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Soluble CD163 is Associated with Shortened Telomere Length in HIV-infected Patients

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Abstract

Telomere length (TL) and immune activation markers were measured in a cohort of HIV-infected (n=102) and age-matched non-HIV-infected (n=41) men. TL was significantly shorter in HIV-infected compared to non-HIV-infected subjects (P = 0.04). Univariate analysis revealed a strong inverse relationship of TL to sCD163, and thus, monocyte/macrophage activation, among the HIV group ($\rho = -0.30$, P = 0.003). In multivariate modeling among the whole group, HIV positive serostatus (P = 0.06) and sCD163 (P = 0.05) were independent predictors of TL controlling for age and smoking status. Our data demonstrate that increased immune activation relates to shorter TL in HIV.

Keywords

sCD163; telomeres; HIV; immune activation; immunosenescence; aging

Introduction

In an era of increasingly efficacious antiretroviral therapy (ART), greater numbers of HIV-infected patients are sustaining longer life expectancies. By the year 2015, more than 50% of HIV-infected patients in the US will be over the age of 50[1]. In 2010, the Centers for Disease Control and Prevention reported that 53% of deaths among HIV-infected patients occurred

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over age 50 (http://www.cdc.gov/hiv/risk/age/olderamericans; accessed April 7, 2014). In this regard, the trajectory of morbidity and mortality from HIV has shifted to non-AIDS defining age-related diseases. Data suggest that HIV-infected patients face several specific age-associated morbidities, such as atherosclerosis, decreased bone mineral density, and dementia, at accelerated rates when compared to the general population[2-6]. Plausible mechanisms for the heightened risk of age-related disease states in HIV infection include immune activation, inflammation and oxidative stress[7,8], but the exact pathophysiology remains uncertain.

We posited that chronic immune activation may perpetuate risk for the premature onset of specific age-related diseases in HIV through telomere shortening. Shortened telomere length (TL) is a hallmark of immunosenescence, and evidence suggests changes in replicative capability in chronic inflammatory states[9] and diseases associated with aging[10-13]. Reduced TL in lymphocyte subsets and increased expression of CDKN2A, a marker of cellular senescence, have been demonstrated in HIV-infected cohorts when compared to non-HIV-infected cohorts[14-18]. The aim of the present study was to evaluate the relationship of TL to immune activation markers among a cohort of HIV-infected and non-HIV-infected men.

Methods and Procedures

Subjects

One hundred and two HIV-infected and 41 non-HIV-infected men ages 18-55 were previously recruited. HIV-infected subjects were required to be on stable ART for >3 months. Detailed recruitment and inclusion and exclusion criteria are described elsewhere[19]. In brief, HIV-infected subjects without known cardiovascular disease were recruited. Non-HIV-infected control subjects from the same community were simultaneously recruited to assure similar demographic characteristics. Institutional Review Boards from the Massachusetts General Hospital and Massachusetts Institute of Technology approved the study; informed consent was obtained from all subjects.

Assessment of Immunologic Parameters

Serum and plasma were aliquoted into 2 mL Sarstedt microtubes and stored at −80 °C. Plasma soluble CD163 (sCD163) (Trillium Diagnostics, Maine, USA) and MCP-1, soluble CD14 (sCD14), and hsIL-6 (R&D Systems, US) were quantified by ELISA. C-reactive protein (CRP) was assessed by the Cobas Integra C-Reactive Protein (Latex) Test. The endpoint limulus amebocyte lysate assay (Associates of Cape Cod, Massachusetts, US) was used to determine levels of lipopolysaccharide (LPS).

Measurement of Serum Telomere Length

Total nucleic acid was extracted from 0.4 mL of serum using the Magmax Viral RNA isolation kit (Ambion/Life Technologies). Mean relative TL was then assayed with a monochromatic multiplex qPCR (MMqPCR) assay developed by Cawthon[20]. Primers for the single copy gene albumin - albu (5' CGG CGG CGG GCG GCG CGG GCT GGG CGG AAA TGC TGC ACA GAA TCC TTG 3', and albd (5' GCC CGG CCC GCC GCG CCC GTC CCG CCG GAA AAG CAT GGT CGC CTG TT 3')-and for telomere - telg (5' ACA

CTA AGG TTT GGG TTT GGG TTT GGG TTT GGG TTA GTG T 3'), and telc (5' TGT TAG GTA TCC CTA TCC CTA TCC CTA TCC CTA TCC CTA ACA 3')- were all used at 0.9 μM final concentration. The thermal cycling profile was 95°C for 15 min, followed by 2 cycles of 94°C for 15 s, 49°C for 15 s, followed by 40 cycles of 94°C for 15 s, 62°C for 10 s, 74°C for 15 s, 84°C for 10 s, and 88°C for 15 s, with signal acquisition at the end of both the 74°C and 88°C steps. Reactions were carried out in triplicate in a 10 μL volume using the SYBR Select Master Mix (Applied Biosystems by Life Technologies) on a LightCycler 480 (Roche). A standard curve prepared with human blood DNA was included in each run and used to estimate telomere (T) and single nuclear gene (S). LightCycler raw text files were converted as described elsewhere[21].

The serum DNA concentrations were low but confirmed to lie well within the linear range of the standard curves. Relative TL was expressed as the average T/S ratio of triplicates. Two internal controls were included in each run. Samples with a coefficient of variation (CV) >10% were repeated. All TL assays were done in a randomized and blinded fashion, and the intra- and inter-run CV were approximately 6% and 7%, respectively. Data relating TL and immune activation were not previously analyzed.

Comparison Between Serum and Whole Blood Leukocyte Telomere Length

Venous blood was collected from 91 additional volunteers who provided informed consent. Serum nucleic acids were extracted as above while whole blood DNA was extracted with QiaCube using the QIAamp DNA Mini (Qiagen). TL was assayed as described above. For each donor, both serum and whole blood TL were placed in the same run. The Pearson's correlation coefficient (r) for T/S ratio between serum and whole blood leukocyte TL was 0.68 ($P<0.0001$).

Statistical Analysis

Analyses were performed using the Student's t test and Wilcoxon rank sums test for normally and non-normally distributed continuous variables, respectively, and by x^2 test for categorical variables comparing variables between the HIV and non-HIV-infected groups. TL was log transformed due to the non-normal distribution. Relationships to TL were assessed using Spearman's correlation coefficient among the entire group and within the HIV and non-HIV-infected groups separately. To further assess the impact of HIV serostatus and immune activation markers on TL as the dependent variable, we performed multivariate regression modeling among all subjects, controlling simultaneously for age and smoking, two variables known to affect TL[18]. A sensitivity analysis was performed assessing for an interaction between HIV serostatus and sCD163 in the multivariate modeling for TL. An additional sensitivity analysis was performed to investigate the above relationships among those HIV-infected subjects on ART with an undetectable viral load (VL) (n=69) compared to controls to determine whether findings were driven by the inclusion of untreated or viremic patients.

Results

Baseline Characteristics

Age was 46.6±6.4 years among the HIV-infected men and 44.6±7.6 years among the non-HIV-infected men (mean ± SD, P=0.13). Additional demographic characteristics including race, age and smoking status were similar between the groups **(Supplemental Table 1)**. Log TL was significantly shorter among the HIV population compared to the control population (1.02 ± 0.04 vs. 1.04 ±0.05, P = 0.04). With regards to inflammatory and immune activation markers, hsIL-6 (0.9 [0.7, 1.5] vs. 0.6 [0.5, 1.0] pg/mL, P = 0.01), LPS (0.10 [0.07, 0.13] vs. 0.07 [0.06, 0.10] ng/mL, P = 0.0004), and sCD163 (1063 [695, 1577] vs. 765 [572, 1054] ng/mL, P = 0.0007) (median [IQR]) were all significantly higher among the HIV cohort compared with the control cohort. In the sensitivity analysis, TL remained low (log relative TL 1.02 ± 0.04 vs. 1.04 ± 0.05, P=0.04) and sCD163 increased (1010 [660, 1517] vs. 765 [572, 1054] ng/mL, P= 0.005) in the HIV group on ART with undetectable VL vs. control subjects.

Demographic, Immune Activation, and HIV Parameters in Relation to Telomere Length Univariate Regression Analysis among All Subjects, HIV and Non-HIV-Infected Cohorts

Among the entire cohort there was a significant inverse relationship of sCD163 to TL (ρ= −0.33, P < 0.0001) **(Figure 1)**, while pack-years of smoking (ρ= −0.15, P = 0.08) and hsIL-6 (ρ= −0.16, P = 0.07) tended to be inversely related to TL. Among the HIV-infected cohort, only the relationship between sCD163 and TL remained significant (ρ= −0.30, P = 0.003), whereas HIV-related parameters, including VL, CD4 count and duration ART use were not significantly associated to TL **(Table 1)**. Other inflammatory and immune markers were not significantly related to TL among the HIV-infected group in univariate regression analysis, although hsIL-6 tended to be associated (ρ= -0.20, P=0.06). Among the non-HIV-infected cohort, the association between sCD163 and TL was ρ= −0.29 (P = 0.07) **(Table 1)**. In addition, the negative correlation between sCD163 and TL remained significant in the ART-suppressed HIV group (ρ=−0.30, P=0.01).

Mulitivariate Regression Modeling

In multivariate modeling for TL, simultaneously assessing sCD163, HIV serostatus, age and smoking as independent variables of interest, sCD163 (P=0.05) was a significant and independent predictor of shortened TL, whereas HIV positive serostatus tended to be independently related to shortened TL (P = 0.06). In contrast, age (P=0.72) and smoking (P=0.82) were not significant in the model (overall P=0.04 for model) **(Supplemental Table 2)**. In a sensitivity analysis to assess for an interaction between sCD163 and HIV, there was no significant interaction (P=0.12) between sCD163 and HIV serostatus with regards to TL. sCD163 (P=0.01) remained significantly and independently associated to shortened TL in this model (overall P= 0.03 for model). Multivariate modeling performed after limiting HIV subjects to those on ART with suppressed VL demonstrated that sCD163 (P=0.006) remained a significant and independent predictor of shortened TL in the subset of well-treated aviremic HIV subjects (overall P=0.007 for this model).

Discussion

To our knowledge, this is the first study to demonstrate a strong association between increased sCD163, a marker of monocyte and macrophage activation, and decreased TL in HIV-infected subjects. Furthermore, we demonstrate that the findings are recapitulated in the large subset with undetectable viral load. sCD163 is related to co-morbidities associated with the premature onset of specific age-related diseases among the HIV population, including cardiovascular and neurological diseases[22,23]. Our data relating sCD163 to telomere length are suggestive of a potential link between chronic immune activation and cellular aging in HIV infection.

Emerging data suggest that chronic immune activation may accelerate the burden of several age-related comorbidities in the HIV population. Young HIV-infected male patients less than 45 years regardless of viremic control presented with a monocyte phenotype that more closely resembled that of aged non-HIV-infected subjects older than 65 years[24]. This particular monocyte phenotype comprised of increased CD11b and decreased CD62L expression has been typically associated with pro-inflammatory states[24]. Circulating levels of immune activation markers sCD163, sCD14, and CXCL10 were significantly elevated in HIV-infected women compared to non-infected women[25]. In fact, Martin et al. reported that levels of sCD163 in the HIV-infected women were comparable to controls 14.5 years older[25].

Limited data are available in the HIV population exploring the interrelationship between markers of immune activation and TL. Data in non-HIV-infected cohorts show that increased CRP[26] and cumulative load of systemic inflammation, such as combined IL-6 and TNFα levels[27], are linked to reduced TL. Hearps et al. demonstrated decreased TL in CD14+CD16+ monocytes in HIV-infected patients when compared to the age matched controls, and TL was negatively associated with CXCL10[24]. Futhermore, Burdo et al. reported that plasma sCD163 levels positively correlate with percentage of CD14+CD16+ monocytes[28]. Taken together, these data from prior studies provide preliminary evidence in support of a link between immune activation and TL. Our data extend this line of evidence to show for the first time that TL is negatively and strongly associated with sCD163, an immune marker which has been more robustly coupled with several age-related diseases in HIV-infected patients. In this regard, increased sCD163 may serve as a marker of immunosenescence. Investigation of a larger HIV cohort may be necessary to demonstrate relationships between TL and other soluble biomarkers of immune activation, such as sCD14.

Zanet et al. reported that HIV-infected patients have significantly shorter leukocyte TL when compared to non-HIV-infected individuals. Shorter TL was significantly and independently associated with older age as well as smoking and HIV status[18]. The current study presents novel data suggesting that immune activation, as measured by sCD163, may be more predictive of shorter TL than traditional factors associated with immunosenescence, such as older age and smoking status. Prior studies investigating immune activation in association with several age-related diseases in HIV have typically recruited cohorts above the age of 50[29,30]. In contrast, our data demonstrate shorter TL in a relatively younger HIV cohort,

which underscores the accelerated onset of an aging phenotype by non-traditional factors, such as innate immune activation. Similar to Zanet et al., we did not find that CD4 count, viral load, and ART are associated with shorter TL.

TL is regulated by telomerase, the role of which is to elongate the ends of chromosomal DNA, thereby attenuating telomere attrition. HIV-infected peripheral blood leukocytes (PBLs) from control subjects have down-regulated telomerase activity when compared to PBLs not infected with HIV[31]. In our study, HIV-infected patients had a long duration of ART exposure and good viremic control, but demonstrated significantly reduced TL. More recent studies have suggested that NRTIs inhibit telomerase activity[32]; however, we did not see an association between shortened TL and use of NRTI in our cohort.

As this study design was cross-sectional, we cannot make definitive conclusions on causality. Further longitudinal studies in the HIV population assessing changes in immune activation and TL over time in relationship to age-related diseases during chronological aging are required. We only studied HIV-infected men, and these findings should be corroborated in HIV-infected women to assess for any gender effects. The reported TL in the HIV cohort should be compared to an elderly population of control subjects to place the shortened TL measurements in context of the expected aging process. In addition, we measured TL in serum, whereas prior studies in HIV-infected patients have used whole blood leukocytes. We have demonstrated that serum TL and leukocyte TL were well correlated in a validation cohort[21], but we are not able to discern the relationship of serum TL specifically to monocyte TL. However, prior studies have recognized the clinical utility of measuring serum TL[33,34]. Further studies investigating circulating sCD163, cell associated CD163 and leukocyte or monocyte specific TL will be informative to assess the relationship in specific cell populations. Indeed, the shortened TL could also be reflective of expanding cell populations and increased replicative capacity in HIV, independent of cellular aging.

Taken together, our data suggest that the predisposition to chronic immune activation may provide a link by which telomere shortening occurs in HIV. In turn, telomere shortening may contribute to the premature onset of several age-related diseases in the HIV population. Understanding the mechanisms that contribute to immunosenescence in HIV infection may have significant implications in creating treatment strategies to reduce the morbidity and mortality associated with several age-related diseases in the HIV population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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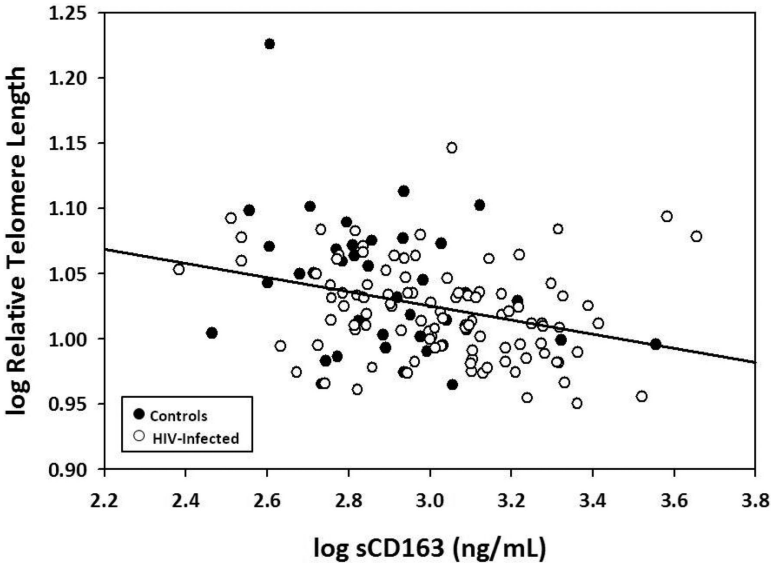

Figure 1. Relationship between sCD163 and telomere length among all subjects

Data are represented as log for both sCD163 and telomere length for purposes of illustrating linear regression (r=0.31, P=0.0002). Black circles represent control subjects and white circles represent HIV-infected subjects.

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Table 1

Univariate Associations with Telomere Length

Parameter	Entire Cohort (n=142)		HIV-infected Subjects (n=102)		Non-HIV-Infected Subjects (n=40)	
	ρ	P-value	ρ	P-value	ρ	P-value
Age (years)	−0.07	0.43	−0.07	0.51	−0.0005	0.998
Smoking history (pack years)	−0.15	0.08	−0.17	0.11	0.06	0.71
BMI (kg/m^2)	0.02	0.82	0.16	0.11	−0.29	0.07
sCD163 (ng/mL)	−0.33	<0.0001	−0.30	0.003	−0.29	0.07
sCD14 (ng/mL)	−0.04	0.64	−0.13	0.19	0.25	0.12
MCP-1 (pg/mL)	0.02	0.83	−0.05	0.64	0.26	0.11
hsIL6 (pg/mL)	−0.16	0.07	−0.20	0.06	−0.02	0.91
LPS (ng/mL)	−0.07	0.43	−0.08	0.43	0.15	0.35
CRP (mg/L)	−0.03	0.72	−0.04	0.71	0.02	0.89
Duration since HIV diagnosis (years)	N/A	N/A	0.004	0.97	N/A	N/A
Duration of ART (years)	N/A	N/A	0.13	0.32	N/A	N/A
Duration of PI use (years)	N/A	N/A	0.03	0.79	N/A	N/A
Duration of NRTI use (years)	N/A	N/A	0.14	0.25	N/A	N/A
Duration of NNRTI use (years)	N/A	N/A	0.18	0.12	N/A	N/A
Current HIV log viral load (#/mL)	N/A	N/A	0.13	0.24	N/A	N/A

ρ represents Spearman's correlation coefficient. BMI, body mass index; sCD163, soluble CD163; sCD14, soluble CD14; MCP-1, monocyte chemoattractant protein 1; hsIL-6, high sensitivity interleukin-6; LPS, lipopolysaccharide; CRP, C-reactive protein; ART, antiretroviral therapy; PI, protease inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; N/A, non-applicable.