

Relationship of Telomere Length to Fat Redistribution in HIV

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Persons with HIV demonstrate increased risk for aging-associated complications and have reduced telomere length (TL) compared with age-matched persons without HIV. Our data show that greater visceral fat is related to reduced TL in HIV, independent of age and smoking. Fat redistribution may be a relevant mediator of TL attrition in HIV.

Keywords. BMI; HIV; telomere length; visceral adipose tissue; visceral fat.

Persons with HIV are at increased risk for several aging-associated diseases including coronary atherosclerosis, stroke, dementia, cancer, and osteoporosis [1–3], complications that may evolve from cellular senescence. Telomere length (TL), an indicator of cellular aging, is reduced among participants with HIV when compared with age-matched uninfected persons [4–6].

General factors including age, smoking, substance use and HIV-specific factors such as the virus itself, and HCV co-infection have all been linked to reduced TL [6]. Antiretroviral therapy (ART) is also associated with TL shortening in vitro, but human studies suggest that ART may be protective for leukocyte TL [7, 8]. We have also previously demonstrated an inverse relationship between TL and soluble CD163, a marker of monocyte and macrophage activation, among participants with HIV [5], which may underscore inflammation as a mediator of cellular senescence. Well-treated participants with HIV on ART are recognized to have abnormal fat redistribution [9], particularly related to abdominal visceral fat accumulation. Expansion of visceral adiposity, a

dysfunctional state, has been linked to many chronic inflammatory diseases of aging among persons with HIV [10–12]. While adipose dysfunction has been recognized to correlate with reduced TL in studies of obesity in the general population [13], no studies to date have investigated the relationship between TL and fat redistribution among participants with HIV.

METHODS

Study Participants

Eighteen men with HIV and 9 men without HIV aged 18–60 years were enrolled in a prior study assessing brown fat biology [14]. Participants with HIV were included if they were on stable ART for >12 months. Participants were excluded for body mass index (BMI) <18 or >35.0 kg/m², history of diabetes, and use of growth hormone or anabolic therapies.

Participant Consent Statement

The participant's written consent was obtained. The design of the work was approved by the Partners Human Research Committee.

HIV-Related Parameters

T-cell counts were quantified by flow cytometry. HIV viral load was assayed using ultrasensitive reverse transcription polymerase chain reaction (RT-PCR; Roche COBAS amplicor).

Body Composition Parameters

Waist and hip circumferences were measured using the iliac crest and the widest diameter of the hip as the anatomic references, respectively. Visceral and subcutaneous adipose tissue (VAT, SAT) measurements were obtained from MRI through an axial T1-weighted water suppressed pulse sequence obtained at the level of the L4 vertebral body.

Telomere Length and Mitochondrial DNA

Peripheral blood mononucleated cell (PBMC) DNA was extracted with QiaCube using the QIAamp DNA Mini kit (Qiagen). Mean relative TL was then assayed with a monochromatic multiplex qPCR (MMqPCR) assay, as described previously [15].

PBMC mtDNA content was measured in the same DNA extract using MMqPCR as previously described [16]. The assays were done in a randomized and blinded fashion. The intra- and inter-run CVs for the assays were approximately 6% and 5% for the TL and mtDNA assays, respectively.

Statistical Analysis

Normality of distribution was determined using the Shapiro-Wilk test. Normally distributed data are presented

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as mean \pm SD, and non-normally distributed variables are presented as median (interquartile range). TL was stratified into above- and below-median values with respect to the median for each group, respectively (participants with HIV and participants without HIV). Comparisons were made between above- and below-median TL using the Student *t* test for normally distributed continuous variables. Multivariable logistic regression was performed to assess independent effects of significant measures of body composition determined to be related to TL, controlling for age and smoking history. Positive smoking history was obtained by self-report of current or past tobacco use. Tests and confidence intervals on odds ratios are likelihood ratio based. Statistical significance was defined as $P < .05$. All statistical analyses were performed using SAS JMP (version 14.0). Data relating TL and body composition have not been previously analyzed.

RESULTS

Demographics and Clinical Characteristics

Age was similar among participants with HIV and without HIV (54 ± 8 vs 55 ± 7 years; $P = .78$) (Supplementary Table 1). Both groups were of similar racial makeup, with the majority identifying as Caucasian. Fifty-six percent of participants with HIV had a history of smoking, compared with 33% of participants without HIV ($P = .27$). Body composition did not differ significantly between the 2 groups. Among participants with HIV, duration of HIV and ART were 20.6 ± 7.0 and 15.6 ± 7.3 years, respectively. Participants with HIV demonstrated immunological control, with a CD4+ T-cell count of 582 ± 280 cells/ μ L and a \log_{10} HIV viral load of 1.43 ± 0.39 copies/mL. TL tended to be reduced among participants with HIV vs participants without HIV (5.05 ± 0.70 vs 5.54 ± 0.61 ;

$P = .08$), and mtDNA was similar between the 2 groups (53.9 ± 11.2 vs 56.8 ± 9.7 ; $P = .50$) (Supplementary Table 1).

Body Composition Measures in Relation to Telomere Length

Iliac waist circumference (WC; 113.4 ± 10.0 vs 102.7 ± 11.5 cm; $P = .05$), waist-to-hip ratio (WHR; 1.06 ± 0.07 vs 0.98 ± 0.09 ; $P = .04$), and VAT (301.5 ± 94.4 vs 187.7 ± 69.6 cm²; $P = .01$) were significantly greater among participants with HIV with below-median TL compared with participants with HIV with above-median TL (Table 1). In contrast, BMI, SAT, adiponectin, and mtDNA did not differ among participants with HIV stratified by above- and below-median TL. In addition, immunologic parameters related to current CD4+ and CD8+ T-cell counts were similar regardless of grouping by above- or below-median TL in HIV. No significant differences in body composition parameters, adiponectin, or mtDNA were observed among participants without HIV grouped by median TL (Table 1).

Independent Effects of Fat Redistribution on Telomere Length Among Participants With HIV

In separate multivariable models, controlling for age, VAT (OR, 4.65 per 100 cm²; 95% CI, 1.09–47.27 per 100 cm²; $P = .04$) and iliac WC (OR, 1.31 per cm; 95% CI, 1.03–2.41 per cm; $P = .02$) remained independently associated with below-median TL among participants with HIV (Table 2). Similarly, other measures of body composition, such as WHR (OR, 5.05 per 0.1 unit; 95% CI, 0.87–68.25 per 0.1 unit; $P = .07$), showed some relation to below-median TL, controlling for age. Separate modeling controlling for history of smoking demonstrated that VAT (OR, 4.82 per 100 cm²; 95% CI, 1.34–32.55 per 100 cm²; $P = .01$) was independently related to below-median TL among participants with HIV. Similarly, iliac WC (OR, 1.11 per cm; 95% CI, 1.01–1.27 per cm; $P = .03$) and WHR (OR, 5.84 per 0.1 unit; 95% CI, 1.20–73.91 per 0.1 unit; $P = .02$) were related to below-median

Table 1. Body Composition Parameters Among Participants With and Without HIV Stratified by Above/Below-Median Telomere Length

	Participants With HIV			Participants Without HIV		
	Above-Median TL	Below-Median TL	<i>P</i> Value	Above-Median TL	Below-Median TL	<i>P</i> Value
Body composition parameters						
BMI, kg/m ²	28.4 \pm 3.9	31.0 \pm 4.3	.20	31.2 \pm 3.6	28.1 \pm 3.6	.24
Iliac waist circumference, cm	102.7 \pm 11.5	113.4 \pm 10.0	.05	106.3 \pm 7.6	99.8 \pm 15.9	.49
Waist-to-hip ratio	0.98 \pm 0.09	1.06 \pm 0.07	.04	1.00 \pm 0.02	0.98 \pm 0.06	.56
Abdominal VAT, cm ²	187.7 \pm 69.6	301.5 \pm 94.4	.01	237.1 \pm 47.8	196.3 \pm 140.7	.61
Abdominal SAT, cm ²	285.3 \pm 120.0	323.6 \pm 112.8	.50	299.9 \pm 80.0	262.2 \pm 128.0	.64
Adiponectin, μ g/mL	5.0 \pm 1.0	5.0 \pm 1.6	.95	5.0 \pm 1.3	4.6 \pm 1.6	.68
Markers of cellular aging/immunologic function						
Age, y	49 \pm 9	59 \pm 5	.01	54 \pm 8	56 \pm 5	.81
mtDNA	57.2 \pm 14.3	50.6 \pm 6.3	.23	61.2 \pm 10.5	51.3 \pm 5.5	.12
CD4 T-cell count, cell/ μ L	613 \pm 357	550 \pm 194	.65	—	—	—
CD8 T-cell count, cell/ μ L	1019 \pm 615	967 \pm 377	.83	—	—	—
CD4/CD8 T-cell ratio	0.68 \pm 0.45	0.67 \pm 0.38	.97	—	—	—

Data reported as mean \pm SD.

Abbreviations: BMI, body mass index; mtDNA, mitochondrial DNA; SAT, subcutaneous adipose tissue; TL, telomere length; VAT, visceral adipose tissue.

Table 2. Multivariable Model to Assess Determinants of Telomere Length Among Participants With HIV

	Below-Median Telomere Length	
	OR (95% CI)	P Value
	Overall model ($R^2 = 0.52$; $P = .002$)	
Age	1.39 (1.05–2.35)	.01
VAT (per 100 cm ²)	4.65 (1.09–47.27)	.04
	Overall model ($R^2 = 0.58$; $P = .0007$)	
Age	1.54 (1.13–3.29)	.001
Iliac waist circumference (per cm)	1.31 (1.03–2.41)	.02
	Overall model ($R^2 = 0.47$; $P = .003$)	
Age	1.35 (1.06–2.09)	.01
Waist-to-hip ratio (per 0.1 unit)	5.05 (0.87–68.25)	.07
	Overall model ($R^2 = 0.28$; $P = .03$)	
History of smoking	0.97 (0.09–13.79)	.98
VAT (per 100 cm ²)	4.82 (1.34–32.55)	.01
	Overall model ($R^2 = 0.22$; $P = .06$)	
History of smoking	0.28 (0.02–2.45)	.25
Iliac waist circumference (per cm)	1.11 (1.01–1.27)	.03
	Overall model ($R^2 = 0.24$; $P = .05$)	
History of smoking	0.40 (0.04–3.55)	.41
Waist-to-hip ratio (per 0.1 unit)	5.84 (1.20–73.91)	.02

R^2 represents the coefficient of determination and the proportion of variance explained by the model. P value represents significance by the whole model.

Abbreviations: OR, odds ratio; VAT, visceral adipose tissue.

TL, controlling for history of smoking (Table 2). We also demonstrate that body composition parameters were related to below-median TL, independent of either CD4+ or CD8+ T-cell count (Supplementary Table 2).

DISCUSSION

We demonstrate for the first time that abnormal fat redistribution in participants with HIV is related to reduced TL. Our data show that among participants with HIV, specific body composition parameters indicative of abdominal visceral fat accumulation (iliac WC, WHR, VAT) were significantly related to reduced TL, whereas BMI, a more generalized measure, was not. Indeed, for a similar BMI, participants with HIV are more likely to have abdominal VAT accumulation compared with participants without HIV [9]. Furthermore, we demonstrated that VAT and other measures of fat redistribution are related to reduced TL independent of 2 well-known mediators of TL attrition (age and smoking history). Visceral adiposity may be an additional relevant mediator of cellular aging unique to HIV.

The SAT depot did not relate to TL among participants with HIV, whereas reduced TL has been associated with SAT in the general population [17]. This highlights a clinical presentation of fat redistribution distinct to participants with HIV, which may contribute to TL attrition and aging-associated disease risk. The visceral depot is a highly inflammatory depot, which may have detrimental effects on cellular aging, immunosenescence, and subsequent metabolic complications.

Our data did not detect higher VAT upon stratification to above- and below-median TL among participants without HIV, a result that stands in contrast to the HIV group; however, our sample was small. In the adipose depot, TL has been negatively correlated with adipocyte hypertrophy in both the SAT and VAT among persons with obesity or diabetes mellitus (DM) [18]. Other studies of obesity also report that reduced TL is associated with total body fat and BMI [19]. One study among participants without HIV examined TL in the adipose depot and found significantly reduced TL in the subcutaneous vs visceral fat depots [20]. This may highlight divergent adipocyte biology, such that SAT may be the predominantly dysfunctional fat depot among other metabolically adverse populations (obesity, DM), contrary to the VAT depot in HIV.

Obesity is an emerging issue in the HIV population, possibly attributed to a complex interplay of factors such as viral-mediated effects, contemporary ART regimens, immune adaptation in the adipose depot, and alterations in the gut microbiome. Accumulation of both visceral and subcutaneous fat depots needs to be explored for its effects on aging among the HIV population who demonstrate obesity [21].

There were a few limitations to our study, primarily its small sample size and the fact that it only included male participants. It is possible that visceral adiposity may promote TL attrition through the generation of inflammatory cytokines, and we were only able to assess adiponectin, which did not appear to differ based on TL. Causality cannot be determined in a cross-sectional study, and it is possible that reduced TL contributes to increased VAT. We did not have information on nadir CD4+

T-cell count, and it could be that severity of HIV affects TL attrition. Future longitudinal studies in HIV should be designed to evaluate the impact of chronic changes in fat redistribution on TL and the subsequent development of aging-associated disease.

The prevalence of aging-associated disease continues to rise among participants with HIV, and there are no HIV-specific prevention strategies. In that regard, strategies aimed at VAT reduction could be potentially leveraged to slow TL attrition among participants with HIV, which may yield benefits toward decreasing aging-related complications.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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