association between TL and CVD outcomes. However, the study[4] with most statistical power observed a 50% higher risk of MI for both short and long telomeres, and demonstrated a tendency of an association between TL and risk of MI in hypertensive and diabetics, but not in the healthy participants. Other studies have included people with pre-existing CVD or with major risk factors,[5,8,11,12] making it difficult to draw conclusions about the independent effect of TL with MI in healthy populations.

Therefore, we aimed to test the hypothesis of TL and incidence of MI in a prospective cohort study of apparently healthy men and women who were 65 years or older at baseline, and followed for up to 15 years.

Methods

Study population

The second wave of Nord-Trøndelag Health Study (the HUNT2-study), a population based prospective study in Norway, was conducted during the period August 1995 to June 1997. The details of the study are described elsewhere.[13] In brief, out of 94,187 invited participants, 65,442 participated in the study, filled out a questionnaire, and attended a clinical examination. To include in the present study, participants had to be aged 65 years or older at baseline examination, not have any self-reported history of CVD, without diabetes mellitus(DM), not taking any thyroid-, blood pressure- or other heart medications, have sufficient DNA-samples for TL assessment, and have responded to the questionnaires which is a part of the HUNT-studies. Sample size calculations estimated that 760 participants were needed for a power of 80% at alpha 0.05, and 995 participants were randomly selected by a computer from the pool of 2193 meeting the inclusion criteria, and followed for up to 15 years.

Telomere analysis

Leucocytes are commonly used for measuring the TL in an individual, and has shown to be highly correlated with TL in other cell types.[14] DNA was isolated from 1-5ml EDTA whole blood or 10ml coagulum by use of PUREGNE DNA Purification Kit from Gentra Systems Inc. from the HUNT biobank,[15] and TL measured in Boston, USA, by Dana Farber/Harvard Cancer Center High throughput Genotyping core by experienced personnel. Relative TL (rTL) of peripheral blood leukocyte DNA was assessed using a modified high-throughput version of the qPCR-based method developed by Cawthon and described in detail previously.[6,16] This process involved comparison between signals from the telomere repeat copy number (T) and a single-copy gene *36B4* copy number (S), and the relative T/S ratio was calculated as $2^{-(\text{T/S of the sample - T/S of the reference DNA})}$, being the T/S ratio of the reference sample subtracted from the T/S ratio of each individual experiment sample. On every plate used, a 5ng DNA standard curve point was included as a reference to help correct for intra-plate variations, and the method has been validated.[17] Out of 995 TL-measurements, 74 had failed and thus excluded from the analysis. Triplicate reactions were performed for each sample, and quality control samples were included to assess inter-plate and intra-plate variability. The coefficient of variance (CV) of the exponentiated relative TL of the quality control samples was calculated to be 12.5%.