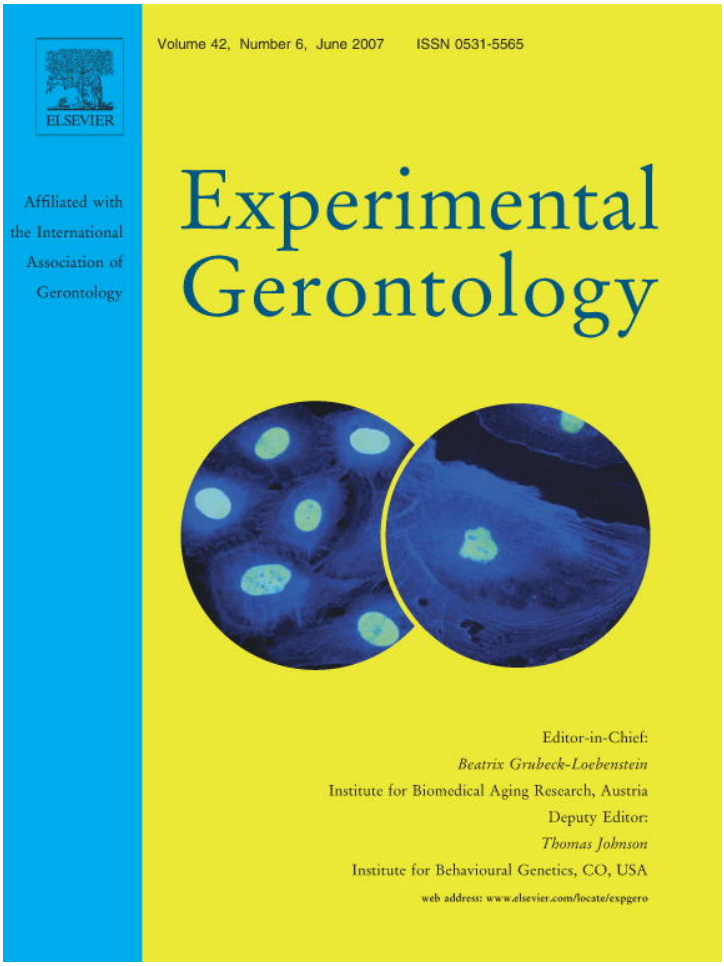

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Short Report

Association between telomere length and heart disease in a narrow age cohort of older people

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Abstract

Telomere shortening is a feature of cellular ageing common to a range of human tissues. Shorter telomeres are associated with an increased likelihood of mortality, including death from heart disease. We examined the association between telomere length and heart disease (present in 33%) in a well-characterised, narrow age cohort of older people ($n = 190$, all born in 1921), and tested for any concomitant effects of medication use. Mean telomere length was significantly shorter in participants who reported heart disease ($p = .001$). Participants with ischemic changes on ECG had shorter telomere lengths (6.67 versus 7.65 kb, $p = .021$) after adjusting for other ECG abnormalities. This finding adds to the growing body of evidence for an association between telomere shortening and ischemic heart disease. Telomere shortening in peripheral blood leukocytes is a promising index of ischemic heart disease risk in older people and deserves further investigation as a potential mechanism.

Keywords: Telomeres; Ageing; Ischemic heart disease; Electrocardiogram; Humans

1. Introduction

Telomere shortening is a feature of cellular ageing common to a range of human tissues (Friedrich et al., 2000). Shorter telomeres are associated with an increased likelihood of mortality, including death from heart disease, in people aged 60 or older, though the association is weaker in people over 75 years (Cawthon et al., 2003). Myocardial infarction was the only disease significantly associated with shorter telomeres in the Leiden 85+ study whose participants had a mean age of nearly 90 years (Martin-Ruiz et al., 2005). One difficulty in interpreting data is that chronological age is associated with both telomere length and incidence of heart disease, so that other age-associated features (e.g. non-telomeric DNA oxidative damage), or other as yet unidentified features, may give rise to a spurious relationship. Some studies attempt to limit this potential confounding by stratifying participants into narrow age bands (Cawthon et al., 2003). Another methodological issue is that drugs commonly prescribed to people with heart disease, themselves, influence telomere biology in cell culture (Spyridopoulos et al., 2004). To address these problems we examined the association between telomere length and heart disease in a well-characterised, narrow age cohort of older people, and tested for any concomitant effects of medication use.

2. Materials and methods

The participants were surviving participants of the 1932 Scottish Mental Survey, all born in the same year, 1921,

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and seen at age 79 years. There was selection bias towards inclusion of participants from professional and semi-professional social classes as described previously (Harris et al., 2006). Disease was categorised as previously reported (Starr et al., 2004), with heart disease classified as definite, possible (e.g. possible angina), or absent. Use of aspirin, β-blockers, ACE inhibitors and statins was recorded. Participants had screening blood tests that included cholesterol and glycated haemoglobin (HbA1c), and a 12-lead resting ECG performed. A single investigator (B.McG.) analysed each ECG applying the 1982 version of the Minnesota coding. The data were then re-coded into 'normal' and 'abnormal' for the following ECG variables: axis, A-V conduction, ventricular conduction, ST depression, ST elevation, T wave, R amplitude. In addition, the ECG's were coded as 'normal' if entirely normal and 'abnormal' if there was any ECG abnormality present. The ECGs were recoded for abnormalities in the following three areas: conduction defect (where there was either AV or ventricular conduction defect), ischemia (where there were ST, T or Q wave abnormalities) and left ventricular hypertrophy (where there was LVH by voltage criteria). Fifty ECG's were re-assessed by an independent examiner (J.M.S.). There was a good inter-rater reliability (kappa for axis = 1.0, $p < .001$, kappa for ST depression = 0.547, $p < .001$).

Methods of mean telomere length measurement have been described in detail for this cohort (Harris et al., 2006). In short DNA was extracted from peripheral blood leukocytes (PBL) following standard procedures. Mean telomere lengths were determined following the method of Cawthon et al. (2003), and validated with control sample DNAs that had mTRF lengths determined previously by standard Southern blotting procedures (Cawthon et al., 2003). There were no significant associations between mean telomere length and sex or cigarette smoking (Harris et al., 2006).

Statistical analyses were performed with the SPSS 13.0 statistical package. To limit multiple hypotheses testing, associations were examined for grouped abnormalities in the following 3 areas: conduction defect, ischemia and LVH.

3. Results

Telomere lengths were calculated for 190 (82 men, 108 women) participants. Mean length was 6.63 kb (median 6.48, range 4.03–10.88 kb). Definite or possible heart disease was reported for 63 (33%) of participants with a trend for it to be more common in men than women (42% versus 27%, Fisher's exact test $p = .077$). 56.3% of participants were on a cardiovascular medication: 32.8% on aspirin or other anti-platelet agent, 20.2% on a β-blocker, 13.7% on an ACE inhibitor and 7.1% on a statin. ECG's were available for 187 participants. Nineteen percent had conduction deficits, 18% voltage criteria for LVH, and 40% ischemic changes, more in men than women (53% versus 30%, Fisher's exact test $p = .003$).

Mean telomere length was significantly shorter in participants who reported heart disease (means for definite = 5.73 kb, SD 1.43; possible = 6.53 kb, SD 1.89; absent = 6.91, SD 1.64; $F = 7.41$, $p = .001$). There was no significant difference between those participants with or without an ECG conduction deficit ($F = .98$, $p = .32$), LVH ($F = .085$, $p = .77$), or ischemia ($F = .021$, $p = .88$) when tested separately. However, a combined model revealed a significant interaction between ischemic changes and conduction deficits ($F = 7.13$, $p = .008$). In this model both ischemia ($F = 5.45$, $p = .021$) and conduction deficit ($F = 6.93$, $p = .009$) also had significant main effects. Estimated marginal means showed that participants with ischemic change had shorter telomere lengths (6.67 versus 7.65 kb), whilst those with conduction deficits had longer telomere lengths (7.71 versus 6.61 kb), but this difference for conduction deficit was accentuated in those participants without ischemic change (8.76 versus 6.54 kb). Once ECG changes were adjusted for, reported heart disease no longer had a significant effect ($F = .58$, $p = .56$). Aspirin/anti-platelets ($F = .56$, $p = .46$), β-blockers ($F = .59$, $p = .44$), ACE inhibitors ($F = 1.66$, $p = .20$) or statins ($F = 1.50$, $p = .22$) had no significant effects on telomere length.

4. Discussion

These data from a narrow age cohort support an association between telomere shortening and ischemic heart disease. ECG data suggest that this association does not apply to non-ischemic heart disease. One hypothesis that would explain this finding is that ischemia results in an intracellular redox shift causing accelerated telomere attrition, but further studies are required to investigate this. Our data are similar to the Leiden 85+ study, though this did not include ECG data (Martin-Ruiz et al., 2005). The ECG data reveal that telomere shortening is present even when ischemic heart disease is asymptomatic. Drugs commonly prescribed to people with ischemic heart disease had no association with telomere length in this sample, though the numbers on statins were too few to detect a moderate effect. We included drugs as potential confounding variables, but further investigation in larger samples is required to test whether these drugs have a significant effect on telomere length. It is unclear why participants without ischemic heart disease but who had a conduction deficit should have longer telomeres, but conduction deficits *per se* do not result in tissue attrition, hence no accelerated telomere erosion would be expected. This result needs to be reproduced before further speculation. The association may have arisen by chance yet had the effect of obscuring the significant association between telomere length and ischemic heart disease in the initial univariate analysis. Furthermore, the nature of the underlying association between PBL telomere lengths and post mitotic tissue function/damage remains to be determined. Possible contributory mechanisms include telomere attrition in mesenchymal stem cells which have proliferated to effect damage repair, or whole body stress induced inflam-

matory processes as a result of cardiac ischemia, or a combination of both (Johnson et al., 2005). Nevertheless, our data support the use of PBL telomere shortening both as an indicator of ischemic heart disease risk in older people and as a potential mechanism deserving further investigation.

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