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HIV-Infected Persons with Type 2 Diabetes have Evidence of Endothelial Dysfunction

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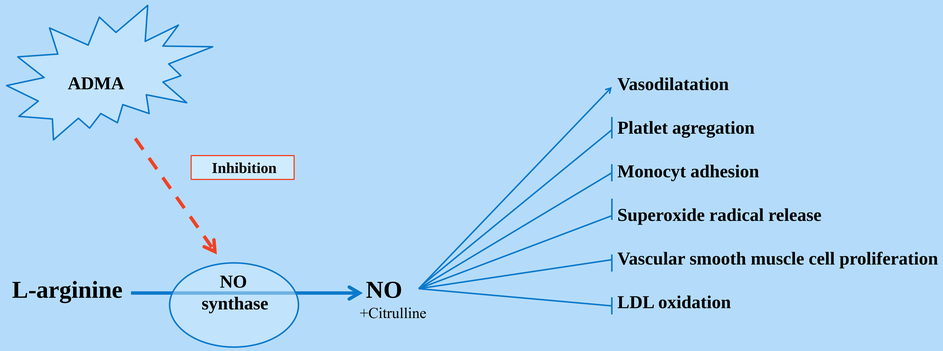
Background

Increased incidence of cardiovascular diseases (CVD) in HIV-infected persons compared to the general population has been described. Likewise, type 2 diabetes (T2D) is an independent risk factor for CVD. T2D is characterized by low-grade inflammation and endothelial dysfunction. Chronic inflammation and endothelial dysfunction, in turn, have been suggested as possible mechanisms leading to increased risk of CVD in HIV infection. Little is known about the combined effect of HIV infection and T2D on inflammation and endothelial function. We hypothesized an additive effect of HIV infection and T2D on inflammation and endothelial dysfunction.



L-Arginine is the natural precursor for NO in the endothelium. Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of the endothelial NO synthase (eNOS) and thereby affects endothelial function by blocking the NO-production from L-arginine. ADMA is a well-established marker of endothelial dysfunction.

Methode

A cross-sectional study was performed including 50 HIV-infected persons on combination anti-retroviral therapy (cART) and with HIV RNA < 200 copies/mL (n=25 with T2D (HIV+T2D+), n=25 without T2D (HIV+T2D-)), and 50 HIV-negative persons (n=22 with T2D (HIV-T2D+) and n=28 without T2D (HIV-T2D-). Groups were matched on age and sex, and groups of HIV-infected patients were matched on CD4 cell count. High sensitive C-reactive protein (hsCRP) was measured using tina-quant CRP immunoturbidimetric assay. Asymmetric dimethylarginine (ADMA) and L-arginine as markers of endothelial function and trimethylamine-N-oxide (TMAO), a microbiota-dependent pro-atherogenic marker were analyzed in snap-frozen EDTA-plasma using high performance liquid chromatography and stable isotope dilution, respectively. Differences between groups were analyzed using one-way ANOVA and *t* test. Data are given as mean and 95% Confidence Interval.

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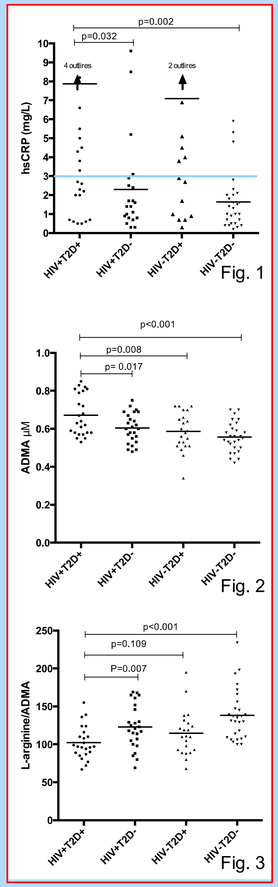

	HIV+T2D+	HIV+T2D-	HIV-T2D+	HIV-T2D-	P
N	**25**	**25**	**22**	**28**	
Age (years)	58 (55-61)	53 (50 -58)	(57 (53-60)	57 (55-60)	0.638
Gender (% male)	92	96	89	72	0.079
CD4 count (cells/µL)	672 (554-790)[a]	663 (520- 807)	1254 (980-1528)	849 (720-978)	<0.001
CD8 count (cells/µL)	994 (675-1312)[a]	884 (645 -1124)	567 (428-706)	458 (372-544)	0.001
Nadir CD4 (cells/µL)	180 (121-240)	266 (171-360)	-	-	0.392
HIV RNA (copies/mL)	26 (16-38)	27 (15-40)	-	-	0.757
Time since HIV diagnosis (months)	200 (153-248)	172 (112-232)	-	-	0.740
Treatment duration (months)	143 (116-170)	124 (89-159)	-	-	0.394
Fasting BG (mmol/L)	8.0 (6.9-9.0)[b,c]	5.3 (5.0-5.4)	9.0 (7.9-10.3)	5.3 (5.1-5.6)	<0.001
BMI	26 (24-28)[a,d]	25(23-27)	28 (27-30)	25 (24-26)	0.007

Differences between groups are analyzed using one-way ANOVA. Results are given as mean and 95% Confidence Interval. a, b, c, d are analyzed using t-test; a: p>0.05 vs. HIV+T2D-, b: p<0.05 vs. HIV+T2D-, c: p>0.05 vs. HIV-T2D+, d: p< 0.05 vs. HIV-T2D+. BMI: Body Mass Index.

Results

HIV+T2D+ had a higher level of hsCRP compared HIV+T2D- and HIV-T2D- (3.2 (0.86-12.0) vs. 1.5 (0.6-3.8) p= 0.032 and 1.1 (0.48 -2.8) p=0.002, respectively) but not compared to HIV-T2D+ (3.2 (0.86-12.0)) vs 2.8 (0.48-2.8), p=0.860). A cut-off at 3 mg/L was used to assess high risk of CVD. The percentage of HIV+T2D+, HIV+T2D-, HIV-T2D+ and HIV-T2D- with hsCRP above cut-off was 50%, 19%, 47% and 11 %, respectively (Fig. 1).

HIV+T2D+ had elevated ADMA (0.67 µM (0.63-0.72) compared to HIV+T2D- (0.60 µM (0.57 - 0.64) p=0.017), HIV-T2D+ (0.57 µM (0.51-63) p=0.008) and HIV-T2D- (0.55 µM (0.52- 0.58) p<0.001) (Fig. 2). Furthermore, L-arginine/ADMA ratio was decreased in HIV+T2D+ compared to HIV+T2D- and HIV-T2D- (102 (93-111) vs. 123 (111-135), p= 0.007) and 138 (125-151), p< 0.001, respectively), but not compared to HIV-T2D+ (102 (93-111) vs. (115 (102-128), p= 0.109 (Fig. 3). In contrast, no differences in TMAO level between the four groups were found. However, we found a positive correlation between ADMA and TMAO in HIV+T2D+ and HIV+T2D- (p=<0.001, r=0.524).

Conclusion

Evidence of elevated inflammation and endothelial dysfunction was found in HIV-infected persons with T2D compared to HIV-infected persons without T2D. Thus, our data indicate an addictive effect of HIV infection and T2D on inflammation and endothelial dysfunction possibly leading to elevated risk of CVD. This underlines the clinical importance of effective CVD prevention strategies in this group of patients.