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Association between kidney function and telomere length: the Heart and Soul Study

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Abstract

Background—Telomere attrition is a novel risk factor for cardiovascular disease. Studies of telomere length in relation to kidney function are limited. We explored the association of kidney function with telomere length and telomere shortening.

Methods—The Heart and Soul study is a longitudinal study of patients with stable coronary heart disease (CHD). Measures of baseline kidney function included: serum creatinine, creatinine-derived estimated glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$), 24-hour urine measured creatinine clearance, cystatin C, cystatin C-derived estimated glomerular filtration rate (eGFRcys) and urine albumin to creatinine ratio. Telomere length was measured from peripheral blood leukocytes at baseline (N=954) and 5 years later (N=608). Linear regression models were used to test the association of kidney function with i) baseline telomere length and ii) change in telomere length over 5 years.

Results—At baseline, mean $eGFR_{CKD\text{-}EPI}$ was 72.6 (± 21.5) ml/min/1.73 m^2, eGFRcys was 71.0 (± 23.1) ml/min/1.73 m^2 and ACR was 8.6 (±12.3) mg/gm. Only lower baseline $eGFR_{CKD\text{-}EPI}$ was associated with shorter baseline telomere length (9.1 [95% CI 1.2–16.9] fewer base pairs for every 5 ml/min/1.73 m^2 lower $eGFR_{CKD\text{-}EPI}$). Lower baseline $eGFR_{CKD\text{-}EPI}$ (and all other measures of kidney function) predicted more rapid telomere shortening (10.8 [95% CI 4.3–17.3] decrease in base pairs over 5 years for every 5 ml/min/1.73 m^2 lower $eGFR_{CKD\text{-}EPI}$). After adjustment for age, these associations were no longer statistically significant.

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Conclusions—In patients with CHD, reduced kidney function is associated with i) shorter baseline telomere length and ii) more rapid telomere shortening over 5 years, however these associations are entirely explained by older age.

Keywords

kidney; CKD; telomere

INTRODUCTION

Telomere length is a novel biomarker of physiologic age and cardiovascular risk. Telomeres are random repeat DNA sequences that form a protective cap at the ends of eukaryotic chromosomes.[1] The role of telomeres is to prevent chromosome ends from being identified as double strand breaks in DNA, thus limiting chromosome shortening and recombination. With natural aging, DNA polymerase is not able to fully replicate the 3′ end of linear DNA, resulting in an obligate and progressive loss of telomere repeats with each cell division – eventually resulting in cellular senescence or apoptosis.[2,3] Chronic diseases may accelerate this process, leading to premature telomere attrition.

Clinical studies have reported that patients with end-stage renal disease (ESRD) may have shorter telomere length and accelerated telomere shortening compared with the general population.[4,5] Studies of severe heart failure patients have reported a strong correlation between reduced kidney function and shorter telomere length, even after adjustment for age.[6,7]

It is possible that chronic kidney disease (CKD) is related to shorter telomere length, and that shorter telomere length may identify individuals with reduced kidney function at highest risk for adverse outcomes. Also, it is possible that persons with decreased kidney function have more rapid telomere shortening over time; however, to our knowledge, no prior study has evaluated this question. The Heart and Soul Study, a cohort of participants with stable coronary heart disease and kidney function ranging from normal to moderate CKD, provides a unique platform to study kidney function and telomere length. Previous studies in Heart and Soul have showed that both shorter telomere length and reduced kidney function are associated with all-cause mortality.[8] [9] In this study, we aimed to test the association of six different measures of kidney function with telomere length and telomere shortening over 5 years.

METHODS

Study design and participants

The Heart and Soul Study is an observational study designed to investigate the influence of psychosocial factors on the progression of coronary heart disease. Methods have been described previously.[10] Briefly, participants were recruited from outpatient clinics in the San Francisco Bay area if they met one of the following inclusion criteria: history of myocardial infarction, angiographic evidence of > 50% stenosis in ≥ 1 coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, history of coronary revascularization, or documented diagnosis of coronary heart disease by an internist or cardiologist. Participants were excluded if they were not able to walk 1 block, had experienced myocardial infarction within the past 6 months, or were likely to move out of the area within 3 years. The study protocol was approved by the Institutional Review Boards of participating institutions, and all participants provided written informed consent. Between September 2000 and December 2002, 1024 participants enrolled and underwent a day-long baseline study appointment that included a medical history, physical examination, and

comprehensive health status questionnaire. Outpatient 24-hour timed urine collections and fasting (12-hour) morning venous blood samples were obtained at baseline. Longitudinal follow-up for the Heart and Soul study is still ongoing.

Measures of Kidney function

All Heart and Soul participants were eligible for our study, regardless of baseline renal function. We evaluated six measures of kidney function: serum creatinine, creatinine-derived estimated glomerular filtration rate (GFR) ($eGFR_{CKD\text{-}EPI}$), creatinine clearance (CrCl), serum cystatin C, cystatin C-derived estimated GFR (eGFRcys) and urine albumin to creatinine ratio. Serum creatinine was measured by the rate Jaffe method (mg/dL). $eGFR_{CKD\text{-}EPI}$ was calculated using serum creatinine.[11] CrCl was measured from 24-hour urine collections by protocol that has been described previously.[12] In brief, participants received detailed instructions on accurate urine collection and specimen refrigeration. Subjects were asked to void at the end of their study appointment and to begin the collection from that point forward. Research personnel arrived at the patient's home 24 hours after the timed collection was initiated to avoid over- or under-collection. If participants reported missing any urine or collections were < 1 or > 3 liters, collections were repeated. When participants were unable to collect all urine for any reason, no data were recorded. Urine volume was recorded (mL), and creatinine was measured by the rate Jaffe method. CrCl was calculated by urine creatinine x urine volume/serum creatinine x 1440 and expressed as ml/min. Cystatin C was measured from frozen samples collected at the baseline study visit with the use of a BNII nephelometer (Dade Behring, Inc, Deerfield, Ill) with a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring, Inc).[13] The intra-assay CV was 2.0–2.8% and the inter-assay CV was 2.3–3.1%. Serum cystatin C was log-transformed for all analyses given the skewed distribution. GFR was estimated using cystatin C with the formula: eGFRcys=76.7x cystatin $C^{-1.19}$.[14] Urinary albumin and creatinine were measured by nephelometry and the rate Jaffe method, respectively. A urine albumin to creatinine ratio was calculated in mg/g and log transformed given the skewed distribution.

Measurement of telomere length

Our study outcomes were: (1) telomere length at baseline and (2) change in telomere length from baseline to year 5. Baseline DNA samples were not available for 70 of the 1024 study participants, so telomere length was measured in 954 participants. Of these, 608 participants (>80% of survivors) had a repeat measurement after 5 years.

At both visits, genomic DNA was isolated according to standard procedures from peripheral blood leukocytes and stored at −70°C. Purified DNA samples were diluted in 96-well microtiter source plates to a fixed concentration of 3 ng/μL.[15] Telomere length was measured by a quantitative polymerase chain reaction (qPCR) assay that compares mean telomere repeat sequence copy number (T) to a reference single-copy gene copy number (S) in each sample and validated by comparison with Southern blot terminal restriction fragment analysis.[16] All PCRs were carried out on a Roche Lightcycler 480 real-time PCR machine (Roche Applied Science, Indianapolis, Indiana).[15]

Telomere length was measured in T/S ratio units. The relative quantity of the single copy gene (S) in each experimental sample was expressed as the level of dilution of the reference DNA sample needed to match it to the experimental sample with regard to the number of cycles of PCR needed to generate a given amount of single copy gene PCR product during the exponential phase of the PCR (T). For each experimental sample the ratio of these dilution factors is the relative telomere to single copy gene (T/S) ratio.[16] Thus T/S = 1 when the unknown DNA is identical to the reference DNA in its ratio of telomere repeat

copy number (T) to single copy gene copy number (S). The reference DNA sample (to which all of the experimental samples in a given study are compared) was from a pooled sample from multiple individuals. The T/S ratio of one individual relative to the T/S ratio of another should correspond to the relative telomere lengths of their DNA. The T/S ratio was measured twice in each individual at each time point, and results were averaged. When the duplicate T/S value and the initial value differed by more than 7%, the sample was run for a third time and the 2 closest values were used to calculate the mean. Approximately 15% of the samples required assay in triplicate. Using this method, we observed inter-assay coefficient of variation (CV) for telomere length measurement is 3.7% and the intra-assay CV is 2.5%.[15] Similar to other analyses within Heart and Soul, we converted the T/S ratio to base pairs using the formula: base pairs=3274 +2413*(T/S).[17]

Covariates

All covariates were taken from the baseline study visit and examination. Demographics (age, sex and race) and medical history (history of smoking, hypertension, diabetes, heart failure, myocardial infarction or stroke) were determined by questionnaire. Participants underwent a complete physical examination that included blood pressure determination by trained study personnel using calibrated sphygmomanometers. Body mass index was calculated by measured weight (kg) divided by height (meters) squared. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications, including aspirin, beta-blockers, angiotensin converting enzymes (ACE) inhibitors and angiotensin receptor blockers (ARBs).

High-sensitivity C-reactive protein was measured with the use of the Roche Integra assay and the Beckman Extended Range assay as previously described[9] and was log-transformed for this analysis. Fasting serum samples were used to measure total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedewald equation.[18]

Statistical methods

We compared baseline characteristics of participants across quartiles of baseline telomere length using t-tests and ANOVA as appropriate. We then used linear regression to explore the cross-sectional association between each of the six measures of kidney function and telomere length at baseline, first in unadjusted analyses and then adjusted for age. Prior work has shown that baseline telomere length is strongly associated with subsequent change in telomere length.[17] Therefore we calculated a change score that was adjusted for baseline telomere length by performing linear regression to examine the association between baseline telomere length and change in telomere length. The residual from the model was used as the outcome variable in subsequent models in which we then examined the association between measures of kidney function and change in telomere length over 5 years (in unadjusted analyses and then in models adjusted for age).

All analyses were conducted using SAS (Cary, NC) and p-values < 0.05 were considered evidence of statistical significance.

RESULTS

Among the 954 participants with telomere measures at baseline, mean age was 66.7 (±11.0) years, 18.6% were female and 16.5% were Black. Mean serum creatinine was 1.1 (± 0.7) mg/dL, $eGFR_{CKD\text{-}EPI}$ was 72.6 (± 21.5) ml/min/1.73 m^2, CrCl was 92.3 (± 35.9) ml/min, cystatin C was 1.20 (± 0.56) mg/L, eGFRcys was 71.0 (± 23.1) ml/min/1.73 m^2 and urine albumin to creatinine ratio was 8.6 (±12.3) mg/gm. Mean baseline telomere length was

5444.502 (± 529.34) base pairs. The ranges for the quartiles of baseline telomere length were as follows: quartile 1 (4294–5062 base pairs), quartile 2 (5065–5388 base pairs), quartile 3 (5391–5778 base pairs) and quartile 4 (5779–7470 base pairs). Those with the shortest telomere length at baseline were older, less likely to be Black, more likely to have a history of stroke and were less likely to be taking aspirin (Table 1).

There was no association between serum creatinine, CrCl, cystatin C, eGFRcys or albuminuria and quartile of baseline telomere length in cross-sectional analyses (Table 2). When entered as continuous variables, $eGFR_{CKD\text{-}EPI}$ was associated with shorter telomere length: for every 5 ml/min/1.73 m^2 lower $eGFR_{CKD\text{-}EPI}$, there were 9.1 fewer base pairs (95% CI 1.2–16.9, p=0.02). However, this association was no longer statistically significant after adjustment for age (Table 3).

In longitudinal analyses, higher serum creatinine, lower CrCl, lower $eGFR_{CKD\text{-}EPI}$, higher Cystatin C and lower eGFRcys were all associated with greater telomere shortening over 5 years (Table 4). Again, after adjustment for age, these associations were no longer statistically significant.

DISCUSSION

Leukocyte telomere length has emerged as a novel cardiovascular risk factor in the general population and with a poor prognosis among patients with existing CHD. However, the relationship of telomere length and kidney function remains unexplored and may be an important contributor to adverse cardiovascular outcomes among patients with CKD. We found that patients with decreased kidney function had greater shortening of telomere length over 5 years. However, after adjustment for age, this association was no longer significant. These findings suggest that telomere shortening and worsening kidney function are parallel processes that occur with aging.

We found that patients with decreased kidney function had greater shortening of telomere length over 5 years. However, after adjustment for age, this association was no longer significant, consistent with natural aging confounding this relationship. There is great interest in studying telomere length in kidney health [19,20] however clinical studies are limited. Previous studies have suggested that telomere length is shorter in patients with ESRD on dialysis compared with the general population. For example, in a study of 15 hemodialysis patients and 15 age-matched controls, the authors found accelerated telomere shortening in the dialysis patients.[21] Another study of 18 diabetic dialysis patients and 20 controls found an inverse correlation between telomere length and length of time on dialysis.[4] A study of 42 hemodialysis patients found that telomerase activity was reduced compared with non-hemodiaysis patients.[5] There are very limited data on the associations between telomere length and kidney function among persons with less severe kidney disease. Similar to our results, a study of older adults in the Cardiovascular health study reported no association between telomere length and Cystatin C after adjustment for age, gender and race.[22] Previous studies of heart failure patients with normal kidney function reported a strong correlation between reduced kidney function and shorter telomere length, even after adjustment for age.[6,7] Our results differ from these prior studies suggesting that associations between kidney function and telomere shortening are entirely explained by age. However these studies evaluated persons with decreased ejection fraction and also relied solely on creatinine-based measurements of kidney function. Our study added to previous studies by examining multiple markers of renal function. In particular, studies of sicker (such as heart failure) or elderly patients may misclassify level of kidney function if they rely on creatinine-based measures of kidney function alone. While our results were differed from the prior studies of ESRD and heart failure patients, they were consistent with the

results of the study of older adults. Further studies are needed to elucidate if telomere biology differs in varying patient populations.

Our findings have implications in the study of cardiovascular risk in patients with CKD. In the general population, shortened telomere length has emerged as a novel risk factor linked to higher rates of cardiovascular disease and mortality. For example, in a nested case-control study of middle aged high risk men, the risk of coronary heart disease was almost double in those in the lower two tertiles of telomere length compared with those in the highest tertile.[23] Another study of 1,136 older participants in the Cardiovascular Health Study found that persons with the shortest quartile of telomere length were more likely to die of any cause compared with persons in the highest quartile.[24] A few studies have also suggested that reduced telomere length is associated with mortality among dialysis patients as well. One study of 175 prevalent hemodialysis patients found that reduced telomere length was associated with mortality even after adjustment for age, gender and inflammation.[25] However our study suggests that accelerated telomere shortening is unlikely to contribute to the high burden of morbidity and mortality among patients with decreased kidney function (not on dialysis) independent of other risk factors such as advanced age.

Our study had several strengths. We studied a relatively large, well-characterized cohort of patients with stable coronary heart disease. We had six unique urine and serum markers of kidney function. We utilized a large cohort with measures of telomere length, many of whom had repeat measures of telomere length after 5 years. Our study also has important limitations. Of the participants with kidney disease, most had mild to moderate CKD, low levels of proteinuria, and well-controlled hypertension, and therefore our results may not be generalizable to a population with advanced stages of CKD due to diabetic nephropathy or glomerulonephritis. Participants were older, mostly male and had stable coronary heart disease. Results may differ in other populations. Telomere length was measured from peripheral leukocytes rather than in directly in renal tubular cells. However this is a commonly used measure of telomere length in clinical studies and widespread renal biopsies are neither practical nor ethical to carry out.

In conclusion, we found that decreased kidney function was not independently associated with shortened telomere length or telomere shortening over 5 years. Further longitudinal clinical studies evaluating other novel factors linked with both decreased kidney function and cardiovascular disease are needed to explore mechanisms linking these two highly prevalent and morbid conditions.

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Table 1

Baseline characteristics of study population by baseline telomere length (N=954)*

Characteristic	Quartile 1 4294– 5062 base pairs N=239	Quartile 2 5065– 5388 base pairs N=238	Quartile 3 5391–5778 base pairs N=238	Quartile 4 5779 –7470 base pairs N=239	P-value
Age (years)	70.0 ± 10.1	66.6 ± 9.9	65.7 ±11.1	64.6 ±12.0	<0.001
Female (%)	17	21	18	18	0.8
Black	11	13	19	23	<0.001
Hypertension (%)	69	69	73	72	0.7
Diabetes (%)	27	30	24	25	0.4
Heart failure (%)	18	17	17	16	0.9
Myocardial infarction (%)	58	53	50	54	0.3
Stroke (%)	21	14	10	11	0.002
Tobacco use (%)	21	18	21	20	0.9
Systolic blood pressure (mm Hg)	132 ± 19	135. ± 24	134 ± 22	132 ± 19	0.2
Diastolic blood pressure (mm Hg)	74 ± 10	75 ± 12	75 ± 12	74 ± 11	0.5
Aspirin use (%)	68	68	76	80	0.006
B-blocker use (%)	53	59	61	59	0.3
ACE inhibitor/ARB use (%)	47	52	53	56	0.3
C-reactive protein† (g/dL)	2.36 (4.19)	2.20 (4.32)	1.99(3.77)	2.42(4.20)	0.7281
HDL cholesterol (mg/dL)	46 ± 15	45. ± 15	45 ± 13	46 ± 14	0.5
LDL cholesterol (mg/dL)	106 ± 36	104 ± 33	102 ± 33	105 ± 34	0.7

* reported as mean ± SD, unless otherwise specified

† median (IQR)

Table 2

Baseline measures of kidney function by baseline telomere length (N=954)*

Measure of kidney function	Quartile 1 4294– 5062 base pairs N=239	Quartile 2 5065– 5388 base pairs N=238	Quartile 3 5391–5778 base pairs N=238	Quartile 4 5779 –7470 base pairs N=239	P-value
Serum creatinine (mg/dL)	1.2 ± 0.6	1.1 ± 0.4	1.2 ± 0.8	1.2 ± 0.7	0.4
Urine CrCl (ml/min/1.73 m^2)	88.8 ± 36.4	94.0 ± 36.4	91.7 ±35.0	94.6 ±35.7	0.3
$eGFR_{CKD-EPI}$ (ml/min/1.73 m^2)	70.2 ± 21.4	73.5 ±20.1	72.7 ±21.6	74.1 ±22.6	0.2
Cystatin C (mg/L)	1.24 ± 0.67	1.16 ± 0.40	1.21 ±0.59	1.18 ±0.57	0.4
eGFRcys (ml/min/1.73 m^2)	70.5 ± 27.5	71.3 ± 21.1	69.7 ±21.0	72.4 ±22.4	0.6
Urine albumin to creatinine ratio (mg/gm)†	8.4 (12.1)	9.4 (13.7)	9.1 (12.2)	8.1 (10.3)	0.3

*reported as mean ± SD, unless otherwise specified

†median (IQR)

Table 3

Cross-sectional association between baseline measures of kidney function and baseline telomere length (N=954)

(coefficients represent change in number of base pairs for each unit of worsening kidney function)

Measure of kidney function	Unadjusted β-coefficient (95% CI)	Adjusted for age β-coefficient (95% CI)
Serum creatinine (per 1 mg/dL increase)	1.0 (−50.9, 52.9)	8.6 (−42.5, 59.7)
CrCl (per 5 ml/min decrease)	−3.8 (−8.7,1.0)	1.7 (−3.5, 7.0)
$eGFR_{CKD\text{-}EPI}$ (per 5 ml/min/1.73 m^2 decrease)	−9.1 * (−16.9, −1.2)	1.6 (−7.1, 10.3)
Log Cystatin C (per log mg/L increase)	−69.2 (−174.3, 36.0)	12.0 (−95.5, 119.4)
eGFRcys (per 5 ml/min/1.73 m^2 decrease)	−3.7 (−11.0, 3.7)	3.3 (−4.3, 10.9)
Log Urine albumin to creatinine ratio (per log mg/gram increase)	−14.8 (−39.7,10.1)	−8.1 (−32.8, 16.6)

* P<0.05

Table 4

Longitudinal association between baseline measures of kidney function and change in telomere length over 5 years (from baseline to Y5)* (N=608)

(Coefficients represent number of base pairs change associated with each unit of worsening kidney function; positive coefficient represents telomere lengthening; negative coefficient represents telomere shortening)

Measure of kidney function	Unadjusted β-coefficient (95% CI)	Adjusted for age β-coefficient (95% CI)
Serum creatinine (per 1 mg/dL increase)	−47.8* (−93.3, −2.2)	−42.1 (−85.8, 1.7)
CrCl by 24 hour urine collection (per 5 ml/min decrease)	−3.6* (−7.8, −0.1)	1.2 (−2.8, 5.1)
$eGFR_{CKD\text{-}EPI}$ (per 5 ml/min/1.73 m^2 decrease)	−10.8* (−17.3, −4.3)	−0.4 (−7.4, 6.7)
Log Cystatin C (per log mg/L increase)	−139.8* (−231.1,−48.6)	−54.6 (−146.2, 37.1)
eGFRcys (per 5 ml/min/1.73 m^2 decrease)	−9.7* (−15.5, −3.9)	−3.4 (−9.4, 2.5)
Log Urine albumin to creatinine ratio (per log mg/gram increase)	−6.9 (−28.5,14.7)	−5.4 (−26.1, 15.4)

*P<0.05