ELEVATED TRIGLYCERIDES AND ENDOTHELIAL VASODILATOR DYSFUNCTION IN ADULTS LIVING WITH HIV-1

777

Vinicius P. Garcia, Kelly A. Stockelman, Anthony R. Bain, Cindy S. Firnhaber, Jared J. Greiner, Brian L. Stauffer, Elizabeth Connick, Christopher A. DeSouza
University of Colorado and University of Arizona

ABSTRACT

Adults living with HIV (ALWH) commonly have high triglyceride (TG) levels contributing to their increased risk of cardiovascular disease (CVD). Indeed, elevated TG levels are independently associated with an increased risk of myocardial infarction in ALWH. A major underlying mechanism for the TG-related increase in CVD is a profound worsening in vascular endothelial function. The influence of high TG levels on vascular endothelial function in ALWH is unknown. We tested the hypotheses that: 1) high TG levels are associated with worse endothelium-dependent vasodilation in antiretroviral (ART)-treated ALWH; and 2) the TG-related reduction in endothelial vasodilator function is due, in part, to diminished nitric oxide (NO) bioavailability. Forty-two sedentary, non-obese, normotensive, non-medicated (aside from ART) middle-aged men were studied: 14 healthy adults (age: 38±3 yr; TG: 73±8 mg/dL); 14 ALWH on stable antiretroviral therapy with normal TG (42±2 yr; 98±7 mg/dL); and 14 ALWH on stable antiretroviral therapy with elevated TG (43±2 yr; 234±17 mg/dL). Aside from TGs all other lipid and lipoproteins, glucose and insulin levels were clinically normal. Forearm blood flow (FBF) responses to intra-arterial infusion of the endothelial agonist acetylcholine (Ach), in the absence and presence of the endothelial NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA), as well as the endothelium-independent vasodilator sodium nitroprusside were determined by venous occlusion plethysmography. FBF responses to ACh were significantly lower (~20%) in the ALWH with normal TG (from 4.5±0.3 to 13.1±0.7 mL/100 mL tissue/min) vs healthy adults (4.9±0.3 to 17.3±0.7 mL/100 mL tissue/min); whereas, the ALWH with high TG (4.3±0.3 to 10.2±1.0 mL/100 mL tissue/min) demonstrated FBF responses to Ach significantly lower than ALWH with normal TG and healthy adults. L-NMMA significantly reduced the FBF response to Ach in the healthy (~30%) and ALWH with normal TG (~25%) but not the ALWH with high TG (~10%). There were no significant group differences in the FBF response to sodium nitroprusside. TG levels were inversely and significantly associated with the FBF response to Ach (r=-0.51; P=0.005) in the ALWH. Elevated TG levels is associated with lower endothelium-dependent vasodilation in adults living HIV-1 due, in part, to reduced NO bioavailability. Diminished NO-mediated endothelium-dependent vasodilation may underlie the increased risk of CVD in ALWH with high TG levels.

BACKGROUND

- Adults living with HIV (ALWH) commonly have high triglyceride (TG) levels contributing to their increased risk of cardiovascular disease (CVD).
- Elevated TG levels are independently associated with an increased risk of myocardial infarction in ALWH.
- Impaired endothelial vasomotor function (vasodilation and vasoconstriction) is a central etiologic feature in the development of CVD.
- The influence of high TG levels on vascular endothelial function in ALWH is unknown.
- Specifically, it is unknown whether nitric oxide (NO)-mediated endothelium-dependent vasodilation is diminished in ALWH with high TG levels.

EXPERIMENTAL AIM

The aim of this study was to determine the influence of high TG concentrations on NO-mediated, endothelium-dependent vasodilation in ALWH.

HYPOTHESIS

We tested the hypothesis that 1) high TG levels are associated with worse endothelium-dependent vasodilation in antiretroviral (ART)-treated ALWH; and 2) the TG-related reduction in endothelial vasodilator function is due, in part, to diminished nitric oxide (NO) bioavailability.

METHODS

Subjects

- 42 sedentary, middle-aged men were studied:
  - 14 healthy adults with normal triglycerides (<150 mg/dL)
  - 14 ALWH (CD4 count: 587.5 cells/μL; Viral load: <50 copies/mL) with normal triglycerides (<150 mg/dL)
  - 14 ALWH (CD4 count: 612.7 cells/μL; Viral load: <50 copies/mL) with high triglycerides (≥150 mg/dL)

Inclusion Criteria

- sedentary
- non-obese
- non-smoker
- normotensive
- normoglycemic
- free of overt cardiovascular disease

Screening and Testing Procedures

- Medical history and physical examination
- Fasting blood chemistries
- Graded exercise treadmill test
- Body composition (dual energy X-ray absorptiometry)

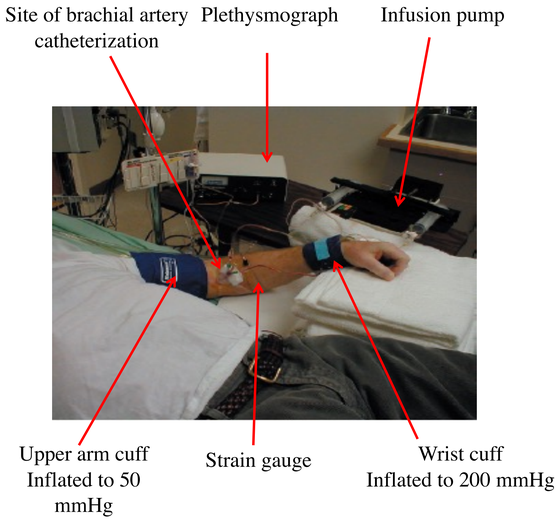
Assessment of Endothelial Vasomotor Function

- The brachial artery of the non-dominant arm was catheterized.
- Forearm blood flow (FBF) was assessed by strain gauge venous occlusion plethysmography in response to intra-arterial:

1) Acetylcholine (ACh; 4-16 μg/100 mL tissue/min)

- In the presence and absence of NG-monomethyl-L-arginine (L-NMMA; 5 mg/min)

2) Sodium Nitroprusside (SNP; 1-4 μg/100 mL tissue/min)



STATISTICAL ANALYSIS

Group differences in subject baseline characteristics were determined by between groups analysis of variance (ANOVA). Group differences in FBF responses to ACh, SNP, and ACh plus L-NMMA were determined by repeated measures ANOVA. Relations between variables of interest were determined using simple linear regression. Statistical significance was set *a priori* at P<0.05. Values are mean±SEM.

RESULTS

I. Selected Physical Characteristics

Variable	Healthy adults Normal TG (n=14)	ALWH Normal TG (n=14)	ALWH High TG (n=14)
Age, yrs,	38±3	42±2	43±2
Body mass, kg	81.3±3.2	79.1±3.9	83.6±3.1
BMI, kg/m2	25.3±0.7	25.2±1.1	26.9±0.8
Body fat, %	19.9±1.3	24.5±2.5	34.2±2.6*
Waist, cm	86.3±3	85.7±2.6	94.0±2.1*#
Systolic BP, mmHg	117±2	117±2	121±2
Diastolic BP, mmHg	72±2	75±2	78±2

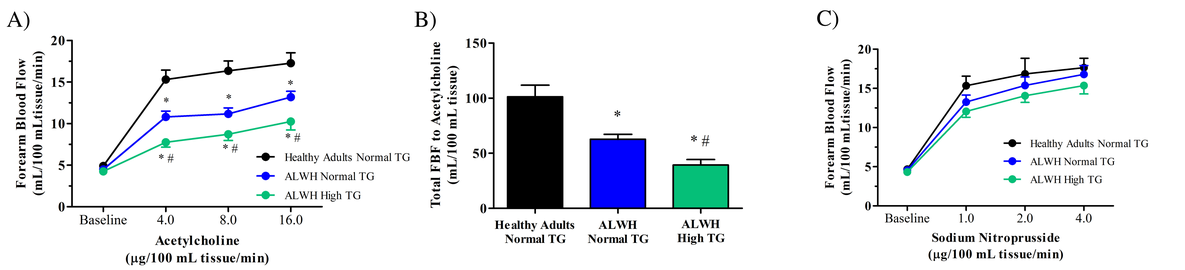
BMI, body mass index; BP, blood pressure; TG, triglyceride. Values are mean±SEM. *P<0.05 vs Healthy adults normal TG; #P<0.05 vs ALWH with TG

II. Metabolic Characteristics

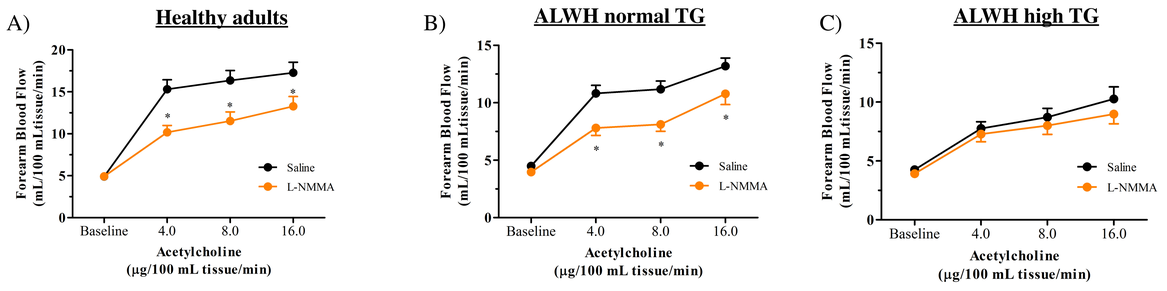
Variable	Healthy adults Normal TG (n=14)	ALWH Normal TG (n=14)	ALWH High TG (n=14)
Triglycerides, mg/dL	73±1	98±7	234±18*#
Total cholesterol, mg/dL	161±10	183±8	193±9*
HDL-cholesterol, mg/dL	47±3	48±3	38±3*#
LDL-cholesterol, mg/dL	99±8	116±8	108±10
Glucose, mg/dL	83±1	87±3	89±3
Insulin, μU/mL	5.3±0.6	6.3±1.1	8.6±1.0*

HDL, high-density lipoprotein; LDL, low-density lipoprotein TG, triglyceride. Values are mean±SEM. *P<0.05 vs Healthy adults normal TG; #P<0.05 vs ALWH normal TG

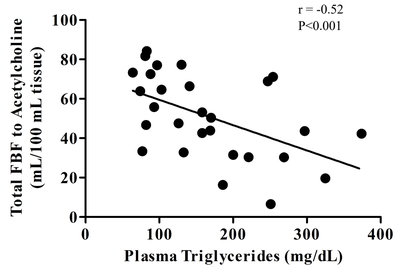
III. FBF response to ACh was ~30% lower (P<0.05) in the ALWH high TG compared with the healthy adults and ALWH normal TG groups (A). Total FBF (area under the curve) was ~50% lower (P<0.05) in the ALWH high TG vs the healthy adults and ALWH normal TG groups (B). The FBF responses to SNP were not significantly different between the groups (C). TG, triglyceride.



IV. L-NMMA significantly reduced (22%) FBF responses to ACh in the healthy adults (A) and ALWH with normal TG (B) but not the ALWH with high TG group (C). TG, triglyceride. * P<0.05



V. Triglyceride levels were significantly (P<0.05) and inversely associated with total FBF response to ACh.



CONCLUSIONS

- These results indicate that high triglycerides concentrations are associated with lower endothelium-dependent vasodilation in adults living HIV-1 due, in part, to reduced NO bioavailability.
- Impaired endothelial vasomotor function may underlie the increased risk of CVD in ALWH with high TG levels.