Telomere Length, Traditional Risk Factors, HIV-related Factors and Coronary Artery Disease Events in Swiss Persons Living with HIV

1844

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BACKGROUND

- In prospective studies and in large meta-analysis of the general population,[1-3] leukocyte telomere length (TL) shortening, as occurs with advancing age,[4] is associated with coronary artery disease (CAD) events.
- People living with HIV (PLWH) may have shorter TL[5-6] and accelerated atherosclerosis compared to the general population
- While the relationship between TL and CAD is likely complex,[7] genetic studies suggest a causal link. [8–10]
- It is unknown whether TL is associated with CAD in PLWH, independent of traditional and HIV-related risk factors.

METHODS

- We measured TL in stored peripheral blood mononuclear cells (PBMC) by quantitative PCR, as previously described,[6] using the single copy albumin gene as control. Relative TL was estimated using a standard curve prepared from healthy blood donors.
- Study population: white Swiss HIV Cohort Study (SHCS; www.shcs.ch) participants.[11] Cases had a 1st CAD event during the study period (1.1.00-31.12.17).
- We used incidence density sampling and matched 1-3 controls (CAD event-free) on gender, age, and date of SHCS registration.[12-15]
- Matching date of controls = CAD event date of corresponding cases
- We obtained univariable and multivariable odds ratios (OR) for a first CAD event from conditional logistic regression analyses
- Variables: TL, age, gender, smoking, family history, hypertension, diabetes, hypercholesterolemia, and HIV-related factors (recent exposure to abacavir,[14] exposure >1 year to indinavir, lopinavir/ritonavir, darunavir;[15] on ART but HIV RNA>50 copies/mL), and CMV seropositivity.[16]

Table: Characteristics of Cases and Controls At the Matching Date

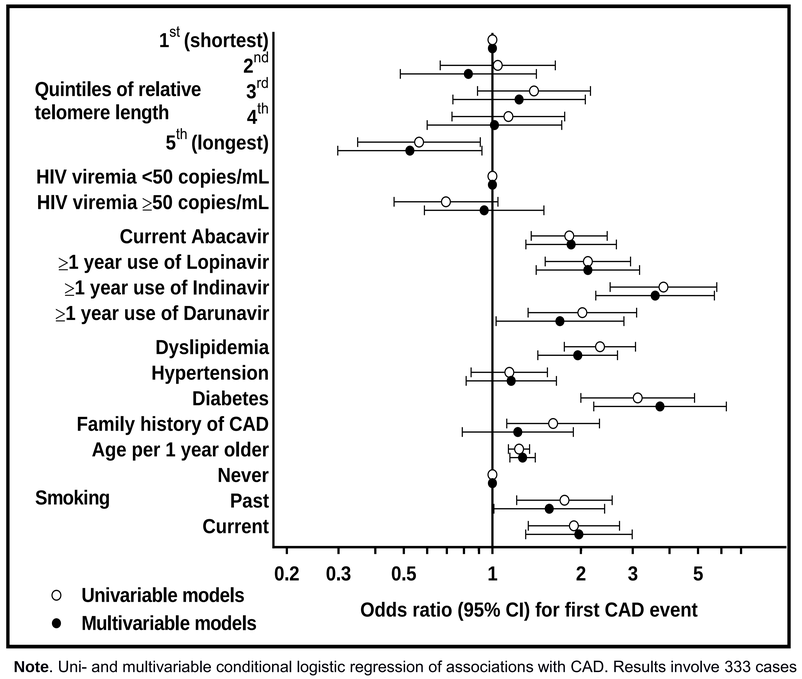
	Cases (n=333)	Controls (n=745)
Male sex, n (%)	287 (86.2)	641 (86.0)
Age (years), median (IQR)	54 (47.6)	53 (47.6)
HIV acquisition mode, n (%)		
• Heterosexual	96 (28.8)	245 (32.9)
• MSM	158 (47.5)	369 (49.5)
• IDU	67 (20.1)	107 (14.4)
Smoking, current n (%)	159 (47.8)	307 (41.2)
Family History of CAD, n (%)	57 (17.1)	84 (11.3)
Diabetes mellitus, n (%)	56 (16.8)	49 (6.6)
Hypertension, n (%)	108 (32.4)	218 (29.3)
Dyslipidemia, n (%)	225 (67.6)	350 (47.0)
Framingham risk score (10-year risk), median (IQR) >10%	188 (56.5)	346 (46.4)
On ART, HIV RNA <50 copies/mL, n (%)	269 (80.8)	588 (78.9)
Currently on Abacavir, n (%)	108 (32.4)	152 (20.4)
Lopinavir/ritonavir, exposure >1 year, n (%)	97 (29.1)	128 (17.2)
Indinavir, exposure >1 year, n (%)	76 (22.8)	58 (7.8)
Darunavir, exposure >1 year, n (%)	49 (14.7)	70 (9.4)
CD4 nadir (cells/µL), median (IQR)	150 (57-238)	209 (130-315)
Hepatitis C Seropositivity, n (%)	86 (25.8)	148 (19.9)

Note. Data are number (%) of participants, unless otherwise indicated. ART, antiretroviral therapy; CAD, coronary artery disease; IDU, intravenous drug use; IQR, interquartile range; MSM, men who have sex with men; CMV, cytomegalovirus

RESULTS

- We included 333 cases and 745 controls (**Table**).
- Median (IQR) time of TL measurement: 9.4 (5.9-13.8) years prior to CAD event.
- Participants in the 5th (longest) TL quintile, compared to the 1st (shortest) TL quintile had univariable CAD odds ratio=0.56 (95% confidence interval, 0.35-0.91; p=0.02), and multivariable OR=0.52 (0.30-0.92; p=0.03; **Figure**).

Figure: CAD Odds Ratio According to Quintiles of Telomere Length, Traditional and HIV-related Risk Factors



Note. Uni- and multivariable conditional logistic regression of associations with CAD. Results involve 333 cases and 745 controls. Multivariable models are adjusted for all variables displayed, i.e. for traditional and HIV-related risk factors

- CMV seropositivity was associated with univariable CAD OR=1.65 (1.11-2.44), and multivariable OR 1.65 (1.06-2.57)
- Sensitivity analysis including CMV seropositivity in the multivariable model: participants in 5th TL quintile had CAD OR=0.52 (0.30-0.93) compared to 1st quintile.
- Sensitivity analysis including CMV and HCV seropositivity and injection drug use (IDU) in the multivariable model: participants in 5th TL quintile had CAD OR=0.53 (0.29-0.98) compared to 1st quintile.
- Sensitivity analysis with adjustment only for Framingham risk score: participants in 5th TL quintile had CAD OR=0.55 (0.34-0.90) compared to 1st quintile.

CONCLUSIONS

- PLWH with the longest telomeres had approximately half the odds of developing CAD of those with the shortest telomeres.
- Results were robust after adjustment for multiple traditional and HIV-associated CV risk factors, when adjusted only for Framingham risk score, and when adjusted for CMV serostatus, HCV serostatus, and IDU.
- TL was associated with acute CAD events when measured >9 years prior to CAD event date, suggesting TL is more than a coincidental surrogate marker, i.e. TL may have important clinical implications in PLWH

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