Coronary Heart Disease (CHD) Risk Factors and Metabolic Syndrome in HIV-Positive Drug Users in Miami

Marianna K. Baum, Carlin Rafie, Shenghan Lai, Li Hua Xue, Sabrina Sales, J. Bryan Page, Ronald Berkman, Linden Karas and Adriana Campa
Florida International University, College of Health and Urban Affairs
University of Miami School of Medicine, Miami, Florida
Johns Hopkins University, Baltimore, Maryland

Abstract: The frequency of coronary heart disease (CHD) is increasing among HIV seropositive persons. This phenomenon may be related to HIV disease itself, the use of antiretroviral medications and increased length of survival, or the synergism of these factors. In this study we have calculated the 10-year CHD risk estimate and the prevalence of metabolic syndrome in a cohort of 118 HIV seropositive chronic drug users, including those who are on HAART with or without protease inhibitors (PI). The results showed that the 10-year coronary heart disease risk among the HIV seropositive drug users was 4.8 ± 5.7, which is within the range of results published for other HIV infected cohorts. The 10-year CHD risk was significantly higher in men (5.9±6.1, p<0.001) than in women (1.7±2.4), due to their gender and the pre-menopausal mean age of the women (39.4±7.3 years of age), despite a significantly higher rate of abdominal obesity (54.8% in women vs. 8.1% in men, p<0.001) and lower HDL (61.3% in women vs. 40% in men, p=0.042). The rate of metabolic syndrome among our female HIV seropositive drug users was significantly higher (29% vs 10.3%, p=0.013) compared to men (10.3%). Participants with metabolic syndrome had a significantly higher 10-year CHD risk (27.8% vs. 10.2%, p=0.041) and higher mean BMI (28.6 ± 4.1 vs. 24.2±4, p<0.001) than those without the syndrome. The predominant proportion of the cohort had a high viral load, suggesting that their use of illicit drugs has an influence on either adherence or effectiveness of antiretroviral medication. Increased viral load was significantly associated with metabolic syndrome (OR=2.23, 95% CI:1.12, 4.47; p=0.023), high fasting glucose (OR=1.61, 95% CI: 1.02, 2.55; p=0.042) and low HDL levels (OR=1.41, 95%CI: 1.01, 1.98; p=0.046), after controlling for age, gender, smoking, PI exposure, BMI and CD4. HAART with or without PI did not significantly impact the 10-year CHD risk estimate or metabolic syndrome in this cohort. The estimated effect of PI, however, was positively and significantly related to triglyceride levels (effect estimate=95.81; 95% CI:39.40, 152.21; p<0.01) after controlling for age, gender, smoking, viral load, CD4 cell count and BMI. Heavy use of cigarettes and crack/cocaine was inversely associated with obesity (OR=0.84, 95% CI:0.67; 0.99; p=0.049; OR=0.43, 95% CI:0.19, 0.98; p=0.044, respectively), while use of marijuana tended to be associated with increased central obesity (p=0.08). Heavy cigarette smoking was significantly associated with low HDL (OR=3.06, 95% CI:1.18; 7.95, p=0.02). The significant association of higher viral load with CHD risk indicates that controlling viral load may be important in reducing CHD risk in HIV infected drug users.

Key words: Coronary heart disease risk, HIV, metabolic syndrome

INTRODUCTION

Highly active antiretroviral therapy (HAART) improves the clinical course, prognosis and survival of HIV infected patients. Its prolonged use, particularly with the protease inhibitors, has been associated with an increase in coronary heart disease (CHD) risk[1-3] and with a number of metabolic abnormalities collectively named metabolic syndrome[4-6]. Metabolic syndrome occurs in approximately one quarter of the US general population[7] and in approximately one third of the HIV infected patients[8-10]. With the diagnosis of metabolic syndrome, the risk of developing CHD increases three-fold and the risk of dying from a heart attack or stroke doubles[11].

Estimate of 10-year coronary heart disease risk uses an algorithm that includes age, gender, blood pressure, total cholesterol and LDL cholesterol, high fasting glucose and smoking status[12]. While a number of studies have been published to demonstrate metabolic abnormalities and CHD risk in HIV seropositive cohorts[11,13-17], to our knowledge no reports focus on cohorts of HIV infected drug users and the contribution of illicit drugs to CHD risk. Moreover,
the factors used to estimate CHD risk in the drug abusing population may not be accurate as the drug abuse itself significantly increases the risk\(^{18}\). In this study we have calculated the 10-year CHD risk estimate and the prevalence of metabolic syndrome in a cohort of HIV seropositive chronic drug users, including those who are on HAART with or without protease inhibitors.

**MATERIALS AND METHODS**

**Study design:** A cross-sectional study was carried out on a cohort of 118 HIV infected drug users recruited between March, 2002 and December, 2003 from the Camillus House, a non-profit organization that provides services to the poor in Miami, Florida. The study protocol was approved by the Florida International University Internal Review Board and consisted of a physical examination including a medical history and laboratory analyses after a 12-hour fast. Documented HIV seropositive status, age 18 to 55 years or older and active drug use (determined by urine toxicology) were inclusion criteria for the study. Sociodemographic, alcohol and drug abuse data were collected. All participants gave written informed consent prior to enrollment in the study.

**Participant examination protocol:** Physical examination and medical history were performed by a nurse practitioner after determination of eligibility. The data collection tools emphasized the history of infectious illness, diabetes, coronary artery vascular disease and hypertension. Drug history included currently prescribed medications, as well as frequency and quantity of cigarette smoking, alcohol consumption and illicit drug use in the previous 6 months. Height, weight and waist circumference were obtained using standard methods and blood pressure was measured in the left arm with the elbow flexed to heart level. Venous blood was drawn for CD4 cell count, viral load, blood chemistry and lipid panel; urine was collected for toxicology.

**Biochemical assays:** Lymphocyte phenotype was determined with four-color immunophenotyping panel of monoclonal antibodies. Differential counts were determined using a Coulter MaxM hematology instrument and corroborated with cytocentrifuge smears. Viral load was obtained by the reverse transcriptase polymerase reaction using the Roche Amplicor reagents and protocol. Triglycerides, total cholesterol and HDL were determined directly using the Aeroset \(^{\text{TM}}\) System (Abbott Laboratories), with calculation of LDL and VLDL levels. C-reactive protein was determined using the CRP Ultra Range Reagent Kit (Equal Diagnostics), a latex-enhanced turbidimetric immunoassay.

**Definition of 10-year cardiovascular risk and metabolic syndrome:** The 10-year CHD risk was determined using the algorithm derived from the Framingham study to estimate cardiovascular risk in the general population\(^{12}\). The risk factors included in the Framingham calculation of 10-year risk are: age, gender, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, elevated fasting glucose and cigarette smoking.

Metabolic syndrome was defined according to the guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment panel ATP III\(^{4}\). Participants having ≥ 3 of the following factors were defined as having metabolic syndrome: waist circumference > 102 cm in men and 88 cm in women, serum triglycerides ≥ 150 mg/dL, high density lipoprotein (HDL) cholesterol ≤ 40 mg/dL in men and ≤50 mg/dL in women; blood pressure ≥ 130/85 mmHg; and serum glucose ≥ 110 mg/dL.

**Statistical analysis:** This is a crosssectional study that explores the associations of HIV disease, antiretroviral treatment and drugs of abuse and CHD risk in a cohort of HIV seropositive drug users in Miami. Our analyses first focused on the calculation of the 10-year CHD risk for the total cohort and by gender using the 10-year risk % derived from the Framingham multiple-risk-factor equation\(^{12}\) and the NCEP Adult Treatment panel ATP III guidelines to diagnose metabolic syndrome\(^{4}\). We compared the rate of 10-year CHD risk and the parameters of disease progression, frequency of drug of abuse, treatment and characteristics of the participants diagnosed with metabolic syndrome to those of participants without the syndrome. The association of parameters of HIV disease (viral load and CD4 cell count), antiretroviral treatment (HAART with and without PIs) and drugs of abuse (alcohol, tobacco, cocaine and marijuana) with CHD risks were examined using univariate analyses. The significant factors were subsequently included in complex regression models adjusting for other significant variables.

Descriptive statistics were used to characterize the population. Student’s t-test was used to evaluate the mean differences and \(\chi^2\) tests were used to evaluate percentage differences. Wilcoxon rank sum tests were used when data were not normally distributed. Univariate analyses were used to assess association between CHD risk factors and parameters of HIV disease status, antiretroviral treatment and the type and frequency of substances abused. Logistic regressions and MANOVA were performed for multivariate analyses.

**RESULTS**

**Characteristics of the population:** The cohort of 118 HIV seropositive drug users consisted of 74% males and 83.2% were Black. The mean age of the cohort was 41.69±6.85 SD. Their mean income was US $393±83 SD and the mean years of education for the cohort were 11.36±2.66 SD. Of the total cohort, 71% were on...
HAART and 36.5% were receiving protease inhibitors. The mean CD4 count was 333±262 cells/mm³ SD (316±238 cells/mm³ SD for men and 382±320 cells/mm³ SD for women), mean viral load was 9.3 ± 2.4 log SD (9.2 ±2.5 log SD for men, 9.6 ± 2.2 log SD for women) and the mean C-reactive protein (CRP) was 4.8 ± 7.8 mg/L SD (7.9 ± 12.8 mg/L SD for men, 4.4 ± 6.9 mg/L SD for women). Daily alcohol consumption was reported by 57.6% of the cohort, while 83.9% smoked cigarettes, 38.1% used marijuana and 67.8% used cocaine/crack. There were no significant differences between the genders in any of these characteristics, although women showed a marked trend (p=0.08) towards using more marijuana than men.

Risk factors for coronary heart disease and metabolic syndrome: As Table 1 shows, the 10-year CHD risk in this cohort of HIV seropositive drug users was 4.8±5.7; the women had significantly lower 10-year CHD risk (1.7±2.4, p<0.001) than men (5.9±6.1). The prevalence of the metabolic syndrome, on the other hand was significantly higher in women (29%, p=0.013) compared to men (10.3 %). The factors influencing this higher prevalence of metabolic syndrome among women included a significantly higher rate of abdominal obesity (54.8% in women vs. 8.1% in men, p<0.001) and lower HDL (61.3% in women vs. 40% in men, p=0.042).

Table 2 shows that participants with metabolic syndrome had a significantly higher estimate of 10-year CHD risk of ≥10% (27.8%, p=0.041) than those without metabolic syndrome (10.2%). The risk factors significantly associated with the metabolic syndrome were male gender (OR=0.28, 95% CI: 0.10, 0.80; p=0.017), Body Mass Index (OR=1.19, 95% CI:1.07, 1.32; p=0.001), which was significantly higher in those with metabolic syndrome (28.6±4.1, p<0.001) compared to those without the syndrome(24.2±4) and viral load (OR=1.61, 95% CI:1.02,2.54; p=0.042). The paradox of the women having lower CHD risk while having higher prevalence of the metabolic syndrome appears to arise from the separate algorithm used for calculating the 10-year CHD risk for women that also takes into consideration their pre-menopausal age, resulting in a lower estimate of the CHD risk for women than men. On the other hand, the definition of metabolic syndrome does not take gender and age into consideration, causing the apparent contradiction in this cohort of the women having lower 10-year CHD risk while having a higher prevalence of metabolic syndrome than men. The analyses, however, indicate that those with metabolic syndrome have a significantly higher 10-year CHD risk.

HIV disease progression, antiretroviral medication, drugs of abuse and CHD risk: Univariate analyses were performed to identify significant associations between HIV disease status, HIV treatment regimens and the types and frequency of drugs of abuse. As shown in Table 3, these analyses show a significant association between the increasing viral load and the risk of metabolic syndrome (OR=1.61; 95% CI:1.02, 2.54; p=0.042), high fasting glucose (OR=1.28; 95% CI:1.03,1.58; p=0.023) and low HDL (OR=1.37; 95% CI:1.03, 1.81; p=0.03). Viral load was also found to be inversely correlated with serum cholesterol levels (r=−0.21, p=0.023) (not shown in the table). There did not appear to be a significant relationship between increased levels of viral load and plasma triglycerides, or blood pressure.

Other factors that contributed significantly to CHD risk were age, which was associated with high blood pressure (OR = 1.1; 95% CI:1.01, 1.19; p = 0.024), high serum triglyceride (OR = 1.07; 95% CI: 1.01, 1.14; p=0.024) and cholesterol (OR = 1.09; 95% CI: 1.01, 1.18; p = 0.019). Obesity, defined as BMI>27 kg/m², was associated with metabolic syndrome (OR=1.19; 95% CI: 1.07, 1.32; p=0.001), high serum cholesterol (OR=1.09; 95% CI:1.00, 1.20; p = 0.05) and central obesity (OR=1.88; 95% CI:1.46, 2.42; p=0.001). Male gender was significantly associated with low levels of HDL (OR=0.42; 95% CI:0.18, 0.98 ; p=0.044), metabolic syndrome (OR=0.28, 95% CI:0.10, 0.80; p=0.017 ), and central obesity (OR=0.07; 95% CI:0.03, 0.21; p<0.001). HAART with or without PI did not contribute to either the 10-year CHD risk or metabolic syndrome in this cohort, and CD4 count was not significantly related to any of the variables analyzed (not shown in tables).

C-reactive protein (CRP), an independent CHD risk factor and a marker of inflammation, was significantly higher in participants with low levels of HDL (7.6±10.6 SD, p=0.008) than in those who did not have overly low levels of HDL (2.4±2.5 SD). In multivariate analysis, abnormal CRP (>3 mg L⁻¹) was significantly associated with low HDL (OR=1.18; 95% CI:1.04,1.35; p=0.012) and this association remain significant after controlling for gender, age, CD4 count, viral load, obesity, HAART and the use of protease inhibitors (not shown in tables).

Analysis of the relationship between drugs of abuse and CHD risk factors indicate that participants who are heavy cocaine/crack users are significantly less likely to be on HAART (35.3%, p=0.015) than those who are not heavy drug users (15.5%). Regarding the univariate association of drug abuse with CHD risk factors, heavy cigarette use was significantly associated with low HDL (OR=3.06; CI:1.18, 7.95; p=0.02). Heavy use of cigarettes and crack/cocaine was inversely associated with obesity defined ad BMI of >27 kg/m² (OR=0.84, 95% CI: 0.67, 0.99; p=0.049; OR=0.43, 95% CI: 0.19, 0.98; p=0.044, respectively), while use of marijuana tended to be associated with central obesity (OR=2.25; CI: 0.96, 1.67; p=0.08).
The results of this study demonstrate that the prevalence of metabolic abnormalities and CHD risk in our cohort of HIV infected chronic drug users is in the range of results published for other HIV infected cohorts. The risk of CHD, however, was considerably higher in participants with metabolic syndrome. Our cohort of drug abusers had a relatively high mean viral load. Increasing viral load was significantly associated with metabolic syndrome, high fasting glucose and low HDL levels. Other factors contributing to CHD risk were age, male gender, the use of protease inhibitors and obesity. Of the drugs of abuse heavy cigarette use was associated with low HDL levels. Marijuana use on the other hand, was associated with obesity, although not significantly, while cigarette smoking and crack/cocaine use were inversely and significantly associated with obesity.

The 10-year CHD risk was calculated using the algorithms developed in the Framingham study to estimate cardiovascular disease risk and validated in the general population. The score takes into account the following parameters: age, gender, total cholesterol, HDL-cholesterol, systolic blood pressure, elevated fasting glucose and smoking[12]. The score has been shown to accurately predict myocardial infarction rates in the Framingham Study[12] and in HIV infected individuals receiving HAART[19]. CHD risk studies in HIV infection showed that while age, gender and smoking were the primary risk factors, adverse effects of HAART added metabolic complications and a substantial risk[19,20].
The prevalence of a 10-year CHD risk in the HIV seropositive population of chronic drug users in Miami (4.8% ± 5.7) was similar to the 4.1-7.6% previously reported for an HIV infected cohort and 5.3% in a matched control group of HIV seronegative men and women from the Framingham data[22]. The 10-year CHD risk for our HIV infected cohort of drug users was also similar to the overall rate (5%) reported for a homeless drug-using HIV seronegative cohort in Toronto[22]. The CHD risk was significantly lower among the HIV infected women drug users (1.7% ± 2.4 SD in women vs. 5.9% ± 6.1 SD in men, p=0.001), which appears to be mainly due to their gender and to the pre-menopausal mean age of the women of 39.4 ± 7.3 SD years[23].

Despite the lower CHD risk, the prevalence of metabolic syndrome was significantly higher among the women (29% vs. 10.3% among men, p=0.013), most likely due to the high rates of abdominal obesity, higher BMI and higher rates of low HDL levels among women. These results are in agreement with a report from another urban HIV positive cohort, which shows similar rates of obesity among HIV infected women[24]. The overall prevalence of 15.1% of metabolic syndrome in our cohort, however, was lower than the estimated 22% prevalence in the US general population[7] and the 33.1% prevalence of metabolic syndrome estimated by Bruno and colleagues[9] in HIV infected patients on HAART.

Participants with metabolic syndrome had a significantly higher estimate of 10-year CHD risk of ≥10% (27.8%, p=0.041) than those without metabolic syndrome (10.2%). This is in agreement with earlier findings that show that metabolic syndrome is an independent cardiovascular risk factor, with a significant 3-fold increase in risk for coronary heart disease and stroke and a markedly increased cardiovascular mortality in both men and women. In addition, Isomaa and colleagues[11] also demonstrated that cardiovascular morbidity and mortality associated with this cluster of risk factors was greater than those related to each component alone. The risk factors that significantly influenced the metabolic syndrome in our cohort were female gender, central obesity and low HDL levels. The apparent paradox in our findings of the low 10-year CHD risk in women, while it was predominantly the women who had the metabolic syndrome and consequently, higher percent of 10-year CHD risk, reflects on one hand the lower risk in females because of their gender and age using the 10-year CHD risk algorithm, while the estimation of metabolic syndrome does not take age and gender into consideration. The analyses indicated however, that the 29% of the women in our cohort with metabolic syndrome have an increased CHD risk.

A primary finding in this study is the observation that increasing viral load was significantly associated with metabolic syndrome, high fasting glucose and low HDL levels and that viral load was inversely associated with total cholesterol in our cohort of HIV infected drug users. Our findings are consistent with recently reported data in HIV infected women showing a significant inverse association between viral load and serum cholesterol level[24] and with results from another study[25] that showed an association between higher HIV RNA levels and lower HDL cholesterol in antiretroviral-naive HIV infected inner city men and women and suggested that high viral replication has a direct effect on serum lipid levels. In addition, other investigators[14,26] have proposed a possible etiological link between inflammation caused by viruses and endothelial dysfunction, which may increase cardiovascular risk by eventually producing clinical atherosclerosis. Our findings also contribute to this hypothesis, as CRP, an independent predictor of CHD[27] and a marker of inflammation[28], was significantly higher in participants with low HDL when compared to those with adequate HDL. Abnormal CRP was also significantly associated with low HDL in our cohort. Elevated levels of CRP were not related to obesity, metabolic syndrome or other variables measured, in contrast to findings from a previous study[24]. Increased viral load in our cohort was associated with elevated levels of fasting glucose, which is likely to contribute to the 10-year CHD risk via the metabolic syndrome[29].

The findings from our cohort indicate that a predominant portion of these HIV infected drug abusers have a high viral load and that increasing viral load was associated with metabolic syndrome, high fasting glucose and low HDL levels. The high mean viral load found in our cohort is consistent with previous reports suggesting that heavy use of illicit drugs has an influence on either adherence or effectiveness of antiretroviral medication and therefore, on viral control in intravenous drug users[30,31].

In our cohort, participants who are heavy cocaine/crack users are significantly less likely to be on HAART (35.3%, p=0.015) than those who are not heavy drug users (15.5%). Moreover, drugs of abuse, particularly the combination of cocaine and ethanol[18,32] were previously reported to have an additive or synergistic effect on cardiovascular events. Concomitant cigarette smoking also has deleterious effects on myocardial oxygen supply and demand[33]. The drugs of abuse of choice of our participants, in order of prevalence were cigarette smoking, cocaine, alcohol and marijuana. Heavy use of cigarettes and crack cocaine were significantly and inversely associated with obesity in our cohort, which is consistent with our previous report linking heavy cocaine use with wasting[34] and with the anorectic effect of these drugs[35,37]. Marijuana use on the other
hand, a known appetite stimulant, tended to be associated with central obesity in our cohort, although not significantly. Evaluating the independent effects on coronary risk of both cocaine and marijuana in this cohort has been rather difficult, because the drugs may be used in combination or singly, depending on the availability. In addition, the purity, mode of ingestion and degree of absorption of street drugs varies greatly, making comparison less meaningful.

Other factors contributing to CHD risk were age, male gender, the use of protease inhibitors and obesity. These findings are consistent with previous studies of CHD risk factors in both HIV seronegative and seropositive populations\textsuperscript{[19,21,29,38]}. The use of protease inhibitors appears to be associated with hypertriglyceridemia and an increased CHD risk\textsuperscript{[16]}. The strong association between the use of protease inhibitors and elevated levels of triglycerides in our cohort is consistent with the previous findings and has an effect on the CHD risk via its contribution to the prevalence of metabolic syndrome. Obesity, through its association with central obesity, is also a contributing factor to metabolic syndrome and consequently to CHD risk, in our cohort\textsuperscript{[39]}.

Overall, the findings from our cohort indicate that a predominant portion of these HIV infected drug abusing participants have a high viral load, suggesting that heavy use of illicit drugs has an influence on either adherence or effectiveness of antiretroviral medication and therefore, on viral control. Increasing viral load was associated with metabolic syndrome, high fasting glucose and low HDL levels. The prevalence of metabolic abnormalities and CHD risk is in the range of results published for other HIV infected cohorts. The 10-year CHD risk was, however, considerably higher in participants with metabolic syndrome. Other factors contributing to CHD risk were age, male gender, abnormal levels of C-reactive protein, the use of protease inhibitors and obesity. Of the drugs of abuse heavy cigarette use was associated with low HDL levels. Marijuana use on the other hand, was associated with obesity, although not significantly, while cigarette smoking and cocaine use were inversely and significantly associated with obesity. Interventions to improve control of viral load and obesity are needed to lower the risks for CHD in this population exposed to chronic HIV-infection, HAART and drug abuse.

**ACKNOWLEDGEMENT**

Supported by the National Institute on Drug Abuse, Grant No. 1R01-DA-14966

**REFERENCES**


