Published in final edited form as:

J Addict Med. 2015 ; 9(1): 31–39. doi:10.1097/ADM.0000000000000078.

Chronic Cocaine Use and Its Association with Myocardial Steatosis Evaluated by ¹H Magnetic Resonance Spectroscopy in African Americans

Shenghan Lai, MD, MPH^{1,2,3}, Gary Gerstenblith, MD², Ji Li, MD, PhD¹, Hong Zhu, MD^{1,4}, David A. Bluemke, MD, Ph.D.⁵, Chia-Ying Liu, PhD^{3,5}, Stefan L. Zimmerman, MD³, Shaoguang Chen, MS¹, Hong Lai, MPH, PhD³, and Glenn Treisman, MD⁶

¹ Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD

² Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

³ Department of Radiology, Johns Hopkins School of Medicine, Baltimore, MD

⁴Department of Epidemiology and Biostatistics, Tianjin Medical University, Tianjin, China

⁵Radiology and Imaging Sciences, NIH Clinical Center, Bethesda, MD

⁶ Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD

Abstract

Objectives—Cardiac steatosis is a manifestation of ectopic fat deposition and is associated with obesity. The impact of chronic cocaine use on obesity measures and on the relationship between obesity measures and cardiac steatosis is not well-characterized. The objectives of this study were to compare obesity measures in chronic cocaine users and non-users, and to explore which factors, in addition to obesity measures, are associated with myocardial triglyceride in African Americans (AAs), using noninvasive magnetic resonance spectroscopy (MRS).

Methods—Between June 2004 and January 2014, 180 healthy AA adults without HIV infection, hypertension and diabetes were enrolled in an observational proton MRS and imaging study investigating factors associated with cardiac steatosis.

Results—Among these 180 participants, 80 were chronic cocaine users, and 100 were non-users. The median age (with IQR) was 42 (34–47) years. Obesity measures trended higher in cocaine users than non-users. The median myocardial triglyceride was 0.6% (IQR:0.4–1.1%). Among the factors investigated, years of cocaine use, leptin and visceral fat were independently associated with myocardial triglyceride. BMI and visceral fat, which were significantly associated with myocardial triglyceride in non-cocaine users, were not associated with myocardial triglycerides content in cocaine users.

Conclusions—This study shows (1) cocaine users may have more fat than nonusers and (2) myocardial triglyceride is independently associated with duration of cocaine use, leptin, and visceral fat in all subjects, while leptin and HDL-cholesterol, but not visceral fat or BMI, in

cocaine users, suggesting that chronic cocaine use may modify the relationships between obesity measures and myocardial triglyceride.

Keywords

Cardiac steatosis; African Americans; Obesity; MR spectroscopy; Cocaine Use

Although cardiac steatosis is common in individuals with diabetes and/or obesity (Wisneski et al., 1987; Szczepaniak et al., 2003; Reingold et al., 2005; McGavock et al., 2006; McGavock et al., 2007; Szczepaniak et al., 2007; van der Meer et al., 2008), and cardiac steatosis is associated with left ventricular dysfunction (McGavock et al., 2007; van der Meer et al., 2008; Szczepaniak et al., 2003), we recently reported that cardiac steatosis was observed in healthy, non-obese men and women without hypertension or diabetes, and that BMI or other markers for obesity (such as, visceral fat) explained less than 50% of the variation in myocardial triglycerides accumulation (Liu et al., 2014). Thus, there is a great need to explore whether factors other than obesity measures are also associated with cardiac steatosis.

Since one of major pharmacological effects of cocaine use is appetite suppression, cessation of cocaine use was found to be associated with weight gain, leading to addiction relapse (Ersche et al., 2013; Cochrane et al., 1998). To explore how the body processes fat during chronic cocaine addiction and also how the body adjusts during withdrawal and recovery from addiction, a landmark paper found a striking reduction in body fat in the cocaine use group relative to the cocaine non-use group, suggesting that cocaine use may lead to the body storing fat differently (Cowan et al., 2007). However, whether and how cocaine influences ectopic fat deposition, such as myocardial triglycerides deposition remains unclear. In a pilot study, we showed that cocaine use was associated with the presence of cardiac steatosis (Liu et al., 2010).

The objectives of this study were (1) to compare the body fat between cocaine users and non-users, (2) to explore whether factors, other than obesity measures are independently associated with myocardial triglyceride contents, and (3) to examine whether cocaine use modifies the relationships between markers for obesity and myocardial triglycerides content in African Americans (AAs) using noninvasive magnetic resonance (MR) imaging.

METHODS

Study Participants

Between June 2010 and January 2014, 436 middle-aged African American men and women with and without HIV infection in Baltimore, Maryland, were consecutively enrolled in a prospective study investigating the alleged effects of HIV infection, exposure to ART, and cocaine use on cardiac steatosis. Cardiac steatosis was measured as myocardial triglyceride content, as indexed by the ratio of the signal of myocardial triglyceride to the signal of myocardial water as measured by magnetic resonance spectroscopy. Of these 436, 216 were HIV negative.

Inclusion criteria were (1) age older than 21 years; (2) HIV negative, (3) cocaine use: chronic or non-use. Chronic cocaine use: defined as use by any route for at least 6 months, administered at least 4 times a month. Infrequent users (fewer than 4 times a month, or <6 consecutive months) were not recruited. Chronic cocaine users who also used other drugs such as opiates, benzodiazepines, methamphetamine, or alcohol were included. Non-cocaine use: defined as never used cocaine or not used in the past 5 years or longer; and (4) AA race (self-designated). Exclusion criteria were (1) any evidence of ischemic heart disease as indicated by clinical history, previous hospitalization for myocardial infarction, angina pectoris, or ECG or echocardiographic evidence of previous ischemic-induced myocardial damage, (2) any symptoms believed to be related to cardiovascular disease, (3) HIV infection, (4) hypertension, (5) diabetes (6) pregnancy, and (7) history of MRI-related claustrophobia.

MR myocardial imaging and proton magnetic resonance spectroscopy (^1H MRS) were performed; and laboratory tests, including lipid profiles, leptin and high sensitivity C-reactive protein (hsCRP) levels were obtained.

During the baseline visit, study participants underwent a detailed interview to obtain sociodemographic and clinical information including medical history, behaviors (alcohol consumption, drug use, and cigarette smoking) and medications, including statins. A medical chart review confirmed the medical history and medication information provided by the study participants. A physical examination was performed and vital signs were recorded. Participants' sitting systolic and diastolic blood pressures were measured twice with a standard mercury sphygmomanometer. Routine clinical laboratory blood chemistry tests were conducted. The following laboratory tests were performed at baseline: total serum cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), glucose, and inflammation markers, including high-sensitivity CRP (hsCRP). MR myocardial imaging and proton magnetic resonance spectroscopy (^1H MRS) were performed. Although the overall investigation is a cohort study, the data presented herein are cross-sectional only.

The Johns Hopkins Medicine Institutional Review Board approved the study protocol and consent form, and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines.

Main Procedures

Myocardial and Hepatic Imaging and Spectroscopy—All studies were performed on a 3.0-T MR scanner (Trio Tim; Siemens, Erlangen, Germany). To measure left ventricular (LV) volumes and ejection fraction, the heart was imaged in both long and short-axis orientation, using retrospectively gated steady state free precession cine images.

Myocardial ^1H -MRS spectra were obtained with electrocardiogram gating during early systole, with navigator gating to enable free-breathing using a single voxel point-resolved spectroscopy sequence. The spectroscopic volume (6- to 8-mL voxel) was positioned within the interventricular septum. One spectrum was recorded with water suppression (32 averages), and another spectrum (eight averages) was recorded without water suppression

(Figure 1). Measurement of hepatic triglyceride content was performed using the same sequence with the MRS voxel placed in the right hepatic lobe. Eight averages of water suppressed as well as eight averages of no water suppressed spectrum were acquired with breath holding.

The distributions of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were assessed by an axial single-shot fast spin echo sequence (slice thickness=10mm). Three contiguous transverse images were acquired at the level of the fifth lumbar vertebrae during one breath hold.

MRI Data Analysis—Java-based MR software (jMRUI v.3.0 software; A. van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium) was used to process spectral data and the reader was also blinded to the participants' characteristics (Naressi et al., 2001). The areas under the resonance frequency estimates of lipids at 0.9 and 1.3 parts-per-million (ppm) were summed to quantify myocardial triglycerides content and related to water in unsuppressed spectra.

Visceral and subcutaneous adipose tissue was identified by selecting the region of interest and thresholding the pixel signal intensity using MASS software. Adipose tissue volumes were quantified by converting the number of pixels to square centimeters and multiplied by the thickness of slices. The total volume of VAT and SAT was calculated by totaling the volumes of the individual slices.

Statistical analysis—Statistical analysis was performed with SAS (SAS 9.3, SAS Institute, Cary, NC). All continuous parameters were summarized by medians (interquartile ranges (IQRs)), and all categorical parameters were summarized as proportions. To compare between-group differences in demographic and clinical characteristics, lipid profiles, and other factors, the non-parametric Wilcoxon test was used for continuous variables and the Fisher's exact test was employed for categorical variables.

Since the distribution of myocardial triglyceride content was considerably skewed, square-root-transformed myocardial triglyceride content was used as the outcome variable in regression analyses. Since the ordinary least-squares regression model minimizes the sum of all the residuals and thus is sensitive to outliers, a robust regression model with the least trimmed squares (LTS) estimation method was used to provide robust results in the presence of outliers (Rousseeuw et al, 1987). The Framingham risk score and 2013 new cardiovascular risk assessment recommended by the American College of Cardiology/American Heart Association (ACC/AHA) were used to estimate the CAD risk (Wilson et al., 1998; Goff et al., 2013). Univariate robust regression models were first fitted to evaluate the crude association between myocardial triglyceride content and each of the factors—including age, sex, total serum cholesterol, HDL-cholesterol, LDL-cholesterol, serum triglycerides, hsCRP, leptin, cigarette smoking, alcohol use, cocaine use, heroin use, glucose level, systolic BP, diastolic BP, body mass index (BMI), and 2013 new cardiovascular risk assessment and Framingham risk score, individually. Those factors that were significant at the $P<0.10$ level in the univariate models were put into the multivariate models to identify the ones independently associated with the presence of cardiac steatosis. Those variables

that ceased to make significant contributions to the models based on these criteria were deleted in a stagewise manner and a new model was refitted. This process of eliminating, refitting, and verifying continued until all of the variables included were statistically significant, yielding a final model. The p-values reported are two-sided. A p-value <0.05 indicated statistical significance.

RESULTS

Among the 216 study participants, 36 with hypertension and/or diabetes were excluded from the analyses (24 with hypertension, 9 with diabetes, and 3 with both hypertension and diabetes). Thus, 180 without hypertension or diabetes were included in this study.

General characteristics

The median age (with IQR) was 42 (34-47) years. One hundred (55.6%) were males. Seventy-four percent were cigarette smokers, and 67% consumed alcohol. According to the Framingham risk score algorithm or the ACC/AHA cardiovascular risk assessment, the majority of study participants had low risk of coronary artery disease (CAD). The median BMI was 28.3 (24.2-33.1) kg/m². Among these 180, 80 were chronic cocaine users, and 100 were non-users. The distribution of myocardial triglyceride content was highly skewed (Figure 2).

The general, laboratory and clinical characteristics of the study participants by sex are presented in Table 1. The median myocardial triglyceride contents for cocaine users, and non-users were 0.8% (IQR: 0.4-1.3), and 0.6 (IQR: 0.3-1.0), respectively.

Comparisons of body fat between cocaine users and non-users

In general, cocaine users tended to have more hepatic fat, myocardial fat, subcutaneous fat and visceral fat than non-users. According to the non-parametric Wilcoxon test, the difference in hepatic fat between cocaine users and non-users was statistically significant (p=0.019) (Table 1). Sex-specific comparisons of body fat measures between cocaine users and non-users are shown in Table 2. BMI, leptin, subcutaneous and visceral fat levels were significantly higher among cocaine using men and not among women.

Factors associated with myocardial triglyceride levels

According to univariate robust regression analyses, factors associated with myocardial triglyceride content at the 0.10 level included male sex, cocaine use, years of cocaine use, leptin, hsCRP, hsCRP>2mg/dL, BMI, waist circumference, hepatic triglyceride, subcutaneous fat, and visceral fat. Male sex was negatively associated with myocardial triglyceride content. Leptin, BMI, visceral fat, and subcutaneous fat explained 21%, 21%, 22% and 21% of variation in myocardial triglycerides, respectively. The multivariate final robust regression model indicated that years of cocaine use, leptin, and visceral fat were independently associated with myocardial triglyceride content (Table 3). These three factors explained 32% of variation in myocardial triglycerides (final model, Table 3).

Factors associated with myocardial triglyceride levels by cocaine use status In non-cocaine users

By univariate robust regression analyses, BMI, waist circumference, leptin, hepatic fat, subcutaneous fat, and visceral fat were significantly associated with myocardial fat with R^2 of 0.43, 0.32, 0.33, 0.21, 0.33, and 0.45, respectively (Table 4). Specifically, BMI and visceral fat explained 43% and 45% of variation in myocardial triglycerides, respectively (Table 4, Figures 3 and 4). Univariate robust regression analyses also showed that factors associated with myocardial triglyceride content at the 0.10 level included male sex, leptin, hsCRP, hsCRP>2mg/dL, fasting glucose, BMI, waist circumference, HDL-cholesterol, Framingham risk score<10%, hepatic triglyceride, subcutaneous fat, and visceral fat (Table 4). The multivariate final robust regression model indicated that only BMI was independently associated with myocardial triglyceride content (Table 5).

In cocaine users

By univariate robust regression analyses, only leptin and subcutaneous fat were significantly associated with myocardial fat with R^2 of 0.14 and 0.10, respectively (Table 4). BMI and visceral fat, which were significantly associated with myocardial triglycerides content with the largest R^2 in non-cocaine users, were not associated with myocardial triglycerides content in cocaine users (their R^2 were both 0.01) (Table 4, Figures 5 and 6). The multivariate final robust regression model indicated that leptin and HDL-cholesterol were independently associated with myocardial triglyceride content (Table 4). These two factors explained 32% of variation in myocardial triglycerides (final model, Table 4).

DISCUSSION

Major findings

In this study, we suggested that (1) In general, cocaine users tended to have more fat than non-users, (2) accumulation of myocardial triglycerides is independently associated with duration of cocaine use, leptin, and visceral fat, and (3) Cocaine use may modify the relationships between obesity measures and myocardial triglycerides content.

Cocaine users had more fat than non-cocaine users

Our data do not support the popular belief that cocaine use is associated with reductions in body weight and other fat measures. To the contrary (Ersche et al., 2013), we found that cocaine users tended to have more body fat than non-users (the median visceral fat for cocaine users, and non-users were 497 (IQR: 397-581), and 402 (IQR: 294-582), respectively, $p=0.07$), especially in men (the median visceral fat for male cocaine users, and male non-users were 457 (IQR: 350-563), and 348 (IQR: 267-458), respectively, $p=0.009$). Furthermore, we also found that cocaine users tended to have more myocardial fat than non-users (the median myocardial fat for cocaine users, and non-users were 0.8 (IQR: 0.4-1.3), and 0.6 (IQR: 0.3-1.0), respectively, $p=0.13$), especially in men (the median myocardial fat for male cocaine users, and male non-users were 0.6 (IQR: 0.4-1.1), and 0.4 (IQR: 0.2-0.8), respectively, $p=0.08$). Cocaine users also had significantly more hepatic fat than non-users (the median hepatic fat for cocaine users, and non-users were 2.8 (IQR: 1.5-5.3), and 1.4

(IQR: 0.7-5.4), respectively, $p=0.019$). In addition, we also found that leptin levels were significantly higher among cocaine using men (the median leptin for male cocaine users, and male non-users were 4.7 (IQR: 4.1-7.6), and 3.7 (IQR: 2.6-6.7), respectively, $p=0.016$) and not among women (the median leptin for female cocaine users, and female non-users were 28.8 (IQR: 21.8-38.0), and 34.0 (IQR: 12.8-46.0), respectively, $p=0.63$). It has been reported that leptin levels in women are significantly higher than that in men (Kennedy et al., 1997), and the impact of cocaine on leptin levels may be much stronger in men than in women.

Factors associated with myocardial triglyceride and cardiac steatosis

Our univariate analysis shows that myocardial triglyceride had outliers and was highly skewed (Figure 2). Thus, the conventional regression analysis (including correlation analysis) may not be adequate for analyzing the data. We used square-root transformed myocardial triglyceride and robust regression analysis to explore factors that were associated with (square-root transformed) myocardial triglyceride.

In the multivariate analyses including all study participants, we found that leptin was independently associated with myocardial triglyceride. Leptin is one of the most important fat-derived hormones, and plasma leptin is strongly associated with abdominal fat, increases in proportion to body fat mass and thus is considered a good indicator of adiposity (Considine et al., 1996; Jung et al., 2013). It was also reported that leptin was univariately associated with myocardial fat in healthy African Americans (Liu et al., 2014). Multivariate analysis also showed that visceral fat was independently associated with myocardial triglyceride content. It was reported that visceral fat was independently associated with myocardial fat and explained 45% of variation in myocardial fat in healthy African Americans (Liu et al., 2014).

One of the most provocative findings of this study is that years of cocaine use was independently associated with myocardial triglycerides content. If chronic cocaine use changes the way the body stores fat, as speculated (Ersche et al., 2013), one conclusion derived from our data is that cocaine use increases fat stores in cardiac tissue, and other nonadipose tissues, such as liver.

Free fatty acids are the major source of energy for the myocardium, and the majority of free fatty acids undergo rapid oxidation and little is stored under normal conditions. However, when fatty acids influx into myocardial cells exceeds the oxidative needs, the excess fatty acids may store as triglycerides, resulting myocardial steatosis (Wisneski et al., 1987). The exact mechanisms by which myocardial steatosis develops are still not fully understood. The mechanism of action of cocaine on myocardial steatosis remains unexplained. A hypothetical mechanism for the effects of cocaine on myocardial steatosis is that cocaine is a potent stimulant of the sympathetic nervous system, and the sympathetic effects of cocaine may inhibit the leptin system, leading to less leptin production (Manetti et al., 2014; Vongpatanasin et al., 1999; Trayhurn P et al., 1998; Rayner et al., 2001; Ersche et al., 2013). Leptin has been recognized as an antisteatotic hormone, preventing the deleterious consequences of ectopic fatty acids overload in nonadipose tissue, such as myocardial tissue (Unger 2002). Our data also suggested that leptin levels in the cocaine group were lower than those in the non-cocaine group, although the difference was not statistically significant.

While some important cardiotoxic effects of cocaine have been recognized (Phillips et al., 2009), bringing new understanding to the mechanisms leading to cardiovascular disease, new findings are still emerging, including the association between cocaine use and myocardial steatosis. Since myocardial steatosis may lead to left ventricular dysfunction, this study may provide some critical information about the etiology of cocaine-induced cardiomyopathy.

It is demonstrated that as an antisteatotic hormone, leptin confines the storage of triglycerides to the adipocytes, and limits ectopic steatosis, its storage in nonadipocytes (Unger et al., 1999; Unger et al., 2000). Our data indicate that long-term exposure to cocaine alters this important aspect of fatty acids homeostasis, although the mechanism is unknown. Despite the facts that long-term use of cocaine is implicated in dilated cardiomyopathy (Wiener et al., 1986; Listenberger et al., 2002) and that cardiac steatosis is linked to left ventricular dysfunction (McGavock et al., 2007; van der Meer et al., 2008; Szczepaniak et al., 2003), the association between cardiac steatosis and long-term use of cocaine has never been investigated.

Cocaine use modifies the relationships between cardiac steatosis and markers for obesity

Another provocative finding of this study is that cocaine use modified the relationships between myocardial fat and makers for obesity. In a recent publication, we showed that the BMI and visceral fat explained 43% and 45% of variation (R^2) in myocardial fat in healthy AAs who never used cocaine and were free of diabetes and hypertension (Liu et al., 2014). In this study, the R^2 for BMI and visceral fat in non-cocaine users were exactly the same as that reported in (Liu et al., 2014) (Table 4). However, the R^2 for BMI, waist circumference, leptin, hepatic fat, subcutaneous fat, and visceral fat in cocaine users is significantly reduced, especially for BMI and visceral fat. The finding that there is no correlation between BMI (or visceral fat) and myocardial triglycerides implies that the mechanism by which excess triglycerides is stored in cardiac tissue in cocaine users differs from that in non-cocaine users.

Potential Mechanisms

The mechanisms responsible for increased cardiac steatosis in long-term cocaine users and for how cocaine use modifies the relationships between cardiac steatosis and obesity measures are unknown and further investigations are needed.

Limitations

This study has several limitations. First, because all the study participants were AAs, some results from this study may not be generalized to other race/ethnic groups without caution. However, since all of the study participants are African Americans, the effects of cocaine on myocardial steatosis derived from this study could not be confounded by race/ethnicity. We recognize that the cardiac, metabolic and other disease burden is high among African-Americans; nevertheless, we have not conducting similar studies in other populations. Second, the data presented here are cross-sectional and causality cannot be inferred. The relationships between changes in myocardial triglyceride and LV function will be investigated when follow-up studies are completed. Third, due to the nature of a cross-

sectional design, some hidden confounding factors, such as socioeconomic status, were not adjusted for. Fourth, the study was not designed to investigate the association between eating behavior on body weight in cocaine users. Therefore, the effects of eating behavior on body weight and cardiac steatosis remain to be explored. Fifth, the study sample was not representative of the population from which it was selected.

CONCLUSIONS

Contrary to popular belief, this study suggests a trend towards higher levels of body fat, including myocardial fat and hepatic fat, in cocaine users. This study's findings also suggest that long-term use of cocaine increases the risk of cardiac steatosis, and may modify the relationships between cardiac steatosis and obesity. Our data may be sufficient to alert physician to inform their obese patients to not indulge in cocaine use because it might result in cardiac steatosis even though a clear causality has not been established. Since cocaine use is prevalent in USA, especially in AAs, and since cardiac steatosis may lead to ventricular dysfunction and cardiomyopathy, prevention of cardiac steatosis is another of the many reasons to prevent and treat cocaine addiction.

ACKNOWLEDGEMENTS

We thank the study participants for their contributions. The study was supported by grants from the National Institute on Drug Abuse, National Institutes of Health (NIH R01-DA 12777, DA25524 and DA15020).

References

- Cochrane C, Malcolm R, Brewerton T. The role of weight control as a motivation for cocaine abuse. *Addict Behav.* Mar-Apr;1998 23(2):201–7. [PubMed: 9573424]
- Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med.* Feb 1; 1996 334(5):292–5. [PubMed: 8532024]
- Cowan J, Devine C. Food, eating, and weight concerns of men in recovery from substance addiction. *Appetite.* Jan; 2008 50(1):33–42. Epub 2007 May 31. [PubMed: 17602790]
- Ersche KD, Stochl J, Woodward JM, et al. The skinny on cocaine: insights into eating behavior and body weight in cocaine-dependent men. *Appetite.* Dec.2013 71:75–80. doi: 10.1016/j.appet.2013.07.011. Epub 2013 Aug 3. [PubMed: 23920064]
- Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Nov 12.2013 pii: S0735-1097(13)06031-2. doi: 10.1016/j.jacc.2013.11.005.
- Jung CH, Kim MS. Molecular mechanisms of central leptin resistance in obesity. *Arch Pharm Res.* Feb; 2013 36(2):201–7. [PubMed: 23359004]
- Kennedy A, Gettys TW, Watson P, et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity, insulin sensitivity, and energy expenditure. *J Clin Endocrinol Metab.* Apr; 1997 82(4):1293–300. [PubMed: 9100610]
- Listenberger LL, Schaffer JE. Mechanisms of lipoapoptosis: implications for human heart disease. *Trends Cardiovasc Med.* Apr; 2002 12(3):134–8. [PubMed: 12007739]
- Liu C, Redheuil A, Ouwerkerk R, et al. Cocaine use as an independent predictor of cardiac steatosis: initial experience by ¹H spectroscopy. *Journal of Cardiovascular Magnetic Resonance.* 2010; 12(Suppl 1):O90. doi:10.1186/1532-429X-12-S1-O90.
- Liu CY, Bluemke DA, Gerstenblith G, et al. Myocardial steatosis and its association with obesity and regional ventricular dysfunction: Evaluated by magnetic resonance tagging and ¹H spectroscopy in

- healthy African Americans. *Int J Cardiol.* Jan 24;2014 pii: S0167-5273(14)00283-6. doi: 10.1016/j.ijcard.2014.01.074.
- Manetti L, Cavagnini F, Martino E. Effects of cocaine on the hypothalamic-pituitary-adrenal axis. *J Endocrinol Invest.* May 23;2014 [Epub ahead of print].
- McGavock JM, Victor RG, Unger RH, et al. American College of Physicians and the American Physiological Society. Adiposity of the heart, revisited. *Ann Intern Med.* Apr 4; 2006 144(7):517–24. [PubMed: 16585666]
- McGavock JM, Lingvay I, Zib I, et al. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. *Circulation.* Sep 4; 2007 116(10):1170–5. [PubMed: 17698735]
- Naressi A, Couturier C, Devos JM, et al. Java-based graphical user interface for the MRUI quantitation package. *Magma.* 2001; 12(2-3):141–152. [PubMed: 11390270]
- Phillips K, Luk A, Soor GS, et al. Cocaine cardiotoxicity: a review of the pathophysiology, pathology, and treatment options. *Am J Cardiovasc Drugs.* 2009; 9(3):177–96. [PubMed: 19463023]
- Rayner DV, Trayhurn P. Regulation of leptin production. Sympathetic nervous system interactions. *J Mol Med (Berl).* 2001; 79(1):8–20. [PubMed: 11327106]
- Reingold JS, McGavock JM, Kaka S, et al. Determination of triglyceride in the human myocardium by magnetic resonance spectroscopy: reproducibility and sensitivity of the method. *Am J Physiol Endocrinol Metab.* Nov; 2005 289(5):E935–9. [PubMed: 15972271]
- Rousseeuw, PJ.; Leroy, AM. Robust Regression and Outlier Detection. John Wiley & Sons; New York: 1987.
- Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. *Magn Reson Med.* Mar; 2003 49(3):417–23. [PubMed: 12594743]
- Szczepaniak LS, Victor RG, Orci L, et al. Forgotten but not gone: the rediscovery of fatty heart, the most common unrecognized disease in America. *Circ Res.* Oct 12; 2007 101(8):759–67. [PubMed: 17932333]
- Trayhurn P, Duncan JS, Hoggard N, et al. Regulation of leptin production: a dominant role for the sympathetic nervous system? *Proc Nutr Soc.* Aug; 1998 57(3):413–9. [PubMed: 9793999]
- Unger RH, Zhou YT, Orci L. Regulation of fatty acid homeostasis in cells: novel role of leptin. *Proc Natl Acad Sci U S A.* Mar 2; 1999 96(5):2327–32. [PubMed: 10051641]
- Unger RH, Orci L. Lipotoxic diseases of nonadipose tissues in obesity. *Int J Obes Relat Metab Disord.* Nov; 2000 24(Suppl 4):S28–32. [PubMed: 11126236]
- Unger RH. Lipotoxic diseases. *Annu Rev Med.* 2002; 53:319–36. [PubMed: 11818477]
- van der Meer RW, Rijzewijk LJ, Diamant M, et al. The ageing male heart: myocardial triglyceride content as independent predictor of diastolic function. *Eur Heart J.* Jun; 2008 29(12):1516–22. [PubMed: 18492680]
- Vongpatanasin W, Mansour Y, Chavoshan B, et al. Cocaine stimulates the human cardiovascular system via a central mechanism of action. *Circulation.* 1999; 100(5):497–502. [PubMed: 10430763]
- Wiener RS, Lockhart JT, Schwartz RG. Dilated cardiomyopathy and cocaine abuse. Report of two cases. *Am J Med.* Oct; 1986 81(4):699–701. [PubMed: 3766598]
- Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998; 97:1837–1847. [PubMed: 9603539]
- Wisneski JA, Gertz EW, Neese RA, et al. Myocardial metabolism of free fatty acids. Studies with 14C-labeled substrates in humans. *J Clin Invest.* Feb; 1987 79(2):359–66. [PubMed: 3805273]

Figure 1. Proton MR Spectroscopic Image of Septal Myocardial Fat

(a) Nonwater-suppressed spectrum of interventricular septal fat. MR image (inset) shows voxel positioning (white rectangle) in the septum. (b) water-suppressed spectrum of the same subject; TG: triglyceride peaks at 0.9 and 1.3 ppm. Amplitude is expressed in arbitrary units.

Figure 2. Distribution of Myocardial Triglyceride Content

The histogram of myocardial triglyceride content with a superimposed normal curve, indicating that the distribution of myocardial triglyceride content was highly skewed.

Figure 3. The Relationship between Myocardial Triglyceride Content (square-root transformed) and BMI in Non-Cocaine Users

Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and visceral triglyceride in non-cocaine users. Robust regression $R^2 = 0.43$. Y is myocardial triglyceride (square-root transformed), while X is visceral triglyceride.

Figure 4. The Relationship between Myocardial Triglyceride Content (square-root transformed) and Visceral Fat in Non-Cocaine Users

Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and visceral triglyceride in non-cocaine users. Robust regression $R^2 = 0.45$. Y is myocardial triglyceride (square-root transformed), while X is visceral triglyceride.

Figure 5. The Relationship between Myocardial Triglyceride Content (square-root transformed) and BMI in Cocaine Users

Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and visceral triglyceride in non-cocaine users. Robust regression $R^2 = 0.01$. Y is myocardial triglyceride (square-root transformed), while X is visceral triglyceride.

Figure 6. The Relationship between Myocardial Triglyceride Content (square-root transformed) and Visceral Fat in Cocaine Users

Univariate robust regression with the LTS estimator was run to investigate the relationship between myocardial triglyceride and visceral triglyceride in non-cocaine users. Robust regression $R^2 = 0.01$. Y is myocardial triglyceride (square-root transformed), while X is visceral triglyceride.

Table 1

Characteristics of 180 African American Study Participants in Baltimore, Maryland

Characteristic	Total (N= 180)	Cocaine-(N= 100)	Cocaine+(N = 80)	p-value
Age (year)	42 (34-47)	37 (28-47)	43 (41-50)	<0.0001
Male gender (%)	55.6	43.0	71.3	0.0002
Cigarette smoking (%)	73.9	61.0	90.0	<0.001
Years of cigarette smoking	13 (0-26)	5 (0-16)	22 (11-30)	<0.001
Alcohol use (%)	66.6	53.0	81.3	<0.0001
Years of alcohol use	5 (0-20)	1 (0-14)	18 (3-25)	<0.0001
Years of cocaine use	0 (0-10)	0 (0-0)	10 (5-20)	<0.0001
BMI (kg/m ²)	28.3 (24.2-33.1)	27.7 (22.5-34.3)	28.6 (25.7-32.0)	0.50
Waist circumference (cm)	94 (85-103)	94 (81-102)	95 (88-104)	0.21
Waist/hip ratio	0.87 (0.82-0.93)	0.85 (0.81-0.92)	0.89 (0.83-0.93)	0.049
hsCRP 2mg/dL (%)	39.4	38.0	41.3	0.66
hsCRP (mg/dL)	1.3 (0.4-3.7)	1.1 (0.4-3.4)	1.5 (0.6-4.5)	0.32
Systolic BP (mm Hg)	118 (107-126)	115 (106-125)	121 (111-128)	0.04
Diastolic BP (mm Hg)	69 (62-78)	66 (60-75)	73 (66-79)	0.0001
Glucose (mg/dL)	82 (77-89)	81 (77-89)	83 (77-87)	0.88
Leptin (ng/mL)	9.4 (4.3-28.4)	11.9 (4.0-36.5)	7 (4-21)	0.19
Total cholesterol (mg/dL)	175 (154-200)	169 (149-196)	177 (156-203)	0.17
LDL-C (mg/dL)	98 (79-120)	98 (78-117)	98 (80-127)	0.46
HDL-C (mg/dL)	55 (49-65)	57 (49-64)	55 (49-67)	0.99
Triglycerides (mg/dL)	80 (58-80)	71 (58-103)	95 (61-137)	0.006
Hepatic triglycerides (%)	1.9 (0.9-5.3)	1.4 (0.7-5.4)	2.8 (1.5-5.3)	0.019
Myocardial triglycerides (%)	0.6 (0.4-1.1)	0.6 (0.3-1.0)	0.8 (0.4-1.3)	0.13
Subcutaneous fat (ml)	831 (486-1180)	796 (475-1295)	850 (500-1090)	0.75
Visceral fat (ml)	443 (323-581)	402 (294-582)	497 (397-581)	0.07
Framingham risk score<10% (%)	93.4	98.0	87.5	0.005
Acc/AHA new risk<7.5% (%)	92.8	97.0	87.5	0.01

* Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Framingham score, Framingham risk score.

Table 2

Sex-specific Comparisons of the Anthropometric, Laboratory, and Ectopic Fat Measures between Cocaine Users and Non-users[†]

	Men		Women	
Characteristic	Cocaine– (N=43)	Cocaine+ (N = 57)	Cocaine– (N = 57)	Cocaine+ (N=23)
BMI (kg/m ²)	25 (21-29)	27(25-30) [*]	31 (26-38)	34 (29-38)
Waist circumference (cm)	90 (81-99)	95 (85-101)	96 (81-106)	95 (92-111)
Leptin (ng/mL)	3.7 (2.6-6.7)	4.7 (4.1-7.6) [*]	34.0 (12.8-46.0)	28.8 (21.8-38.0)
Hepatic triglycerides (%)	1.1 (0.4-1.9)	2.5 (1.1-5.3) ^{**}	2.0 (0.8-5.7)	3.4 (1.7-5.5)
Myocardial triglycerides (%)	0.4 (0.2-0.8)	0.6 (0.4-1.1)	0.7 (0.4-1.1)	0.9 (0.6-1.6)
Subcutaneous fat (ml)	441 (253-733)	597 (434-910) [*]	1105 (730-1420)	1190 (960-1820)
Visceral fat (ml)	348 (267-458)	457 (350-563) ^{**}	473 (337-650)	566 (442-650)

Abbreviations: BMI, body mass index (kg/m²).

[†] Median (IQR) for the measures, and Wilcoxon test was used to compare the differences in the measures between groups.

^{*} p<0.05

^{**} P<0.01.

Table 3

Demographic, laboratory, and clinical factors in relation to myocardial triglyceride *content* (square-root transformed), robust regression analysis with LTS estimation

Variable	Myocardial triglyceride content (square-root transformed)				
	Univariate analysis			Final regression model $R^2=0.32$	
	regression estimate (SE)	R^2	p-value	regression estimate (SE)	p-value
Age (year)	0.0036 (0.0975)	0.01	0.13		
Male sex	-0.1397 (0.0448)	0.06	0.002		
Cigarette smoking	0.0504 (0.0523)	0.02	0.34		
Years of cigarette smoking	0.0026 (0.0018)	0.04	0.15		
Alcohol use	0.0281 (0.0485)	0.00	0.56		
Years of alcohol use	0.0009 (0.0019)	0.00	0.63		
Cocaine use	0.1092 (0.0457)	0.02	0.017		
Years of cocaine use	0.0068 (0.0027)	0.03	0.01	0.0071 (0.0024)	0.0033
Heroin use	0.0612 (0.0493)	0.005	0.21		
Years of heroin use	0.0030 (0.0026)	0.003	0.25		
Leptin (ng/mL)	0.0043 (0.0010)	0.21	<0.0001	0.0033 (0.0011)	0.0017
hsCRP (mg/dL)	0.0140 (0.0042)	0.14	0.0009		
hsCRP>2 mg/dL	0.1218 (0.0485)	0.12	0.01		
Systolic BP (mmHg)	0.0002 (0.0020)	0.00	0.91		
Diastolic BP (mm Hg)	0.0020 (0.0025)	0.02	0.43		
Fasting glucose (mg/dL)	0.0034 (0.0025)	0.06	0.18		
BMI (kg/m ²)	0.0147 (0.0034)	0.21	<0.0001		
Waist circumference (cm)	0.0060 (0.0018)	0.13	0.0009		
Waist/hip ratio	0.2846 (0.3069)	0.01	0.35		
Total cholesterol (mg/dL)	-0.0005 (0.0007)	0.03	0.46		
LDL-C (mg/dL)	-0.0002 (0.0007)	0.00	0.80		
HDL-C (mg/dL)	-0.0000 (0.0015)	0.01	0.98		
Triglycerides (mg/dL)	-0.0002 (0.0004)	0.03	0.16		
Framingham score<10%	0.0243 (0.0940)	0.00	0.80		
ACC/AHA new risk<7.5%	0.0668 (0.0901)	0.00	0.46		
Hepatic triglyceride (%)	0.0215 (0.0042)	0.12	<0.0001		
Subcutaneous fat (mL)	0.0002 (0.0000)	0.21	<0.0001		
Visceral fat (mL)	0.0005 (0.0001)	0.22	<0.001	0.0003 (0.0001)	0.022

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Framingham score, Framingham risk score.

Table 4

Variations in Myocardial Triglycerides Content Explained by Anthropometric, Laboratory, and Ectopic Fat Measures by Cocaine Use Status (R^2 derived from univariate robust regression analysis)

	Outcome variable: Myocardial Triglycerides Content (square-root transformed)		
Characteristic	Cocaine- (N=100)	Cocaine+ (N = 80)	All (N=180)
Body mass index (kg/m ²)	$R^2=0.43$ $p<0.0001$	$R^2=0.01$ $P=0.29$	$R^2=0.21$ $P<0.0001$
Waist circumference (cm)	$R^2=0.32$ $P=0.0003$	$R^2=0.03$ $P=0.99$	$R^2=0.13$ $P=0.0009$
Leptin (ng/mL)	$R^2=0.33$ $P<0.0001$	$R^2=0.14$ $P=0.008$	$R^2=0.21$ $P<0.0001$
Hepatic triglycerides (%)	$R^2=0.21$ $P<0.0001$	$R^2=0.10$ $P=0.29$	$R^2=0.12$ $P<0.0001$
Subcutaneous fat (ml)	$R^2=0.33$ $P=0.0003$	$R^2=0.10$ $P<0.0001$	$R^2=0.21$ $P<0.0001$
Visceral fat (ml)	$R^2=0.45$ $P<0.0001$	$R^2=0.01$ $P=0.43$	$R^2=0.22$ $P<0.0001$

Table 5

Demographic, laboratory, and clinical factors in relation to myocardial triglyceride (square-root transformed), robust regression analysis with LTS estimation (Outcome variable: Myocardial triglyceride content (square-root transformed))

Variable	Cocaine negative				Cocaine positive			
	Univariate analysis		Final model, $R^2=0.43$		Univariate analysis		Final model, $R^2=0.24$	
	regression estimate (SE)	R^2	p-value	regression	p-value	regression estimate (SE)	R^2	p-value
Age (year)	0.0030 (0.0026)	0.02	0.25			-0.0012 (0.0058)	0.01	0.83
Male sex	-0.1606 (0.0545)	0.08	0.003			-0.2141 (0.0877)	0.08	0.01
Cigarette smoking	-0.0277 (0.0577)	0.02	0.63			0.1546 (0.1304)	0.12	0.24
Years of cigarette smoking	0.0001 (0.0026)	0.02	0.96			0.0027 (0.0032)	0.09	0.41
Alcohol use	-0.0304 (0.0565)	0.04	0.59			0.0622 (0.1037)	0.01	0.55
Years of alcohol use	0.0003 (0.0025)	0.00	0.92			-0.0025 (0.0032)	0.00	0.44
Leptin (ng/mL)	0.0041 (0.0010)	0.33	<0.0001			0.0050 (0.0019)	0.14	0.008
hsCRP (mg/dL)	0.0138 (0.0058)	0.20	0.018			0.0104 (0.0064)	0.08	0.10
hsCRP > 2 mg/dL	0.1776 (0.0608)	0.26	0.004			0.0632 (0.0805)	0.00	0.43
Systolic BP (mmHg)	0.0015 (0.0024)	0.03	0.55			-0.0046 (0.0034)	0.03	0.18
Diastolic BP (mm Hg)	0.0011 (0.0031)	0.03	0.72			-0.0027 (0.0048)	0.02	0.58
Fasting glucose (mg/dL)	0.0055 (0.0031)	0.09	0.08			-0.0023 (0.0041)	0.00	0.57
BMI (kg/m ²)	0.0168 (0.0031)	0.43	<0.0001	0.0168 (0.0031)	<0.0001	0.0079 (0.0075)	0.01	0.29
Waist circumference (cm)	0.0061 (0.0017)	0.32	0.0003			0.0000 (0.0036)	0.03	0.99
Waist/hip ratio	1.2212 (0.3804)	0.11	0.001			-0.8241 (0.6215)	0.04	0.18
Total cholesterol (mg/dL)	-0.0007 (0.0008)	0.03	0.37			-0.0014 (0.0012)	0.00	0.25
LDL-C (mg/dL)	0.0006 (0.0009)	0.00	0.46			-0.0022 (0.0013)	0.01	0.08
HDL-C (mg/dL)	-0.0043 (0.0016)	0.11	0.006			0.0099 (0.0025)	0.13	<0.0001
Triglycerides (mg/dL)	0.0000 (0.0007)	0.00	0.96			-0.0014 (0.0006)	0.11	0.01
Framingham score < 10%	-1.1548 (0.2736)	0.01	<0.0001			0.0741 (0.1145)	0.00	0.52
ACC/AHA new risk < 7.5%	0.0758 (0.1946)	0.00	0.70			0.1382 (0.1137)	0.01	0.22
Hepatic triglyceride (%)	0.0303 (0.0055)	0.21	<0.0001			0.0017 (0.0016)	0.10	0.29
Subcutaneous fat (mL)	0.0002 (0.0000)	0.33	0.0003			0.0003 (0.0001)	0.10	<0.0001

Variable	Cocaine negative				Cocaine positive			
	Univariate analysis				Univariate analysis			
	regression estimate (SE)	R ²	p-value	Final model, R ² =0.43	regression estimate (SE)	R ²	p-value	Final model, R ² =0.24
Visceral fat (mL)	0.0006 (0.0001)	0.45	<0.0001		0.0002 (0.0002)	0.01	0.43	

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Framingham score, Framingham risk score.