

Association of Leukocyte Telomere Length With Circulating Biomarkers of the Renin-Angiotensin-Aldosterone System The Framingham Heart Study

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Background—Leukocyte telomere length (LTL) chronicles the cumulative burden of oxidative stress and inflammation over a life course. Activation of the renin-angiotensin-aldosterone system is associated with increased oxidative stress and inflammation. Therefore, LTL may be related to circulating biomarkers of the renin-angiotensin-aldosterone system.

Methods and Results—We evaluated the cross-sectional relations of LTL (dependent variable) to circulating renin and aldosterone concentrations and the renin-to-aldosterone ratio (all logarithmically transformed; independent variables) in 1203 Framingham Study participants (mean age, 59 years; 51% women). We used multivariable linear regression and adjusted for age, blood pressure, hypertension treatment, smoking, diabetes mellitus, body mass index, hormone replacement therapy, serum creatinine, and the urine sodium-to-creatinine ratio. Overall, multivariable-adjusted LTL was inversely related to renin (β coefficient per unit increase, -0.038 ; $P=0.036$), directly related to aldosterone ($\beta=0.099$; $P=0.002$), and inversely related to the renin-to-aldosterone ratio ($\beta=-0.049$; $P=0.003$). Relations of LTL to biomarkers were stronger in those with hypertension, although a formal test of interaction was not statistically significant ($P=0.20$). Individuals with hypertension displayed significant associations of LTL with renin ($\beta=-0.060$; $P=0.005$), aldosterone ($\beta=0.134$; $P=0.002$), and renin-to-aldosterone ratio ($\beta=-0.072$; $P<0.001$). Participants with hypertension who were in the top tertile of the renin-to-aldosterone ratio had LTL that was 182 base pairs shorter relative to those in the lowest tertile.

Conclusions—In our community-based sample, LTL was shorter in individuals with a higher renin-to-aldosterone ratio, especially in participants with hypertension. Additional investigations are warranted to confirm our observations. (*Circulation*. 2008;117:1138-1144.)

Key Words: aldosterone ■ epidemiology ■ hypertension ■ oxidative stress ■ renin ■ telomere

Telomeres are tandem repeats of TTAGGG at the ends of chromosomes that preserve genomic integrity and progressively shorten with replication of cultured somatic cells.¹ Telomeres demonstrate age-dependent shortening in proliferative somatic cells in vivo.² Therefore, at any age, leukocyte telomere length (LTL) represents the balance between LTL at birth and the attrition that occurs thereafter. In clinical studies, shorter age-adjusted LTL has been associated with metabolic (oxidative stress, inflammation),³⁻⁶ structural (ath-

erosclerosis and arterial stiffness),⁷⁻¹⁰ and environmental (cigarette smoking and obesity)^{11,12} indices of cardiovascular disease.

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Telomere length is a record of the replicative history of somatic cells¹³ because telomere repeats are lost with each cell division; such a loss is heightened with oxidative stress.^{14,15} These features might render LTL a valuable index

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of metabolic factors predisposing to atherosclerosis. First, inflammation, which enhances the turnover rate of leukocytes, increases the pace of LTL shortening. Second, as oxidative stress increases the rate of telomere attrition per cell division, it also accelerates LTL shortening. Accordingly, LTL chronicles the cumulative burden of inflammation and oxidative stress over the lifetime of an individual. Both inflammation and oxidative stress are major determinants in atherosclerosis, a process that is contingent on the continued recruitment of leukocytes¹⁶ and increased oxidative stress at the interface of the endothelium with blood.¹⁷ Such a process usually takes place over the course of many years, and it would be expressed by a higher pace of LTL attrition and shorter LTL.

On a parallel note, substantial data implicate increased activation of components of the renin-angiotensin-aldosterone system (RAAS) in the atherosclerotic process. The 2 major components of the RAAS are its primarily vasoactive arm, the renin-angiotensin system (RAS), and its primarily sodium-regulating arm, aldosterone, both of which evoke oxidative stress and inflammatory responses.^{18–21} We do not know, however, which of these 2 arms of the RAAS provokes comparatively more inflammation/oxidative stress *in vivo* and therefore might increase atherosclerotic risk more relative to the other. Given that LTL attrition chronicles the cumulative burden of inflammation/oxidative stress and is associated (inversely) with atherosclerosis,^{7,9,10} our objective was to relate LTL to circulating renin and aldosterone concentrations in a community-based sample to obtain insights into the issues noted above.

Methods

Study Sample

In 1971, 5124 offspring (and their spouses) of the original Framingham Heart Study participants were enrolled in the Framingham Offspring Study.²² The sixth examination of this cohort occurred from 1995 to 1998 and was attended by 3532 individuals. In total, 1589 DNA samples from the sixth examination were available for LTL analysis. These subjects were selected to be biologically unrelated. Among the 1589 subjects, we excluded 386 individuals because of missing data on plasma renin or serum aldosterone ($n=41$) or inadequate quality or amount of DNA for LTL measurements ($n=345$). After these exclusions, 1203 individuals remained eligible for the present investigation. Participants included in the present investigation were not systematically different from the sample of eligible attendees who were not included (Appendix Table I in the online Data Supplement). The study protocol was approved by the Institutional Review Board at Boston University Medical Center, and all participants provided written informed consent.

Clinical Evaluation

At the sixth examination cycle (referred to as the index examination), all attendees underwent standardized evaluations, including medical history and physical examination, anthropometry, and laboratory assessment of cardiovascular risk factors. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications.²³ Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or use of insulin or hypoglycemic medications.²⁴ Participants were considered current cigarette smokers if they reported having smoked cigarettes regularly during the previous year.

Measurement of Renin, Aldosterone, and Urinary Sodium

At the index examination, venous blood was drawn from fasting study participants, typically between 8 AM and 9 AM, with the participants in a recumbent position for ≈ 5 to 10 minutes before the phlebotomy; participants were ambulatory before the blood draw. Blood specimens were centrifuged immediately, and serum/plasma was stored at -80°C without repeat freeze-thaw cycles until their assay in 2002.

Serum aldosterone concentration was measured from extracted and fractionated serum with a highly sensitive and specific radioimmunoassay (Quest Diagnostics, Cambridge, Mass) with a sensitivity of <1 ng/dL.²⁵ The intra-assay coefficient of variation (CV) ranges from 3.8% (for high concentrations) to 6% (low concentrations) with corresponding interassay CVs varying from 4.0% to 9.8%. Plasma renin concentration was measured with a highly sensitive and specific immunochemiluminometric assay (Nichols Advantage Direct Renin Assay, Quest Diagnostics).²⁶ The intra-assay CV ranges from 3.7% (at high levels) to 7.2% (at low levels), with the corresponding interassay CV ranging from 4.9% to 10%. This direct renin assay yields measurements that have a high degree of correlation with the plasma renin activity.^{27,28} Serum high-sensitivity C-reactive protein was measured with a Dade Behring BN100 nephelometer (Dade Behring Inc, Newark, Del) with an intra-assay CV of 2.2%.

Spot urine samples (3 mL) were collected at the index examination at the time of phlebotomy, temporarily stored at -4°C for up to 4 hours, and maintained at -20°C until analysis. Urine samples were thawed at room temperature, and urine sodium was measured with an automated ion-electrode method. Samples were analyzed in duplicate with an average intra-assay CV of 0.8%. Urinary creatinine concentration was determined by use of a modified Jaffe method with an average intra-assay CV of 1.7% to 3.8%. Urinary sodium excretion was expressed as millimoles of sodium per gram of urinary creatinine (referred to as urine sodium index).²⁹

LTL Measurements

We performed Southern blot analyses and obtained the mean of the terminal restriction fragment lengths in DNA extracted from leukocytes. We refer to this mean as the LTL. Details of the method to measure LTL, including an illustrative figure (Appendix Figure I), are presented in the online Appendix. The CV for this approach (for samples measured in duplicate or triplicate on different gels and occasions and by 2 researchers) was 2.4%.

Statistical Analyses

We used multivariable linear regression models to relate serum aldosterone and plasma renin (independent variables modeled jointly) to LTL (dependent variable). Serum aldosterone and plasma renin concentrations were treated as continuous variables (natural logarithmic-transformed values because of a positively skewed distribution). We also related LTL to the ratio of the 2 biomarkers and present the results for the renin-to-aldosterone ratio (as opposed to the more conventionally used aldosterone-to-renin ratio) for ease of interpretation (see Results). The renin-to-aldosterone ratio was modeled as a continuous ratio and as tertiles. Because no evidence was found of effect modification of the relations of serum aldosterone and plasma renin and LTL by sex, all analyses were sex pooled, with sex incorporated as a covariate.

Two sets of models were constructed, a model that adjusted for age and sex alone and multivariable models that additionally adjusted for covariates known to influence LTL^{3,4,6,11,12} and plasma renin and aldosterone concentrations^{30,31}: age, sex, systolic and diastolic blood pressures, hypertension treatment, current smoking status, diabetes mellitus, serum creatinine, urine sodium index, body mass index, and hormone replacement therapy. We tested for effect modification by age and hypertension status by incorporating corresponding interaction terms in multivariable models.

Because any association of biomarkers of the RAAS with LTL may be mediated by their proinflammatory effects, we performed

Table 1. Characteristics of Framingham Heart Study Sample and Nonhypertensive Subgroup at Examination 6

	Entire Sample (n=1203)*		Nonhypertensive† Sample		Hypertensive Participants	
	Men (n=580)	Women (n=623)	Men (n=314)	Women (n=371)	Men (n=263)	Women (n=251)
Age, y	60±10	59±9	57±9	56±9	64±9	62±8
Body mass index, kg/m ²	28.5±4.5	27.3±5.6	28.2±4.7	26.4±4.9	28.9±4.1	28.8±6.2
Systolic blood pressure, mm Hg	131±18	129±20	121±10	118±12	143±18	145±19
Diastolic blood pressure, mm Hg	77±9	74±9	75±7	71±7	80±11	78±10
Hypertension at exam 6,‡ %	46	40	0	0	100	100
On any treatment	70	65
On diuretics	11.0	25
On ACE inhibitors	32	26
On β -blockers	23	26
On calcium channel blockers	26	19
On α -1 AR blockers	2	0.4
Ratio of total to HDL cholesterol	4.82±1.5	3.93±1.4	4.86±1.6	3.80±1.5	4.77±1.4	4.12±1.3
Diabetes mellitus,§ %	16	10	12	5	20	18
Current smoker, %	13	15	16	16	10	13
Prevalent cardiovascular disease, %	14	7	9	3	21	14
Premenopausal, %	...	24	...	32	...	11
Postmenopausal on HRT, %	...	26	...	26	...	27
Postmenopausal no HRT, %	...	50	...	42	...	61
Serum creatinine, mg/dL	1.26±0.2	1.11±0.3	1.25±0.2	1.1±0.2	1.27±0.2	1.14±0.4
Urine Na-to-Cr ratio, mmol/g	106	121	104	117	108	125
Serum aldosterone, ng/dL (Q1, Q3)	10 (7, 14)	10 (7, 15)	10 (7, 14)	10 (7, 14)	10 (7, 14)	10 (7, 15)
Plasma renin, μ U/mL (Q1, Q3)	15 (8, 25)	11 (6, 20)	15 (9, 24)	11 (7, 18)	14 (7, 31)	11 (5, 28)
Renin-to-aldosterone ratio, μ U \cdot mL ⁻¹ /ng \cdot dL ⁻¹ (Q1, Q3)	1.5 (0.9, 2.6)	1.1 (0.6, 2.0)	1.55 (1.0, 2.3)	1.2 (0.7, 1.9)	1.4 (0.8, 3.2)	1.0 (0.5, 2.4)
Leocyte telomere length, kb (Q1, Q3)	6.88±0.56	7.04±0.59	6.95±0.57	7.08±0.60	6.80±0.54	6.97±0.57

Values are reported as mean±SD for continuous traits and percent for dichotomous traits. Because serum aldosterone, renin, and renin-to-aldosterone ratio are skewed, median values (25th percentile to 75th percentile) are shown. ACE indicates angiotensin-converting enzyme; AR, adrenergic receptor; HDL, high-density lipoprotein; Na, sodium; and Cr, creatine.

*For Hypertension at exam values, see Hypertensive Participants.

†Nonhypertensive participants at baseline exam 6 were defined by systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, and absence of antihypertensive treatment.

‡Shown are the percentages of participants with treated and untreated hypertension.

§Diabetes was determined by use of hypoglycemic agents or fasting glucose \geq 126 mg/dL.

||Note that the urine Na-to-Cr ratio was available for the subset of 1066 (511 men).

secondary analyses adjusting for C-reactive protein in the multivariable models, in addition to the covariates listed above. Antihypertensive agents differentially affect plasma renin and aldosterone concentrations: Diuretics raise aldosterone and renin levels; angiotensin-converting enzyme inhibitors raise renin levels but lower aldosterone levels; β -blockers inhibit renin; and calcium channel blockers are generally neutral. Therefore, we conducted exploratory analyses to assess whether the association of LTL with biomarkers varied among treated and untreated participants with hypertension by incorporating appropriate interaction terms for use of antihypertensive medications in a model that evaluated the subgroup of participants with hypertension.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

General Characteristics

The characteristics of our study sample (mean age, 59 years; 51% women) are displayed in Table 1. More than 40% of

men and women in our sample had hypertension; Appendix Table II in the online-only Data Supplement details the use of antihypertensive medications in these individuals by drug class. The mean values and overall distribution of serum aldosterone were similar in men and women, whereas plasma renin levels were slightly higher in men, consistent with our prior reports on a larger sample.^{30,31}

Serum aldosterone and plasma renin were positively correlated (age- and sex-adjusted Spearman $r=0.21$, $P<0.001$). The rate of LTL attrition with age for the entire cohort was 22 ± 1.7 base pairs (bp) per year ($r=-0.35$, $P<0.001$). Age-adjusted LTL was longer in women than men (by 124 bp; men, 6.90 ± 0.02 kilobases (kb); women, 7.02 ± 0.02 kb; $P<0.001$) and in “never smokers” than current smokers (never smokers, 7.0158 ± 0.03 kb; current smokers, 6.84 ± 0.04 kb; $P=0.0012$). Body mass index was related inversely to LTL (decrease of 11 ± 3 bp per unit increase; $P<0.001$).

Table 2. Regression of LTL on Log (Aldosterone) and Log (Renin) Conjointly and on Log (Renin-Aldosterone Ratio)

Model, Adjustment/Variable	All Participants			Nonhypertensive			Hypertensive		
	β	SE	<i>P</i>	β	SE	<i>P</i>	β	SE	<i>P</i>
Incorporating aldosterone and renin conjointly									
Age, sex									
Log (aldosterone)	0.082	0.03	0.004	0.063	0.04	0.15	0.092	0.04	0.02
Log (renin)	−0.039	0.02	0.012	−0.009	0.03	0.77	−0.053	0.02	0.003
Multivariable									
Log (aldosterone)	0.099	0.03	0.002	0.058	0.05	0.22	0.134	0.04	0.002
Log (renin)	−0.038	0.02	0.036	0.001	0.03	0.99	−0.060	0.02	0.005
Incorporating the renin-aldosterone ratio									
Age, sex									
Log (ratio)	−0.047	0.02	0.002	−0.022	0.03	0.45	−0.058	0.02	<0.001
Multivariable									
Log (ratio)	−0.049	0.02	0.003	−0.014	0.03	0.67	−0.072	0.02	<0.001

Multivariable models adjusted for age, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment (when appropriate), current smoking status, diabetes mellitus, serum creatinine, urine sodium-to-creatinine ratio, body mass index, and hormone replacement therapy. SE indicates standard error of β . β is the regression coefficient per unit increase in log (predictor).

Associations Between LTL and Aldosterone, Renin, and Renin-to-Aldosterone Ratio

Table 2 displays the results of regression analyses relating aldosterone, renin, and the renin-to-aldosterone ratio to LTL in the whole sample and stratified by hypertension status. Modeled together, after adjustment for covariates, LTL was inversely related to renin ($P=0.036$) and directly related to aldosterone ($P=0.002$). Results were similar when renin and aldosterone were modeled individually (online-only Data Supplement Appendix Table III). LTL was inversely related to the renin-to-aldosterone ratio ($P=0.003$).

We did not observe effect modification by hypertension status ($P=0.20$ for interaction). Nevertheless, we stratified all analyses by hypertension status (Table 2), given the limited power to detect significant interactions and the fundamental role of the RAS in hypertension. In these analyses, we observed in participants with hypertension statistically significant relations of LTL with renin (inverse; $P=0.005$), aldosterone (positive; $P=0.002$), and renin-to-aldosterone ratio (inverse; $P<0.001$). Relations of LTL to RAAS biomarkers

were not statistically significant in nonhypertensive individuals. It is noteworthy that we had adequate statistical power to detect associations of a similar magnitude in the subsets without and with hypertension; we had 80% power to detect partial correlations of the biomarkers with LTL of 0.107 ($R^2=1.1\%$) and 0.124 ($R^2=1.54\%$), respectively, in the 2 groups.

The Figure displays the adjusted least-squares mean LTL according to tertiles of the renin-to-aldosterone ratio in the overall sample and in nonhypertensive and hypertensive participants. In the overall sample, individuals in the top tertile of the ratio had an LTL that was 108 bp shorter relative to those in the lowest tertile. Corresponding differences among nonhypertensive and hypertensive individuals (top compared with lowest tertile) were 59 and 182 bp, respectively.

Table 3 displays the results of analyses with additional adjustment for C-reactive protein. The associations seen in Table 2 remain robust after additional adjustment for C-reactive protein.

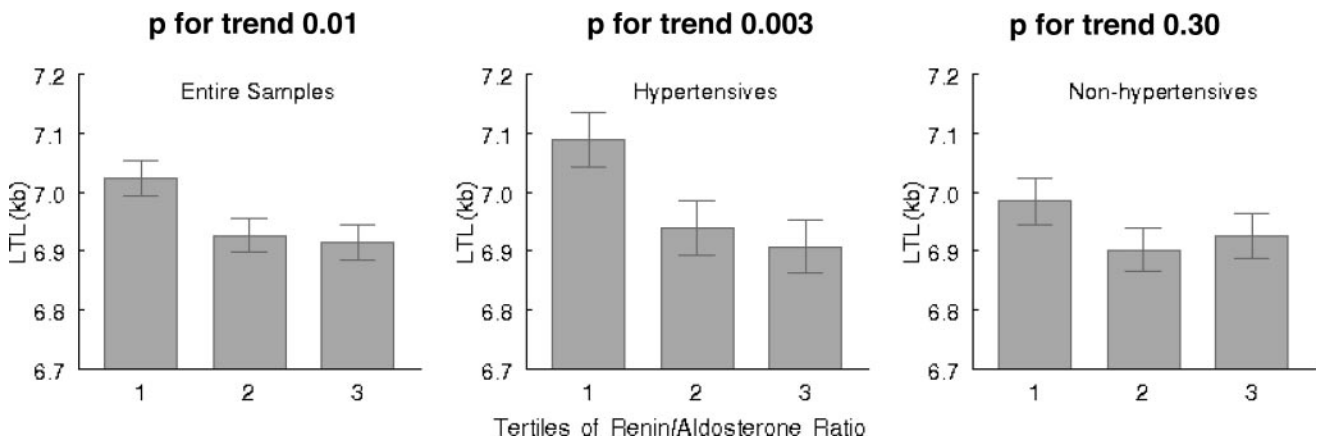


Figure. Least-squares means for adjusted LTL according to tertile of the renin-to-aldosterone ratio in the entire sample (left), hypertensive individuals (middle), and nonhypertensive participants (right). *P* values indicate trend across tertiles of the ratio.

Table 3. Regression of LTL on Log (Aldosterone) and Log (Renin) Conjointly and on Log (Renin-Aldosterone Ratio) With Additional Adjustment for C-Reactive Protein

Model, Adjustment/Variable	All Participants			Nonhypertensive			Hypertensive		
	β	SE	P	β	SE	P	β	SE	P
Incorporating aldosterone and renin conjointly									
Age, sex									
Log (aldosterone)	0.082	0.03	0.004	0.063	0.04	0.15	0.092	0.04	0.02
Log (renin)	−0.039	0.02	0.012	−0.009	0.03	0.77	−0.053	0.02	0.003
Multivariable									
Log (aldosterone)	0.099	0.03	0.002	0.051	0.05	0.29	0.146	0.04	0.001
Log (renin)	−0.034	0.02	0.06	−0.002	0.03	0.95	−0.055	0.02	0.01
Incorporating the renin-aldosterone ratio									
Age, sex									
Log (ratio)	−0.047	0.02	0.002	−0.022	0.03	0.45	−0.058	0.02	<0.001
Multivariable									
Log (ratio)	−0.046	0.02	0.007	−0.010	0.03	0.75	−0.070	0.02	<0.001

Multivariable models adjusted for age, sex, systolic blood pressure, diastolic blood pressure, hypertension treatment (when appropriate), current smoking status, diabetes mellitus, serum creatinine, urine sodium-to-creatinine ratio, body mass index, hormone replacement therapy, and C-reactive protein. SE indicates standard error of β . β is the regression coefficient per unit increase in log (predictor).

We performed secondary analyses focusing on the association of biomarkers with LTL in untreated (n=166) versus treated (n=347) participants with hypertension. No effect modification by antihypertensive medication use was observed (all $P \geq 0.50$ for interaction terms).

Discussion

Principal Findings and Related Considerations

We observed that across a wide range of sodium intake (expressed in urinary sodium output) and after adjustment for sex, smoking, and blood pressure status, age-adjusted LTL correlated positively with plasma aldosterone and negatively with plasma renin. Thus, shortened age-adjusted LTL was expressed more frequently in individuals with the phenotype of a high renin-to-aldosterone ratio, ie, a more active RAS. In large measure, this association was driven by the individuals with hypertension. Both angiotensin II^{18,21} and aldosterone^{20,21} provoke inflammation/oxidative stress. One potential explanation for our finding may be that a preferential reliance on the RAS over aldosterone to maintain blood pressure could generate more inflammation/oxidative stress and pose greater atherosclerotic risk. This speculation is based on findings that shortened LTL ostensibly reflects an increased cumulative burden of inflammation/oxidative stress and is strongly associated with atherosclerosis.^{7,9,10}

Individuals with higher plasma renin levels have been reported to have increased mortality risk, thereby implicating increased activity of the RAS in disease states.^{32–35} The stronger associations we noted in hypertensive individuals are consistent with greater activation of the RAS in those with elevated blood pressure. Angiotensin II is a powerful activator of the p53/p21 pathways, which play a key role in cellular senescence.³⁶ Indeed, shortened LTL has been observed in a host of aging-related diseases, particularly atherosclerotic cardiovascular disease,^{6,8–10,37} the common

denominator for which is increased burden of oxidative stress and inflammation.

The positive association of LTL with aldosterone concentrations in our investigation conflicts with a recent report by Benetos et al,³⁸ who observed that LTL was inversely correlated with plasma aldosterone in normotensive and mildly hypertensive men. That report was based on a small sample (n=75), and the investigators adjusted only for age (raising the issue of residual confounding). No measurements of plasma renin were available in that study.

We note that LTL is heritable^{11,39–42} and that shortened LTL is associated with a host of risk factors for cardiovascular disease and diminished lifespan, including male sex,^{6,11,43} insulin resistance,^{4,44} low socioeconomic status,⁴⁵ cigarette smoking,^{11,12} and generally unhealthy lifestyle.⁴³ The shorter LTL in smokers than nonsmokers is in line with the concept that the smoking-induced increased burden of oxidative stress and inflammation^{46–48} accelerates not only cardiovascular aging but also systemic aging.⁴⁹

Postulated Mechanisms Underlying the Principal Findings

Considerable interaction was observed between angiotensin II and aldosterone, and the targets of both agents are diverse and not mutually exclusive.^{18–21} For instance, angiotensin II is a determinant in aldosterone release from the adrenal gland and has a major impact on renal sodium reabsorption in the proximal tubules, whereas the targets of aldosterone include the heart and vasculature. That said, we can still broadly divide the RAAS into its renin-angiotensin (RAS) arm and the aldosterone arm. For a given sodium intake, the relative dependency on aldosterone versus angiotensin II for maintaining blood pressure homeostasis might be an important determinant of the correlates of LTL. Our findings raise the possibility that a preponderance of angiotensin II activity (as reflected by renin levels) relative to aldosterone for the

modulation of blood pressure (as evidenced by a high renin-to-aldosterone ratio) may promote an increased burden of inflammation and oxidative stress, expressed in a shorter LTL. This proposed paradigm may serve as a theoretical framework that integrates blood pressure regulation, sodium homeostasis, vascular tone, RAAS, and vascular aging, and it merits further study.

Study Strengths and Limitations

The strengths of this work include the community-based sample, the blinded assessments of LTL and biomarkers of the RAAS, and adjustment for multiple confounders in multivariable analyses. However, several limitations of our study should be noted. First, circulating biomarkers may not adequately reflect the degree of activation of the RAAS in tissues. Second, whereas LTL might be a record of the cumulative burden of oxidative stress and inflammation during the lifetime of the individual, the single measures of renin and aldosterone reflect the current status of the RAAS in ambulatory individuals. Additionally, we did not evaluate biomarkers of oxidative stress at the index examination. However, we have previously reported⁴ an inverse association of LTL and urinary excretion of isoprostanes (an index of systemic oxidative stress) measured at an examination \approx 4 years after the examination at which LTL measurements were obtained. Finally, our sample comprised predominantly middle-aged to elderly whites of European descent. The generalizability of our findings to younger individuals or other ethnicities is unknown.

Conclusions

Our observations in a moderate-sized community-based sample indicate that individuals, primarily those with hypertension, with a higher renin-to-aldosterone ratio display shorter LTL. We hypothesize, on the basis of these observations, that a greater dependency on angiotensin II versus aldosterone to regulate blood pressure entails a relative increase in the cumulative burden of oxidative stress and inflammation and heightens the atherosclerotic risk. In this regard, a recent study showed that shortened LTL predicts coronary artery disease events.¹⁰ Both cross-sectional and longitudinal studies are warranted to confirm the link between LTL and the RAAS.

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Disclosures

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CLINICAL PERSPECTIVE

Leukocyte telomere length (LTL) reflects the cumulative burden of oxidative stress and inflammation experienced over a life course. Activation of the renin-angiotensin-aldosterone system is associated with increased oxidative stress and inflammation. We tested the hypothesis that LTL may be related to circulating biomarkers of the renin-angiotensin-aldosterone system by examining the cross-sectional relations of LTL and circulating renin and aldosterone concentrations in 1203 Framingham Heart Study participants. In multivariable analyses adjusting for confounders, LTL was inversely related to renin and the renin-to-aldosterone ratio but directly related to aldosterone. Relations of LTL to renin-angiotensin-aldosterone system biomarkers and to the renin-to-aldosterone ratio were stronger in those with hypertension. Participants with hypertension who were in the top tertile of the renin-to-aldosterone ratio had an LTL that was 182 base pairs shorter relative to those in the lowest tertile. These observations raise the hypothesis that the renin-to-aldosterone ratio may be a biomarker of the cumulative exposure to oxidative stress and inflammation, especially in people with high blood pressure. Additional investigations are warranted to confirm our observations.