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HIV Infection and Cocaine Use Induce Endothelial Damage and Dysfunction In Africa Americans

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Abstract

Background—Clinical and epidemiological evidence suggests that HIV infection and cocaine use are associated with an increased risk of premature atherosclerosis. The underlying mechanisms linking HIV infection and cocaine use with early atherosclerosis remain elusive.

Methods and Results—Endothelin-1 (ET-1) levels in 360 African American participants in Baltimore, Maryland were measured. Quantile regression analysis was performed to examine the associations between ET-1, HIV infection, cocaine use, and other relevant clinical factors. The median of ET-1 in plasma, (1.05 pg/ml with interquartile range: 0.73, 1.40) for those with HIV infection was significantly higher than values for those without HIV infection (0.74 pg/ml with interquartile range: 0.61, 0.93). The median of ET-1 was markedly higher in chronic cocaine users (0.96 pg/ml with interquartile range: 0.71, 1.36) than that in non-cocaine users (0.72 pg/ml with interquartile range: 0.58, 1.06). Multivariate quantile regression suggested that HIV infection and duration of cocaine use were independently associated with plasma ET-1 levels after controlling for potential confounding factors.

Conclusions—This study may provide insight into the mechanism of premature atherosclerosis in HIV-infected cocaine users and suggest that measurement of ET-1 in plasma can be used as a marker of early atherosclerosis in HIV infected patients and cocaine users.

Keywords

HIV infection; Cocaine use; Endothelin-1; Africa Americans

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Conflict of Interest
None declared.

Introduction

HIV infection is implicated in the development of premature cardiovascular disease [1, 2]. Despite the extensive research attempting to explain the increased incidence of coronary artery disease (CAD) among persons with HIV infection, the mechanisms linking HIV infection with early atherosclerosis are not well described. In our previous publications, we have demonstrated that both HIV infection and cocaine use are associated with an increase risk of atherosclerosis [3–13]. Endothelial dysfunction represents the first step in the pathogenesis of atherosclerosis [14]. It has been demonstrated that early coronary atherosclerosis in humans is characterized by increased coronary and circulating ET-1 and is associated with coronary endothelial dysfunction [15].

In many patient populations, particularly our patient population, drug abuse is found in patients with HIV. The drug cocaine has been especially implicated in a wide variety of cardiac pathology. Despite recognition that cocaine abuse promotes atherosclerosis, most human studies of the impact of cocaine use on atherosclerosis have focused on clinical cardiovascular disease. Most importantly since patients with HIV may use cocaine, it is important to study the effect of cocaine in patients with HIV who may have endothelial dysfunction related to HIV infection. Our study objectives are (1) to explore whether HIV infection and cocaine use, especially duration of cocaine use are independently associated with endothelial damage or dysfunction, measured with the use of ET-1 levels; and (2) to examine whether HIV infection and cocaine use influence ET-1 levels differently for those with average ET-1 levels than for those with elevated ET-1 levels.

Methods

Study participants

Between June 2008 and September 2009, 360 African American participants were consecutively enrolled in an observational study investigating novel circulating biochemical markers of atherosclerosis in relation to HIV infection and chronic cocaine use at the Johns Hopkins Hospital, Baltimore, Maryland.

Inclusion criteria were age of 25 years or older and African American race (self-designated). Exclusion criteria were (1) any clinical, scintigraphic or laboratory evidence of CAD, (2) any symptoms believed to be related to CAD, such as chest pain. Each subject was interviewed to obtain information on sociodemographic characteristics, cigarette smoking, alcohol use, illicit drug-use behaviors, medical history, and all medications used. Cocaine use was defined as chronic use of cocaine by any route for at least 6 months, administered at least four times a month. Information was collected about the frequency (how many times a day in the past week, in the past month), patterns/forms of cocaine (speedball, crack, etc.), administration mode (injection, smoking, etc.), and duration of cocaine use.

Information was also collected about use of other drugs, such as opiates, benzodiazepines, or methamphetamine. A medical chart review was used to confirm information on medical history and medications that was provided by the subjects. Each subject also had a physical

examination, and several tests were performed: namely, a fasting lipid profile, high-sensitivity C-reactive protein (hs-CRP) test, and ET-1.

The Committee on Human Research at the Johns Hopkins School of Medicine approved the study protocol, and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines.

Blood collection

Blood samples were drawn using standard technique to include a serum sample for high-sensitivity C-reactive protein (hs-CRP), glucose and lipid profiles and another citrated blood sample. This sample centrifuged at 3000g for 15 min and then stored at -80°C until assayed for ET-1.

Human ET-1 assay

An extraction procedure of plasma sample, assay procedure and calculation of results followed ELISA kit of ET-1 (R&D Systems, Inc.). Standards of different concentration, control and the samples extracted were assayed simultaneously in duplicate. The within run precision correlation of variation was 5%.

Statistical analysis

Statistical analysis was performed with SAS 9.2 (SAS Institute, Cary NC). All continuous parameters were summarized by medians and interquartile ranges (IQRs), and all categorical parameters were summarized as proportions. To compare between-group differences in demographic and clinical characteristics, laboratory parameters, and other factors, the nonparametric Wilcoxon two-sample test was used for continuous variables and the Fisher's exact test was employed for categorical variables.

Since the associations between ET-1 and other factors may vary according to different ET-1 levels and since the frequency distribution of ET-1 levels may not be normally distributed, quantile regression analysis was performed to investigate changes in the quantiles of ET-1 levels as a function of other clinical factors described below.

To identify factors that were independently associated with ET-1 levels, median regression as performed as follows: an initial model included all relevant factors, including age, female gender, cigarette smoking, years of cigarette smoking, alcohol use, years of alcohol consumption, cocaine use, years of cocaine use, high-sensitivity C-reactive protein, the presence of HIV infection, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, LDL, HDL, and triglyceride (TG). Those variables that did not make significant contributions to the models were deleted in a backward manner, yielding the final models.

Then, a multivariate quantile regression analysis, including those variables in the final median model was performed with 9 quantiles (0.1 through 0.9). With the use of multivariate quantile regression, the relationships between ET-1 and other factors on any specific quantile of ET-1 levels could be compared to the relationships on other quantiles of

ET-1 levels while demographic and potential confounding factors were controlled for. The *P*-values reported are two-sided. A *P*-value <0.05 indicates statistical significance.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology : Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles [30].

Results

General Characteristics

The demographic and clinical characteristics of the study participants are presented in table 1. The median age was 45 years and 42% were women. Among the 360 participants, 72% were chronic cocaine users, and 71% were HIV infected. The median of duration of cocaine use was 7.0 years (interquartile range: 0.0 – 16.0). The median systolic blood pressure was 120mmHg (interquartile range: 109, 130) and the median diastolic blood pressure was 78 mmHg (interquartile range: 69, 84). Sixty-two participants (17.2%) were hypertensive.

ET-1

The median ET-1 was 0.92 pg/mL (interquartile range: 0.67, 1.29). The ET-1 levels by the related factors are shown in Table 2. The median ET-1 levels were 0.94 pg/mL (interquartile range: 0.67, 1.31) and 0.85 pg/mL (interquartile range: 0.71, 1.28) for those without hypertension and with hypertension, respectively ($p=0.30$, Wilcoxon nonparametric test). The median ET-1 levels were 0.85 pg/mL (interquartile range: 0.64, 1.20) and 1.04 pg/mL (interquartile range: 0.73, 1.42) for those aged < 45 years and aged ≥ 45 years, respectively ($p=0.0004$, Wilcoxon nonparametric test). The median ET-1 levels were 0.74 pg/mL (interquartile range: 0.61, 0.93) and 1.05 pg/mL (interquartile range: 0.73, 1.40) for those without HIV infection and with HIV infection, respectively ($p<0.0001$, Wilcoxon nonparametric test). The median ET-1 levels were 0.72 pg/mL (interquartile range: 0.58, 1.06) and 0.96 pg/mL (interquartile range: 0.71, 1.36) for those who did not use cocaine and who used cocaine, respectively ($p<0.0001$, Wilcoxon nonparametric test). The median ET-1 levels were 0.82 pg/mL (interquartile range: 0.61, 1.12) and 1.10 pg/mL (interquartile range: 0.75, 1.45) for those with triglycerides < 94 mg/dL and triglycerides ≥ 94 mg/dL, respectively ($p<0.0001$, Wilcoxon nonparametric test).

Median Regression Analysis

The results of multivariate median regression analysis are shown in Table 3. The final model analysis indicated that age, serum triglyceride level, years of cocaine use and the presence of HIV infection were independently and significantly associated with plasma ET-1 levels.

Multivariate Quantile Regression Analysis

The associations between ET-1 levels and the associated factors identified in median regression analyses at specific quantiles are shown in Table 4. The associations between ET-1 and the associated factors were not significant until the 0.2 quantile (corresponding to ET-1 level of 0.68 pg/mL) (Table 4). For age, the multivariate quantile regression coefficients were gradually increased with the quantiles. For years of cocaine use, the

regression coefficient was also gradually increased when the ET-1 quantile increased (Table 4 and Figure 1). The association between ET-1 and the presence of HIV infection was increased before ET-1 level reached the 0.9 quantile (corresponding to endothelin-1 level of 1.64 pg /mL). Finally, for triglycerides, the multivariate regression coefficient was steeply increased when ET-1 level reached the 0.6 quantile (corresponding to endothelin-1 level of 1.09 pg/mL) (Table 4 and Figure 1).

Discussion

The findings of this study show that HIV infection, duration of cocaine use, age and triglycerides levels were independently associated with ET-1 levels in African American adults. We found that the duration of cocaine use was linearly associated with plasma ET-1 levels. Although previous studies have shown cocaine use increased the ET-1 release in vitro and in vivo [16–18], our results suggest a response-relationship between duration of cocaine use and plasma ET-1 levels in this population.

Since elevated ET-1 levels may reflect endothelial dysfunction and damage [19], and since cocaine use has shown to be associated with an increased risk of atherosclerosis, this study suggests that cocaine use, especially long-term cocaine use may cause endothelial damage and dysfunction, leading to atherosclerosis. According to quantile regression analysis, the duration influences ET-1 levels differently for those with low ET-1 levels than those with elevated ET-1 levels. For those with less than or equal to the 0.2 quantile of ET-1 levels (corresponding to ET-1 level of 0.68 pg/mL), duration of cocaine use had no influence on ET-1 levels. However, the influence of duration of cocaine use on ET-1 levels was gradually increased when the ET-1 quantile increased. This suggests that cocaine use may be more detrimental to those who have endothelial damage or dysfunction.

HIV infection was independently associated with increased ET-1 levels. Previous studies have found that HIV infection induces endothelial damage and dysfunction [20, 21]. According to our median regression analysis, change in HIV status (from HIV negative to HIV positive) represented an increase of 0.242 ng/mL in the median ET-1 level. The influence of HIV infection on ET-1 levels was greater when the ET-1 quintile increased, suggesting that HIV infection is more detrimental to those who have endothelial damage or dysfunction.

Furthermore, this effect may be even greater in older individuals. We found that age was independently associated with ET-1 levels in plasma. The median of plasma ET-1 (1.04 ng/mL) for the persons of 45 years old or older was significantly higher than that (0.85 ng/mL) for those of <45 years old. According to our quartile regression, the influence of age on plasma ET-1 levels gradually increased when the ET-1 quantiles increased. As this population ages, greater attention to preventive strategies for atherosclerosis or interventions may be needed.

Finally, this study also suggests that triglycerides levels were independently and significantly associated with ET-1 levels in plasma. The relationship between triglyceride and ET-1 had been reported [22,23]. Hypertriglyceridemia is a risk factor for CAD. The

lesions of hypertriglyceridemia to coronary artery may be attributable to increase of ET-1 release and to decrease of NO release which promotes the process of atherogenesis resulted from platelet aggregation [24], inflammatory response, macrophage replication and fibroproliferative response [25].

ET-1 as a vasoconstrictor has been well identified. The negative effects of ET-1 binding to ET_A receptor on maintaining vascular tone have been confirmed by selective antagonists of ET_A receptor [26–28]. However, ET-1 levels into quartile regression analysis in our study do not show significant difference between those subjects without hypertension and those subjects with hypertension. A recent study suggests that there is an association between high level plasma ET-1 and the development of hypertension in general population in Japan [29]. Our finding is in contrast to the study. There are two potential explanations for this discrepancy. First, our study was cross-sectional, and the study [29] was a longitudinal study. The second explanation is that our study participants were relatively younger, although this may be speculative. Further work is required to assess the potential association between high level plasma ET-1 and the development of hypertension in this study population.

Several potential limitations of this study merit discussion. First, because the study participants were not a random sample of the people in the community, the results should be interpreted with caution. Second, because the study is cross-sectional in nature, no causal relationships can be established. Also, due to the nature of the cross-sectional design, some hidden confounding factors, such as socioeconomic status, were not adjusted for. Third, although the information about cocaine use was initially based on self-reported data and then confirmed by urine tests, false-negatives may still exist.

Despite its limitations, the study's findings of significant associations between HIV infection, duration of cocaine use and ET-1 levels have important implications for early prevention of atherosclerosis in HIV-infected cocaine users.

In conclusion, the study suggests that HIV infection, and duration of cocaine use were independently associated with ET-1 levels in this population. Furthermore, this study also suggests that HIV infection and duration of cocaine use influenced ET-1 levels differently for those with average ET-1 levels than for those with elevated ET-1 levels. This study may provide insight into the mechanism of premature atherosclerosis in HIV-infected cocaine users and suggest that measurement of ET-1 in plasma can be used as a marker of early atherosclerosis in HIV infected patients and cocaine users.

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Estimated Parameter by Quantile for endothelin-1 With 95% Confidence Limits

Figure 1.

Multivariable-Adjusted Quantile Point Estimates and 95% Confidence Bands (shaded areas) – Factors Associated with Endothelin-1 Levels.

Abbreviation: HIV, the presence of HIV infection; syrsoc, square-root transformed years of cocaine use; triglycerides, serum triglycerides.

This analysis suggests that the relationships between endothelin-1 levels and age, cocaine use years, HIV infection and serum triglycerides varied according to different endothelin-1 levels. For example, the magnitudes of the association between endothelin-1 and age became stronger when participants' endothelin-1 levels were exceeded the 0.6 quantile.

Table 1:

Demographic and clinical characteristics of study participants

Variable	Median (IQR)	Proportion (%)
Age	45.0 (41.0, 50.0)	
Female gender		41.6
BMI	25.8 (22.5, 31.0)	
Systolic BP mm Hg	120.0 (109.0, 130.0)	
Diastolic BP mm Hg	78.0 (69.0, 84.0)	
hsCRP mg/dl	2.0 (0.6, 4.6)	
Glucose mg/dl	86.0 (80.0, 94.0)	
Total cholesterol mg/dl	164.0 (143.0, 193.0)	
LDL cholesterol mg/dl	88.0 (69.0, 111.0)	
HDL cholesterol mg/dl	52.0 (40.0, 63.0)	
Triglyceride mg/dl	94.0 (67.0, 144.0)	
Cocaine use		
No		28.4
Yes		71.6
Years of cocaine use	7.0 (0.0, 16.0)	
Cigarette smoking		
No		19.0
Yes		81.0
Years of cigarette smoking	21.5 (5.0, 30.3)	
Alcohol use		
No		12.1
Yes		87.9
Years of alcohol use	15.0 (4.0, 28.0)	
HIV infection		
No		29.4
Yes		70.6
Endothelin-1 pg/ml	0.92 (0.67, 1.29)	

Table 2:

Endothelin-1 levels by the associated factors

Variable	Median(IQR)	P-value
Age (years)		0.0004
<45	0.85 (0.64, 1.20)	
45	1.04 (0.73, 1.42)	
Gender		0.11
Male	0.96 (0.71, 1.33)	
Female	0.87 (0.64, 1.25)	
BMI		0.25
<26	0.95 (0.69, 1.36)	
26	0.89 (0.66, 1.25)	
Systolic BP mmHg		0.30
<120	0.94 (0.67, 1.31)	
120	0.85 (0.71, 1.28)	
Diastolic BP mmHg		0.78
<78	0.93 (0.64, 1.28)	
78	0.89 (0.70, 1.33)	
hsCRP mg/dl		0.28
<2.0	0.93 (0.64, 1.25)	
2.0	0.92 (0.70, 1.36)	
Glucose mg/dl		0.36
<86	0.89 (0.65, 1.30)	
86	0.96 (0.71, 1.29)	
Total cholesterol mg/dl		0.63
<164	0.92 (0.67, 1.25)	
164	0.93 (0.69, 1.33)	
LDL cholesterol mg/dl		0.94
<88	0.94 (0.67, 1.29)	
88	0.90 (0.69, 1.31)	
HDL cholesterol mg/dl		0.40
<52	0.93 (0.71, 1.36)	
52	0.91 (0.66, 1.25)	
Triglyceride mg/dl		<0.0001
<94	0.82 (0.61, 1.12)	
94	1.10 (0.75, 1.45)	
Chronic use of cocaine		<0.0001
No	0.72 (0.58, 1.06)	
Yes	0.96 (0.71, 1.36)	
Cigarette smoking		0.0005
No	0.72 (0.58, 1.06)	
Yes	0.96 (0.71, 1.36)	

Variable	Median(IQR)	P-value
Alcohol use		0.90
No	1.02 (0.62, 1.26)	
Yes	0.92 (0.69, 1.31)	
HIV infection		<0.0001
No	0.74 (0.61, 0.93)	
Yes	1.05 (0.73, 1.40)	

Table 3:

Median regression analysis: associations between endothelin-1 and other factors

Factor	Initial model			Final model		
	Coefficient	Regression S.E	P-value	Coefficient	Regression S.E	P-value
Age	0.0060	0.004	0.16	0.008	0.004	0.019
Female	−0.0451	0.059	0.45			
Cigarette smoking	−0.0009	0.13	0.99			
Smoking years	0.0069	0.02	0.79			
Cocaine use	0.1976	0.10	0.055			
Cocaine years	−0.0232	0.02	0.34	0.03	0.014	0.038
Alcohol use	−0.0131	0.11	0.37			
Alcohol years	0.0111	0.02	0.58			
HIV infection	0.2463	0.06	0.0003	0.242	0.060	<0.0001
SysBP	−0.0013	0.002	0.62			
DiaBP	0.0014	0.003	0.70			
BMI	−0.0015	0.0047	0.751			
hsCRP	0.0378	0.02	0.11			
Glucose	−0.0005	0.0007	0.468			
Cholesterol	0.0005	0.015	0.972			
LDL	0.0000	0.015	0.99			
HDL	0.0012	0.015	0.93			
Triglycerides	0.0016	0.003	0.62	0.0007	0.0003	0.009

Table 4:
Regression coefficients (S.E) of factors associated with endothelin-1 levels by regression at specific quantiles

Quantile	10%	20%	30%	40%	50%	60%	70%	80%	90%
Age	0.006(0.003)	0.006(0.003)	0.007(0.003)*	0.007(0.003)*	0.008(0.004)*	0.007(0.004)	0.008(0.004)	0.012(0.005)*	0.017(0.008)*
Cocyear	0.018(0.013)	0.020(0.010)	0.031(0.013)*	0.031(0.013)*	0.030(0.014)*	0.040(0.015)**	0.038(0.018)***	0.047(0.022)*	0.054(0.034)
HIV	0.034(0.054)	0.105(0.043)	0.183(0.054)*	0.181(0.054)***	0.242(0.060)***	0.332(0.063)***	0.334(0.076)	0.379(0.095)***	0.239(0.145)
TG	0.0001(0.0002)	0.0006(0.0002)*	0.0006(0.0002)**	0.0006(0.0002)*	0.0007(0.0003)**	0.0005(0.0003)	0.0007(0.0003)*	0.001(0.0001)**	0.002(0.0006)**
Endothelin-1	0.56	0.68	0.76	0.86	0.96	1.09	1.19	1.37	1.64

Abbreviations: Cocyear, square-root transformed years of cocaine use; HIV, the presence of HIV infection; TG, serum triglycerides (mg/dL). Endothelin-1 was the predicted values.

* P<0.05;

** P<0.01,

*** P<0.0001.