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ORIGINAL PAPER

Renal dysfunction is associated with shorter telomere length in heart failure

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Abstract
Background Renal dysfunction is a frequent comorbidity associated with high mortality in patients with chronic heart failure (CHF). The intrinsic biological age might affect the ability of the kidney to cope with the challenging environment caused by CHF. We explored the association between leukocyte telomere length, a marker for biological age, and renal function in patients with CHF.
Methods and results Telomere length was determined by a real-time quantitative polymerase chain reaction in 866 CHF patients. Renal function was estimated with the simplified Modification of Diet in Renal Disease equation. The median age was 74 (interquartile range 64–79) years, 61% male, left ventricular ejection fraction of 30 (23–44)%, and the estimated glomerular filtration rate was 53 (40–68) ml/min/1.73 m^2. Telomere length was associated with renal function (correlation coefficient 0.123, $P < 0.001$). This relationship remained significant after adjustment for age, gender, age of CHF onset (standardized-beta 0.091, $P = 0.007$). Also additionally adjusting for the severity of CHF and baseline differences did not change our findings.
Conclusion The association between shorter leukocyte telomere length and reduced renal function in heart failure suggests that intrinsic biological aging affects the ability of the kidney to cope with the systemic changes evoked by heart failure.

Keywords Telomere · Renal function · Heart failure

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Introduction

Chronic heart failure (CHF) is an age-associated disease with a high prevalence and incidence in Western Society [8, 24]. Risk factors associated with increased mortality in patients with CHF include, hypotension, anaemia, increased BNP levels, activation of the renin-angiotensin system, and decreased renal function [2, 7, 9, 10, 13, 18, 22, 27]. The precise nature of renal dysfunction in CHF patients remains to be elucidated. It has been suggested that the decreased cardiac output, increased inflammation and oxidative stress may challenge the function and integrity of the kidney in patients with CHF [4, 17]. At some point, a glomerulus may be irreversibly damaged, leading to "nephron dropout" and accumulating into a progressive decline of renal function. Recently, we provided preliminary data suggesting a possible association between shorter telomere length and reduced renal function in a retrospective study [23]. We hypothesized that a more advanced intrinsic biological age, reflected by telomere length, increases the susceptibility of the kidney to lose function in the challenged physiological environment evoked by CHF.

Telomeres are considered indicators of biological age and are heritable structures located at the extreme ends of chromosomes. Telomeres consist of specific nucleotide

repeats, in humans TTAGGG [3, 5, 16]. In conjunction with several telomere-binding proteins, telomeres protect chromosomes from recognition and degradation by DNA damage signalling pathways [6]. When telomeres become critically short, they lose their protective function and cells become genetically instable, causing senescence or apoptosis [3]. Telomeres are incompletely replicated by DNA polymerase, causing cumulative attrition of length after each cell division and marking replicative history [16]. Additional telomere attrition can be caused by damaging external factors (e.g., oxidative stress, activation of the renin-angiotensin system) [25, 26]. The aim of our study is to explore whether systemic leukocyte telomere length is associated with renal function in patients with CHF.

Methods

This study was a sub-study of the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) of which the main findings have been published [11, 12]. The COACH-study assessed the value of additional support by a specialized heart failure nurse in the treatment of CHF. Eligible patients were aged 18 years or older, had typical signs and symptoms, and evidence for structural heart disease confirmed by cardiovascular imaging. Patients did not necessarily have to have impaired left ventricular ejection fraction (LVEF). At hospital discharge, patients were stable and on oral heart failure medication. In total, 157 (15%) of the 1,023 patients who participated in the COACH were not included in this sub-study, mainly because of no available DNA ($n = 133$) or missing serum creatinine values ($n = 18$). This study has been approved by the local Medical Ethics Committee. All patients gave written informed consent.

Renal function and telomere length

Glomerular filtration rate (GFR) was estimated at enrollment with the simplified Modification of Diet in Renal Diseases equation [$186.3 \times (\text{serum creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203}$, in women multiplied by 0.742], which is one of the most precise and accurate formulas for calculating GFR [19]. A venous blood sample was taken from the patients during the first outpatient visit and DNA isolated from it according to standard protocols (Qiagen, subsidiary Benelux B.V. Venlo, The Netherlands; QIAmp 96 DNA Blood kit, catalog no. 51162). Mean leukocyte telomere length was measured by quantitative polymerase chain reaction (PCR) in leukocytes, as previously described in detail [21]. Telomere length is expressed as T/S ratio, which is the relative ratio of telomere repeat copy number "T" to a single-gene copy number "S" (36B4). All samples were assayed in triplicates on separate PCR plates, but in same well positions. The mean ± SD coefficient of variation was 7 ± 5% for the T-assay, and 6 ± 4% for S assay.

Statistical analysis

Telomere length ratio was natural log transformed to obtain a normal distribution. Baseline characteristics were compared among quartiles of estimated glomerular filtration rate (eGFR) by one-way analysis of variance, Kruskal–Wallis test, or Chi-square when appropriate. Pearson correlation coefficient was used to assess the association between leukocyte telomere length and renal function. Standard linear regression techniques were used to adjust for age and gender in a second model and additionally for age of CHF onset in a third model. This third basic model was used to subsequently adjust for baseline differences. Because renal function cannot be assumed to be linearly related to leukocyte telomere length, it was also modeled as a fractional polynomial function. A two-sided P value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with use of STATA version 10.0 for Windows software (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics according to quartiles of eGFR are presented in Table 1. The study population consisted of 61% men, median age was 74 years, median LVEF was 30%, with most patients in NYHA class II and III (together 97%). Patients with decreased renal function were less likely to be men, and more likely to be older of age, to have higher NYHA class, hypertension, diabetes, atrial fibrillation or flutter, lower hemoglobin levels, and a previous admission for CHF (Table 1).

Estimated GFR decreased with age at a yearly rate of 0.70 ± 0.058 ml/min/1.73 m^2 ($P < 0.001$). Telomere length ratio decreased steadily at a mean rate of 0.0035 ± 0.00064 per year of increase of age ($P < 0.001$).

Telomere length was 0.719 (interquartile range 0.609–0.881) in the quartile with the highest eGFR, 0.710 (0.604–0.855) in quartile 2, 0.673 (0.582–0.834) in quartile 3, and 0.667 (0.571–0.825) in the quartile with the lowest eGFR ($P = 0.031$). When leukocyte telomere length was modeled as a continuous predictor, renal function decreased gradually with shorter telomere length. Pearson correlation coefficient for the association between telomere length and eGFR was 0.123 ($P < 0.001$). The relationship between renal function and telomere length remained significant after adjustment for gender and age (standardized-beta

Table 1 Baseline characteristics

Patient characteristics	Quartiles of estimated GFR (eGFR)				Total, $n = 866$	P value
	1, $n = 216$	2, $n = 217$	3, $n = 216$	4, $n = 217$		
eGFR (ml/min/1.73 m^2)	79 (73–88)	61 (57–65)	46 (43–49)	31 (26–36)	53 (40–68)	Defining criterion
Creatinine (μmol/l)	83 (71–91)	104 (90–113)	131 (113–141)	174 (153–205)	113 (91–144)	<0.001
Telomere length (T/S ratio)	0.72 (0.61–0.88)	0.71 (0.60–0.85)	0.67 (0.58–0.83)	0.67 (0.57–0.82)	0.69 (0.59–0.85)	0.031
Natural log T/S ratio	−0.37 ± 0.28	−0.34 ± 0.28	−0.32 ± 0.27	−0.31 ± 0.28	−0.34 ± 0.28	0.031
Age	66 (57–74)	73 (64–79)	75 (67–81)	78 (71–81)	74 (64–79)	<0.001
Male gender, *n* (%)	148 (69)	140 (65)	134 (62)	107 (49)	529 (61)	<0.001
NYHA class, *n* (%)						
II	135 (63)	112 (53)	99 (46)	87 (41)	433 (51)	0.001
III	78 (36)	93 (44)	109 (51)	115 (54)	395 (46)	
IV	3 (1)	7 (3)	6 (3)	10 (5)	26 (3)	
Age of onset CHF (year)	64 (54–73)	71 (62–76)	71 (63–78)	74 (68–79)	71 (61–78)	0.001
LVEF (%)	30 (22–40)	30 (21–44)	30 (23–45)	33 (25–43)	30 (23–44)	0.44
Body mass index (kg/m^2)	26.0 (23.5–29.4)	26.3 (23.9–29.7)	26.2 (23.7–29.7)	26.1 (23.0–29.4)	26.1 (23.5–29.6)	0.71
Blood pressure (mmHg)						
Systolic blood pressure	110 (100–125)	120 (105–130)	115 (105–130)	120 (100–137)	115 (101–130)	0.002
Diastolic blood pressure	65 (60–76)	70 (60–80)	65 (60–70)	65 (60–75)	69 (60–75)	<0.001
Heart rate (beats/min)	76 (66–86)	72 (66–80)	72 (64–80)	72 (64–80)	72 (64–82)	0.03
Medical history, *n* (%)						
Diabetes	52 (24)	52 (24)	60 (28)	81 (37)	245 (28)	0.005
Hypertension	81 (38)	77 (35)	93 (43)	113 (52)	364 (42)	0.002
Myocardial infarction	77 (36)	85 (39)	97 (45)	103 (47)	362 (42)	0.05
Atrial fibrillation/ flutter	76 (44)	91 (42)	107 (50)	110 (51)	384 (44)	0.003
Stroke	18 (8)	17 (8)	26 (12)	26 (12)	87 (10)	0.29
Laboratory measurements						
NT-pro-BNP (pg/ml)	2,027 (1,259–4,242)	1,983 (1,130–3,624)	3,016 (1,202–4,742)	4,572 (1,506–10,664)	2,530 (1,259–5,548)	<0.001
Hemoglobin (mmol/l)	8.7 (8.0–9.3)	8.8 (7.9–9.3)	8.3 (7.6–9.1)	7.8 (7.1–8.6)	8.4 (7.6–9.2)	<0.001
Previous admission, *n* (%)	48 (22)	56 (26)	69 (32)	102 (47)	275 (32)	<0.001
Current medication, *n* (%)						
RAS-inhibitors	189 (88)	189 (87)	182 (84)	155 (71)	715 (83)	<0.001
Beta-blockers	145 (67)	149 (69)	141 (65)	135 (62)	570 (66)	0.52
Diuretics	205 (95)	212 (98)	205 (95)	206 (95)	828 (96)	0.39
Digoxin	77 (36)	63 (29)	74 (34)	52 (24)	266 (31)	0.034
Statins	78 (36)	91 (42)	85 (39)	79 (36)	333 (38)	0.56

Normally distributed data is presented as mean ± SD, skewed distributed data as median (interquartile range). The body-mass index is the weight in kilograms divided by the square of the height in meters. Diuretics include loop diuretics, thiazides, and aldosterone antagonists

eGFR estimated glomerular filtration rate, *NYHA* New York Heart Association functional class, *CHF* chronic heart failure, *LVEF* left ventricular ejection fraction, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide, *RAS-inhibitors* renin-angiotensin-system inhibitors (angiotensin-converting enzyme inhibitor and/or angiotensin-receptor blocker)

0.090; Table 2). In the third basic model we also adjusted for the age of CHF onset (Fig. 1). Our findings did not change after additionally adjusting for baseline differences (diabetes, hypertension, history of myocardial infarction, NYHA class, systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, NT-pro-BNP,

Table 2 Univariate and adjusted standardized beta for association between renal function and telomere length

	Standardized-beta	95%CI	*P* value
Model 1	0.123	0.057–0.189	<0.001
Model 2	0.090	0.023–0.157	0.008
Model 3	0.091	0.024–0.158	0.007
Model 3			
+ Diabetes	0.090	0.023–0.157	0.008
+ Hypertension	0.091	0.024–0.159	0.008
+ Previous myocardial infarction	0.092	0.024–0.158	0.007
+ NYHA class	0.085	0.018–0.153	0.013
+ Systolic blood pressure	0.088	0.021–0.155	0.010
+ Diastolic blood pressure	0.090	0.023–0.157	0.009
+ Heart rate	0.090	0.023–0.157	0.009
+ Atrial fibrillation/flutter	0.091	0.024–0.157	0.008
+ NT-pro-BNP	0.103	0.011–0.194	0.028
+ Hemoglobin	0.100	0.010–0.187	0.029
+ RAS-inhibitors	0.074	0.007–0.142	0.031
+ Digoxin	0.094	0.027–0.161	0.006

Model 1: univariate; Model 2: adjusted for age and gender; Model 3; adjusted for age, age of heart failure onset, and gender

NYHA New York Heart Association functional class, *NT-pro-BNP* N-terminal pro-B-type natriuretic peptide, *RAS-inhibitors* renin-angiotensin-system inhibitors (angiotensin-converting enzyme and/or angiotensin-receptor blocker)

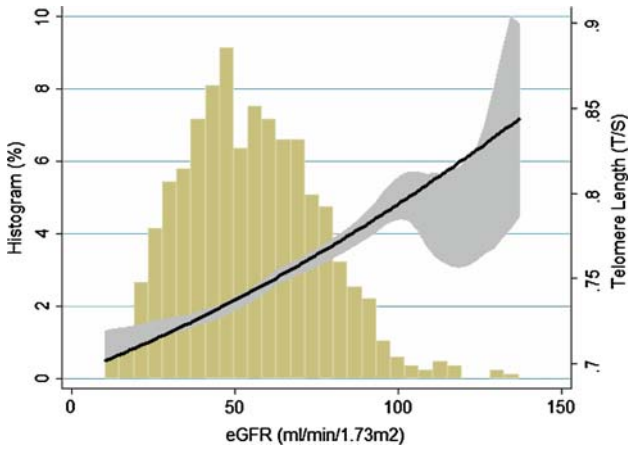

Fig. 1 Renal function histogram and association with telomere length. *Bars* represent the histogram of renal function (*left Y*-axis; percentage of subjects per bar). *Black line* represents the squared relationship between renal function and telomere length after adjustment for age, age of heart failure onset, and gender. The *shaded area* indicate the 95% confidence limits as estimated by the fractional polynomial function

hemoglobin levels, use of renin-angiotensin system inhibitors, and digoxin; Table 2).

Discussion

A frequent co-morbidity factor and powerful predictor of mortality in CHF is decreased renal function [7, 10, 13]. The main finding of this study is that reduced leukocyte telomere length, as a marker for advanced intrinsic biological age, is associated with decreased renal function in patients with CHF. This observation remained significant after adjustment for several confounders, including age, age of CHF onset, and severity of CHF.

Telomere length is associated with CHF. We recently demonstrated telomere length to be shorter in 620 patients with CHF compared to healthy controls [21]. This was also observed by others [15]. In addition, levels of TRF2—one of the telomere-stabilizing proteins—in the myocardium of heart failure patients was found to be down-regulated by approximately 50% compared to healthy controls [15]. Interestingly, Werner et al. found that physical exercise in mice up-regulated TRF2, and protected the myocardium from doxorubicin-induced apoptosis [28]. Thus, telomere biology is not only associated with CHF, but seems to be a modifiable factor in heart failure. Possibly, telomeres are a new therapeutic target in heart failure.

A retrospective analysis of the cohort of 620 CHF patients suggested a potential association between telomere length and renal function [23]. Obviously, retrospective analysis is susceptible to type-1 errors. The current prospective study, however, provides important independent confirmation of these preliminary findings. Reduced renal function might be associated with shorter telomere length in patients with CHF for several reasons. First, the processes biological aging and renal senescence associated with renal function decline includes a decreased ability of aged nephrons to cope with diseased states. CHF elicits systemic changes, including decreased cardiac output, inflammation, oxidative stress, and activation of the renin-angiotensin system [4, 22]. Nephrons with shorter telomeres might be less resistant to these challenges and more likely to enter a senescence state, become dysfunctional or even apoptotic. The phenotype of human renal senescence has indeed been described

previously as the loss of mass and function, including a loss of GFR [14]. Second, leukocytes telomeres mark replicative history and therefore might mark the cumulative inflammatory burden a patient has been exposed to [1]. Inflammation is a major causal factor of vasculo- and glomerulopathy and consequently might cause a decrease in renal function. Finally, other factors associated with biological aging (e.g., accumulation of advanced glycation endproducts) might cause renal dysfunction and coincide with shorter telomere length [20].

The cross-sectional nature of our study does not allow drawing definite conclusions concerning the nature of the observed association. Although we used multiple statistical adjustments, we cannot exclude possible confounding factors that may have obscured the observed relationship.

In conclusion, decreased renal function was associated with reduced leukocyte telomere length in patients with CHF. This observation support the hypothesis that increased intrinsic biological age affects the kidney in its ability to cope with the systemic changes evoked by CHF and might explain, at least in part, why renal function is closely related to mortality in patients with CHF.

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