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Cocaine Use and Subclinical Coronary Artery Disease in Caucasians

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Abstract

Objective: Cocaine remains among the most commonly used and trafficked illicit drug in the world, and its use increases myocardial demand from elevated heart rate and blood pressure, and causes coronary vasospasm leading to myocardial infarction (MI). Surrogate markers for atherosclerosis of sub-clinical coronary artery disease (CAD) are often used to assess the presence of atherosclerosis in high-risk patients. Carotid intima media thickness (CIMT) as a surrogate marker for atherosclerosis is an independent predictor of future cardiovascular (CV) events and is routinely used in clinical studies. The objective of this preliminary study is to provide the baseline information on the presence of subclinical CAD in Caucasians with chronic cocaine use disorder using CIMT as a surrogate marker.

Method: The study inclusion criteria included: a) Caucasian adult, 18 yrs and older with cocaine use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5); and b) able to understand and sign the consent form (provided in English only). 40 participants were selected using convenient sampling, approached, and screened.

Result: The mean LDL (low density lipoprotein), HDL (high density lipoprotein), and total cholesterol of the participants were within normal ranges. The mean right CIMT was 0.57 mm (± 0.01) and left CIMT was 0.59 mm (± 0.1). CIMT was found to be associated with route administration (p=0.0036) and smoking route had a significant positive association with the CIMT.

Discussion: This study's preliminary findings of no association between chronic cocaine use and sub-clinical CAD measured by CIMT in asymptomatic, young-to-middle-aged adult Caucasian cocaine users are new and in order to support these findings, larger prospective studies are warranted.

Keywords: Cocaine users; Atherosclerosis; Carotid intima media thickness; Surrogate marker; Cardiovascular disease; Myocardial infarction; Cocaine

Introduction

Cocaine remains among the most commonly used and trafficked illicit drug in the world after cannabis and heroin, respectively [1]. It is used by more than 17.24 million people worldwide [2] and is a significant public health problem that has somatic, psychological, psychiatric, and socio-economic complications. Cocaine use is responsible for nearly half of the emergency room visits due to illicit drug use [3]. Some of the most frequent complications associated with cocaine use are cardiovascular effects (acute coronary syndrome, cardiac arrhythmias, increased blood pressure [BP]), respiratory effects (fibrosis, interstitial pneumonitis, pulmonary hypertension, alveolar haemorrhage, asthma exacerbation; emphysema), neurological effects (strokes, aneurysms, seizures, headaches), risk for contracting communicable diseases such as HIV/AIDS, hepatitis B and C, and sexual transmitted diseases (STDs) [4].

Pathologically, cocaine use increases myocardial demand from elevated heart rate and blood pressure, and causes coronary vasospasm leading to myocardial infarction (MI) [5]. Acute coronary events/MI usually occurs minutes to hours after cocaine administration. However, it is unclear if these acute hemodynamic effects fully explain the pathological association between coronary events and cocaine use, and if this association is due to active inflammation.

Surrogate markers for atherosclerosis of sub-clinical coronary artery disease (CAD) are often used to assess the presence of atherosclerosis in high-risk patients. These markers such as carotid intima media thickness (CIMT) and coronary artery calcium scoring (CACS), have been validated in several studies for their reproducibility in assessing sub-clinical atherosclerosis [6]. CIMT as a surrogate marker for atherosclerosis is an independent predictor of future cardiovascular (CV) events and is routinely used in clinical studies [7,8]. Use of non-invasive CV markers have been studied in cocaine users for CAD predictability. However, almost all the studies are in African American (AA) chronic cocaine users, primarily with HIV infection [9,10]. To our knowledge, there is no work done in

Caucasian cocaine users on assessing sub-clinical CAD. This is important to understand because, in addition to risk factors, long-term cocaine use may have a direct effect on accelerated and premature CAD, possibly resulting from mechanisms that are unknown at this point. The objective of this preliminary study is to provide the baseline information on the presence of subclinical CAD in Caucasians with chronic cocaine use disorder using CIMT as a surrogate marker.

Methods

The study was approved by the Institutional Review Board (IRB) at the University of Florida-Jacksonville (UF-JAX) and was conducted at an accredited drug treatment center: River Region Human Services (RRHS). Because of the absence of a formal IRB at RRHS, it received approval from the UF-Gainesville IRB before the study began. RRHS is a non-profit 501-(c)-3 corporation, which provides a comprehensive array of substance abuse prevention, intervention, and treatment services for persons residing in Baker, Clay, Duval, Nassau, and St. John's Counties in Northeast Florida (FL). RRHS provides services beginning pre-conception and continuing throughout childhood, adolescence, and adulthood, including specialized services for the elderly. RRHS also provides preventive and counseling services including HIV/AIDS related health care services and referral services throughout the community. Substance abuse, mental health and co-occurring services include outpatient, residential, day/night, medication, case management and continuing care services.

The study inclusion criteria included: a) Caucasian adult, 18 yrs and older with cocaine use disorder, as defined in Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [11]; and b) able to understand and sign the consent form (provided in English only). RRHS provided a list of cocaine users, who were actively attending their treatment clinics, from which, 40 participants were selected using convenient sampling, approached, and screened. Exclusion criteria included: a) those with a known mental disorder or other disability that might affect normal behavior. The research team explained the purpose of the study and obtained consent from each participant at RRHS. Information was collected from the participants on a study data collection form that included socio-demographic information, past medical history, family history, and drug history, and route of administration for cocaine. Participants' blood samples were collected at RRHS and sent to a commercial accredited laboratory (LabCorp, Inc) for testing. Blood tests included lipids, comprehensive metabolic panel, complete blood count, HIV, and Syphilis testing. Participants were compensated for their time and travel with a $20 gift certificate.

Carotid intima media thickness (CIMT)

B-mode ultrasound scanning of bilateral carotid arteries was performed by a trained physician in a quiet temperature-controlled room at RRHS. In order to maintain consistency, the same carotid IMT Doppler machine was used (MTurbo machine by SonoSite, Inc Bothell, WA with edge detection algorithms for measuring CIMT). An HFL38 probe with operating frequencies between 6.0-13.0 MHz was utilized. Both common carotid arteries were scanned with the participants in a supine position and head elevated at a 45° angle. IMT thickness was measured 1cm proximal to the bifurcation of the common carotid artery. In addition to measuring IMT, presence of atherosclerotic plaque was also noted. Carotid plaque is defined as a thickness ≥ 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface [12].

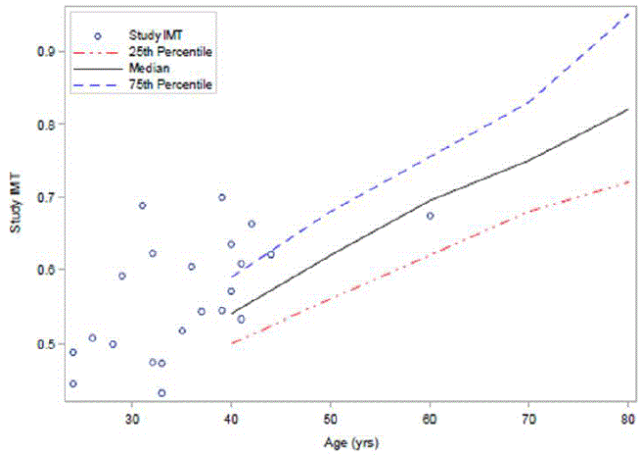

Figure 1: Carotid intima media thickness (CIMT) by age in women [13].

Characteristics	
Age [mean ± sd]; n=33	36.8 ± 9.3
Female Gender [frequency (%)]; n=33	22 (67%)
Employment Status [frequency (%)]; n=31	
Unemployed	22 (71%)
Employed	4 (13%)
Disabled	5 (16%)
Total Annual Income [frequency (%)]; n=30	
Less than $25,000	25 (83%)
Highest Education Completed [frequency (%)]; n=31	
Less than High school	8 (26%)
High school/GED	18 (58%)
Post High school degree	5 (16%)
Last Cocaine use [frequency (%)]; n=31	
Less than 1 month	19 (61%)
More than 1 month	12 (39%)
Route of Administration [frequency (%)]; n=31	
Snorted	11 (36%)
Injected	8 (26%)
Smoked	8 (26%)
Multiple	4 (13%)
Smoker [frequency (%)]; n=31	
Yes	29 (94%)
Health Insurance [frequency (%)]; n=31	

Yes	26 (84%)
Pregnant [frequency (%)]; n=22	
Yes	6 (27%)
Past Medical History of CVD [frequency (%)]; n=32	
Yes	4 (13%)
Family History [frequency (%)]; n=32	
Yes	9 (28%)
HIV Status [frequency (%)]; n=29	
Positive	1 (4%)
Height (in) [mean ± sd]; n=31	67.1±4
Weight (lbs) [mean ± sd]; n=31	168.3 ± 31.1
BMI [mean ± sd]; n=31	26.2 ± 4.1
Systolic Blood Pressure (mmHg) [mean ± sd]; n=33	127.8 ± 14.3
Diastolic Blood Pressure (mmHg) [mean ± sd]; n=33	82.7 ± 11.5
Heart Rate (HR) [mean ± sd]; n=33	76.7 ± 14.8
Total Cholesterol [mean ± sd]; n=28	160.1 ± 41.3
High Density Lipoprotein (HDL) [mean ± sd]; n=28	47 ± 14.2
Low Density Lipoprotein (LDL) [mean ± sd]; n=28	88.9 ± 31.9
Right Common Carotid Artery [mean ± sd]; n=33	0.568 ± 0.096
Left Common Carotid Artery [mean ± sd]; n=33	0.591 ± 0.096

Table 1: Summary of demographic and clinical characteristics of population of cocaine users.

Sample, power calculation and data analysis

This is as a pilot project for a future powered clinical trial; therefore formal power calculation was not performed. A sample of 40 eligible participants was recruited (based on available funding). Detailed descriptive summaries (e.g., means, standard deviations, percentiles, ranges) and graphical displays (e.g., scatter plots and diffogram) were estimated to explore CIMT results in comparison to non-cocaine comparable groups. Two-factor analysis of variance (ANOVA) models were fit to these data with side (right, left) and other potential predictors (one predictor per model) as factors and the interaction of these two terms. Potential confounding variables included gender, employment status, total annual income, maximum education level, health insurance, route of administration (injecting, smoking, snorting, and multiple), pregnancy in females, and past medical and family history of CV or cerebro-vascular disease. Adjusted (least-square) means were estimated and pairwise comparisons were performed with a Tukey-Kramer adjustment for multiple comparisons. A diffogram graphically displayed the results of these pair-wise comparisons. Residuals were plotted to assess the assumption of normality. All analyses were performed in SAS® for Windows Version 9.3 or later.

Results

Of the 40 patients who agreed to participate, 33 (83%) completed the CIMT evaluation and therefore were included in the final analysis. Table 1 describes the socio-demographics and clinical characteristics of study participants. The mean age of the participants was 37 (± 9) years with 67% of them being females. The majority had a high school diploma (74%), was unemployed (71%), had an income of less than $25,000 (83%), and was insured through Medicaid (84%). The most common route of administration of cocaine was snorting (35%), but injecting, smoking, and use of multiple routes were reported by 8 (26%), 8 (26%), and 4 (13%) participants, respectively. Participants' personal and/or family history of cardiovascular diseases (CVDs) was unremarkable, and only one participant reported as being HIV-positive. (Table 1) The mean LDL (low density lipoprotein), HDL (high density lipoprotein), and total cholesterol of the participants were within normal ranges (Table 1).

Quartile	Female	Male	Total
<25th	16	7	23
25th-75th	5	2	7
>75th	1	2	3
Total	22	11	33

Table 2: Carotid IMT (CIMT) of participants compared to normal population [15,23].

Characteristics	N	p-value*
Gender	33	0.0915
Employment status	31	0.1321
Total annual income	30	0.5113
Maximum education level	31	0.0584
Last cocaine use	31	0.3935
Route of Administration	31	<0.0001
Health insurance	31	0.4946
Pregnancy	22	0.2616
Past Medical History of CVD	32	0.0517
Family History of CVD	32	0.0415

Table 3: Predictors of CIMT. CVD: Cardiovascular disease; *using analysis of variance model term for each characteristic (in separate models).

The mean right CIMT was 0.57 mm (± 0.01) and left CIMT was 0.59 mm (± 0.1). Only one female and 2 male cocaine users had mean CIMT values in the 75th percentile for age when compared to age-matched US controls (Table 2). However, when compared with European age-matched controls (Figures 1 and 2), the mean CIMT values for female cocaine users in our study were higher [13]. Male cocaine users in the study did not show similar results when compared to their normal counterparts in the same study. Furthermore, in ANOVA analyses, CIMT was found to be associated with route

administration (p=0.0036, Table 3) and smoking route had a significant positive association with the CIMT as seen in Figure 3. Additionally, CIMT was also associated with past medical history of CVD as well as family history of CVD. Figure 3 (Diffogram) summarizes the adjusted means for route of administration and the pair-wise differences among these adjusted (least-square) means. Briefly, the adjusted mean CIMT was significantly higher for smoking route (mean=0.69) than for injecting (0.57), snorting (0.54) or multiple routes (0.53). There were no significant differences among the latter three routes. Other predictors showed no significant association with cocaine use in either gender and there were no significant interactions or differences due to left *vs* right side.

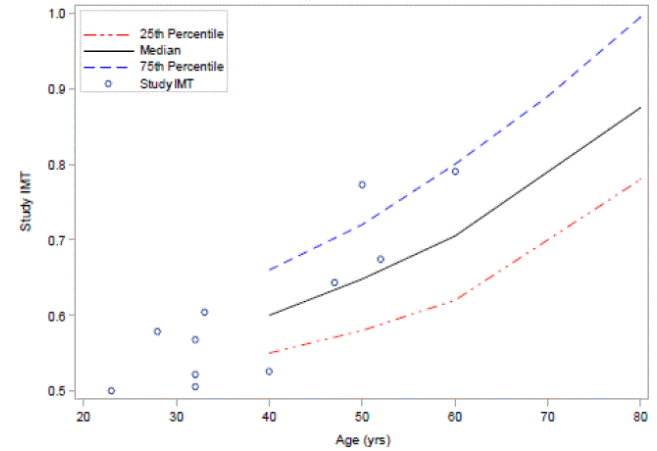

Figure 2: Carotid intima media thickness (CIMT) by age in Men [13].

Discussion

Atherosclerotic vascular disease begins in childhood and progresses over decades [14-16]. To prevent death and morbidity from CVD, there is great interest in identifying asymptomatic patients at high risk who would be candidates for more intensive, evidence-based medical interventions that reduce CVD risk. Imaging of arteries to identify and quantify the presence of subclinical vascular disease has been suggested to further refine CVD risk assessment [17]. As a screening test, imaging must be safe, be sensitive, be affordable, and lead to interventions that can favorably alter the natural history of CVD. Measurement of CIMT with B-mode ultrasound is a noninvasive, sensitive, and reproducible technique for identifying and quantifying atherosclerotic burden and CVD risk. It is a well-validated research tool that has been translated increasingly into clinical practice [18-21]. The US Centers for Medicare and Medicaid has established a current procedural terminology code (CPT code 0126T) for common CIMT study for evaluation of atherosclerotic burden or CAD risk factor assessment in high-risk groups such as cocaine users.

To our knowledge, sub clinical CAD in Caucasians has not been studied in the past and this small pilot presents preliminary findings for future larger studies. When comparing the results with limited published work on CIMT in Caucasians cocaine users and considering comparison of mean CIMT in age and gender matched groups, in a population-based, cross-sectional study, it was shown that non-cocaine user men had higher mean CIMT measures than non-cocaine user women and that CIMT was associated with sex, age, pulse pressure, HDL (high density lipoprotein) cholesterol, and smoking in men [13]. Our small study findings did not show such associations. However, we did find a significant difference among routes of cocaine administration, with subjects who smoked cocaine having higher CIMT than those who used other routes of administration.

In studies of cocaine users of other races, significant sub-clinical CAD has been identified in AA cocaine users with HIV [22]. However, our findings in Caucasians differed as majority of subjects had CIMT values below age-matched 25th percentile levels [15,23]. According to the American Society of Echocardiography (ASE) Consensus Statement, CIMT measures less than or equal to 25th percentile are considered low CVD risk. There can be several reasons for these differences. One major reason for significant sub-clinical CAD in AAs cocaine users was the presence of HIV infection (on highly active antiretroviral therapy) that in itself is a well-known risk factor for increased CAD risk. Secondly, Lai et al. [22] assessed the sub-clinical CAD using coronary artery calcium scores (CACS) measured by cardiac computerized tomography (CT), therefore results from this study may not be comparable with our study. Larger studies are needed on cocaine users without HIV infection in order to assess the independent effect of cocaine use on sub-clinical CAD.

The study participants in our study had normal lipid levels, similar to previous studies in AA cocaine users [23]. This finding is not unusual and may indicate that cocaine use might promote an increased atherosclerosis risk by pathways other than inflammation. One possible mechanism that needs to be investigated is the conversion of anti-inflammatory HDL to pro-inflammatory "dysfunctional" HDL form, which is seen during pro-oxidative and inflammatory states [24] Dysfunctional HDL has increased redox activity and reduced antioxidant properties which may contribute to atherogenesis [25]. Other mechanisms for atherosclerosis in cocaine users could be elevated levels of adventitial mast cells, seen in some studies [26]. Additional increases include increase concentration of plasminogen-activator inhibitor, endothelial permeability to low-density lipoprotein, and platelet activation and aggregability seen in cocaine users warranting further research [27].

Limitations

This study has several potential limitations. First, selection bias may affect any cross-sectional study, and this study is no exception. This is a highly selected sample taken from a treatment clinic. It should not be considered representative of the more general US population of chronic cocaine users. Also, the sample included a higher number of females than males, which also is not representative of the general population. Second, the cross-sectional design, along with a small sample size (n=33) does not allow to estimate causal association between risk factors and CIMT. Given the number of tests performed and the small sample size, the findings should be viewed as descriptive rather than definitive. Third, there was only one subject who reported to be positive for HIV, which also is not representative of general population of chronic cocaine users. Lastly, two participants presented with plaques, but were still included in the study analysis.

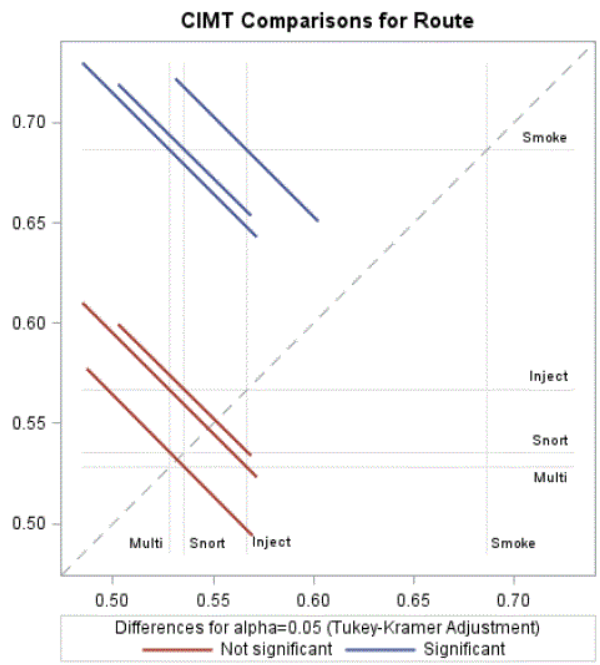

Figure 3: Diffogram (and associated 95% Tukey-Kramer-adjusted confidence intervals) comparing pairs of adjusted (least-square) mean CIMT values by route of exposure. Graph abbreviations: 'Smoke' for smoking, 'Inject' for injecting, 'Snort' for snorting, and 'Multi' for multiple routes. To determine the difference in adjusted means for a pair of routes determine intersection of vertical line for one route and horizontal line for the other route. The confidence interval is interpreted as being perpendicular to the diagonal (45°) dashed line. In particular, a confidence interval that crosses the diagonal line indicates a pair of means is not significantly different from each other (e.g. Snorting and Injecting) while a confidence interval that does not cross the diagonal line indicates a pair of means that are significantly different from one another (e.g. Smoking and Injecting).

Despite its limitations, this study's preliminary findings of no association between chronic cocaine use and sub-clinical CAD measured by CIMT in asymptomatic, young-to-middle-aged adult Caucasian cocaine users under addiction treatment are new and not well studied. Future larger studies confirming these findings that can be generalized to an urban, Caucasian population are warranted. Moreover studies on the assessment of sub-clinical CAD with better predictive markers such as CACS in cocaine users are warranted. This is an area of further research.

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