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Telomere length and psychological well-being in patients with chronic heart failure

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Abstract

Background: psychological stress and depressive symptoms have been implicated with accelerated ageing and increased progression of diseases. Shorter telomere length indicates a more advanced biological age. It is unknown whether psychological well-being is associated with telomere length in patients with the somatic condition of chronic heart failure (CHF).
Design: a cross-sectional analysis was used.
Setting: patients were admitted to the hospital with signs and symptoms of CHF.
Objective: the study aimed to assess the association between telomere length and psychological well-being in patients with CHF.
Methods: telomere length was determined by quantitative polymerase chain reaction in 890 patients with New York Heart Association functional class II to IV CHF. We evaluated the perceived mental health by the validated RAND-36 questionnaire. Depressive symptoms were assessed by the Centre for Epidemiologic Studies Depression scale (CES-D), and the presence of type D personality was evaluated by the DS14.
Results: a lower perceived mental health on the RAND-36 score was associated with shorter telomere length. Adjustment for age and gender did not change our findings (standardised beta, 0.11; *P*-value, 0.002). Telomere length was not associated with the CES-D or DS14 score.
Conclusion: decreased perceived mental health is associated with shorter leukocyte telomere length in patients with CHF. Future work should determine whether psychological stress accelerates biological ageing.

Keywords: *heart failure, telomere, ageing, psychological well-being, quality of life, elderly*

Introduction

Telomeres are the protective caps at the ends of linear chromosomes. Telomeres play an important role in the preservation of the genomic integrity and stability by preventing them from being recognised as double-stranded DNA breaks [1]. During every cell division, the very final part of the telomere fails to be replicated and as a consequence telomeres become progressively shorter. In addition to this replicative stress, other biological stressors can cause additional telomere attrition. In this regard, oxidative stress is among the best studied factors causing telomere erosion [2]. Telomeres are considered a marker of both cumulative cell divisions and presence of other stressors and can therefore be seen as a marker of biological ageing. Eventually, telomeres will reach a critical short length which will prevent further cell divisions and can cause decreased cellular functioning [3]. Various ageing associated cardiovascular disease entities, including chronic heart failure (CHF), have been associated with reduced telomere length in humans [4–6].

Several small-scale studies have implicated shorter telomere length with mood disorders [7]. In addition, increased levels of perceived psychological stress and the chronicity of stress are associated with shorter leukocyte telomere lengths in apparently healthy subjects [8–10]. In older men, telomere length was associated with socioeconomic status possibly mediated via psychosocial stress [11]. The biological basis for these associations is not known but speculated to originate from neurohormonal activation and increased oxidative stress [9, 10, 12].

Patients with cardiovascular diseases are particularly susceptible to depressive symptoms and increased perceived psychological stress [13–15]. The presence of comorbidity frequently associated with CHF (diabetes, chronic

obstructive pulmonary disease (COPD) and stroke) has an additional deteriorating effect on quality of life [14, 16]. Decreased mental health and the presence of depressive symptoms in patients with cardiovascular disease are associated with faster disease progression and worse outcome [17, 18]. In medical inpatients over 65 years of age, depressive symptoms were associated with an increased likelihood of inpatient death [19]. It is unknown whether the association between telomere length and mental health continues to persist in the presence of the severe chronic somatic condition of CHF. Therefore, we investigated the potential association of telomere length with psychological well-being using well-validated questionnaires in subjects with CHF.

Methods

Patients

DNA was collected from 890 CHF patients who participated in the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) study [20]. Patients were 18 years or older and had evidence of an underlying structural heart disease shown by cardiovascular imaging. Patients were in New York Heart Association (NYHA) class II–IV [21].

Telomere length

Telomere length was determined in duplicate in leukocytes using a real-time quantitative polymerase chain reaction as described in detail previously [4, 22]. We determined the relative ratio of the Telomere repeat copy numbers (T) to the Single-copy reference gene (S; gene 36B4). Telomere length is expressed as the T/S ratio. All samples were compared to the same reference DNA pool.

Assessment of psychological well-being

During index hospitalisation, psychological well-being was measured by well-validated questionnaires: the RAND-36 (perceived mental health), the Centre for Epidemiologic Studies Depression scale (CES-D, depressive symptoms) and the DS14 (type D personality).

The RAND-36 was used to evaluate perceived mental health, one of the domains of the Medical Outcome study 36-item General Health Survey. This is a validated self-report questionnaire consisting of 36 items on general health summarised into nine health concepts that represent dimensions of quality of life. One of the dimensions is mental health which comprises of items 9b, 9c, 9d, 9f and 9h. The questions asked in these items are (9b) have you been a very nervous person?, (9c) have you felt so down in the dumps that nothing could cheer you up?, (9d) have you felt calm and peaceful?, (9f) have you felt downhearted and blue? and (9h) have you been a happy person? The mental health domain has a score between 0 and 100 and a higher score means better mental health [23]. We asked patients the remaining items of the RAND-36; however, these domains were omitted from the analyses since they focus more on social and physical aspects instead of the desired domain of mental health in which we were interested in. The RAND-36 was completed by 847 (95%) of participating patients.

The CES-D is a validated self-report questionnaire for the general population and the medical ill to measure depressive symptoms [24]. A cut-off point of 16 out of maximum 60 points is commonly used to define the presence of depressive symptoms [25]. For the COACH study, a third category was created based on the median CES-D score of patients with depressive symptoms which was 24. In creating this third category (no, moderate and severe depressive symptoms), a graded effect of depressive symptoms could be examined [17]. Of all patients, 835 (94%) completed the CES-D questionnaire.

Type D personality was assessed with the validated type D scale 14 (DS14) questionnaire. This questionnaire consists of 14 items with a response scale ranging from 0 (false) to 4 (true), of which seven items refer to negative affectivity and seven to social inhibition. The presence of type D personality is defined as having a score of at least 10 points on both subscales [26]. Type D denotes the synergistic effect of negative affectivity (tendency to experience negative emotions) and social inhibition (tendency to inhibit self-expression). Type D personality is considered a rather stable trait, and persons with this personality are believed to experience more stress [26]. The type D questionnaire was completed by 820 (92%) of the patients.

Statistical analysis

Telomere length was log-transformed to improve the normality of the distribution. Differences between groups were tested by students T-test, one way analysis of variance and Chi^2 test when appropriate. In order to adjust for potential confounders, we used standard linear regression models. All tests were performed in SPSS, version 14.0 (SPSS Inc., Chicago, IL). A two-sided P-value of 0.05 or less was considered to indicate statistical significance.

Results

We studied 890 patients (39% female) with a median age of 73 and an interquartile range (IQR) of 64–79. Baseline characteristics are presented in Table 1. At time of inclusion, 51% of patients were in NYHA class II, 46% in class III and 3% in class IV. The median telomere length was 0.69 (IQR = 0.59–0.85) and, as expected, was correlated well with age ($r = -0.19$, $P < 0.0001$).

As expected, perceived mental health score correlated negatively with CES-D score ($r^2 = 0.39$, $P < 0.001$). Having a type D personality was associated with lower perceived mental health ($r^2 = 0.13$, $P < 0.001$) and a higher CES-D score ($r^2 = 0.13$, $P < 0.001$).

Table 1. Baseline characteristics

Patient characteristic	(n = 890)
Age (years)	73 [64–79]
Male (n (%))	535 (61)
eGFR (mL/min/1.73 m^2)	53 [40–68]
Creatinine (μmol/L)	113 [90–144]
Age of onset CHF (years)	71 [61–77]
Body mass index (kg/m^2)	26 [24–30]
Left ventricular ejection fraction (%)	30 [23–44]
NYHA class (n (%))	
II	438 (51)
III	397 (46)
IV	27 (3)
Haemoglobin (mmol/L)	13.5 [12.2–14.8]
Heart rate (beats/min)	72 [64–80]
Blood pressure (mm Hg)	
Systolic	115 [101–130]
Diastolic	70 [60–76]
Medical history (n (%))	
Myocardial infarction	369 (42)
Hypertension	367 (41)
Diabetes mellitus	246 (28)
Atrial fibrillation/flutter	388 (44)
Stroke	88 (10)

Data is presented as 'median [interquartile range]' or 'number (%)'. The body mass index is the weight in kilogrammes divided by the square of the height in metres. eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association functional class; CHF, chronic heart failure; LVEF, left ventricular ejection fraction.

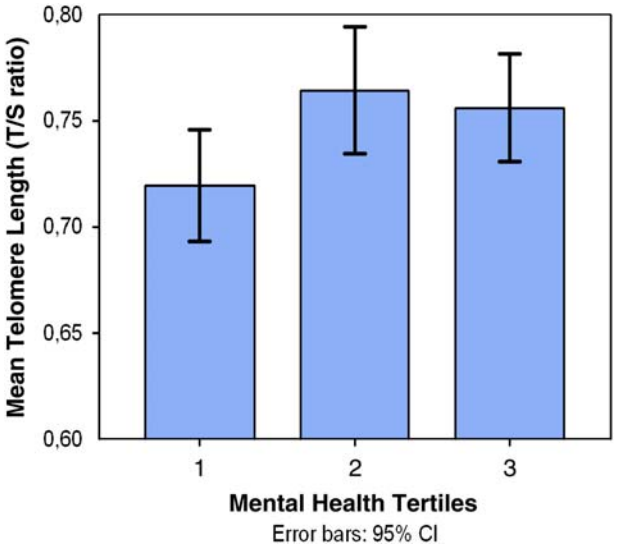

Figure 1. Mean telomere length per mental health tertile.

Table 2. Multivariate linear regression analysis

Characteristics	Mental health		
	Beta	95% Confidence interval	P-value
Model 1			
Telomere length	8.29	2.96 to 13.62	0.002
Age (years)	0.38	0.25 to 0.52	< 0.001
Female gender	−5.0	−8.08 to −1.90	0.002
Model 2			
Telomere length	6.79	0.98 to 12.60	0.022
Age (years)	0.45	0.29 to 0.60	< 0.001
Female gender	−4.61	−8.06 to −1.16	0.009
NYHA class	−4.70	−7.68 to −1.72	0.002
LVEF	−0.01	−0.13 to 0.11	0.865
eGFR (mL/min/1.73 m^2)	2.61	−1.57 to 6.80	0.221
Presence of COPD	−3.53	−7.34 to 0.26	0.068
History of stroke	−4.09	−9.56 to 1.38	0.142
Presence of diabetes	1.19	−2.50 to 4.88	0.526

NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease.

The median score on the mental health scale was 69 (IQR: 48–84) out of 100. Patients in the lowest tertile of the mental health domain in the RAND-36 questionnaire had shorter telomeres (median T/S ratio = 0.67 (0.55–0.81)) than patients in the second tertile (T/S = 0.70 (0.61–0.86); P = 0.01) and third tertile (T/S = 0.70 (0.60–0.88); P = 0.02) (see Figure 1). In standard linear regression analysis, the relation between telomere length and mental health score persisted after adjustment for age and gender (standardised beta = 0.11, P = 0.002; Table 2) and also after further adjustment for variables known to be associated with the severity of heart failure (NYHA class, left ventricular ejection fraction and estimated glomerular filtration rate) or otherwise affecting quality of life (presence of COPD, diabetes and history of stroke) (standardised beta = 0.08, P = 0.022; Table 2).

The median CES-D score of this population was 13 out of 60 (IQR: 7–21). In total, 299 patients (36%) had depressive symptoms (CES-D score ≥ 16) of whom 154 (18%) had severe depressive symptoms (CES-D score ≥ 24). In total, 536 patients (64%) had no depressive symptoms. There were no significant differences in telomere lengths among these groups (P = 0.51). We also did not find a relation between the CES-D score as a continuous variable and telomere length.

Of all patients, 105 (13%) had a type D personality versus 715 (87%) who did not have this personality. Patients with type D personality had a median telomere length of 0.68 (IQR: 0.56–0.82) and patients without type D personality had 0.70 (IQR: 0.60–0.86). There was no statistical significant difference in telomere length between these groups (P = 0.32).

Discussion

This is the first study to show that reduced perceived mental health, as assessed by the RAND-36 questionnaire, is associated with shorter telomere length in patients with CHF. The mechanism by which psychological well-being is associated with telomere length remains to be clarified. However, our observation is consistent with the evidence suggesting that chronic stress may accelerate biological age-

ing [27]. Stress has been associated with chronic increased neurohormonal activation and elevation of blood pressure, which adversely affects outcome in CHF [28, 29]. In addition, psychological stress has also been directly associated with increased levels of oxidative stress [28]. Epel *et al.* suggested that increased oxidative stress explains the association between psychological stress and telomere length in presumably healthy subjects [9, 10]. Thus reduced levels of perceived mental health may have physical repercussions that translate back into progression of CHF. We previously showed that performance score (6-min walk test) of CHF patients is strongly associated with reduced perceived mental health [30]. Telomere length and psychological well-being are both related to the severity of CHF [4, 31]. However, the observed association between telomere length and psychological well-being persisted also after adjustment for several measures of heart failure severity (ejection fraction, NYHA functional class and renal function). Taken together, reduced perceived mental health clusters with shorter telomere length and is associated with decreased functional status. Because of the cross-sectional design, we cannot draw definite conclusions on whether decreased telomere length is a cause or a consequence of reduced perceived mental health.

Others have also reported circumstantial proof of the relationship between stress and telomere biology. Recently, a higher level of pessimism was associated with shorter telomere length in leukocytes of healthy post-menopausal women [32]. In this study, pessimism was also associated with higher basal levels of IL-6, an indicator of systemic inflammation and possibly immune system ageing. Interestingly, also activation of the renin-angiotensin-aldosterone system is associated with increased oxidative stress and inflammation [33]. Recently, activation of the renin-angiotensin-aldosterone system has been associated with reduced leukocyte telomere length in participants of the Framingham Heart Study [34].

Our findings further support the notion that psychological well-being might be implicated in accelerated biological ageing. Given the importance of psychological well-being in determining cardiovascular disease and outcome, our findings might have potential clinical relevance [18, 35]. However, as we do not have longitudinal telomere or psychological stress measurements, we are not able to draw conclusions regarding the causality of the observed relationship. Future studies are needed to (i) replicate our findings and (ii) to study the nature of the observed associations.

Although a clear association seems to exist between telomere length and reduced perceived mental health in general, we were unable to confirm previously reported associations with depressive symptoms and reduced telomere length in leukocytes [7]. This might be due to the simple fact that telomere length is a reflection of cumulative environmental factors over time, and the CES-D score is based on the situation of the patient in the past week only. In addition, this null finding could be due to the population under study as in CHF the additional influence of depressive symptoms on telomere length might be relatively small compared to the condition of CHF itself. In conclusion, shorter telomere length was associated with lower perceived mental health in patients with CHF. Future replication and longitudinal mechanistic studies will be needed to address the causality of this relationship.

Key points

- Telomere length is a marker of biological ageing, and patients with CHF have shorter telomeres than healthy age-related subjects.
- Telomere length is decreased in subjects with psychological disorders.
- Decreased psychological well-being is associated with telomere shortening in patients with CHF.
- Telomere length may be involved in the somatic effects of psychological well-being.

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Conflicts of interest

None declared.

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