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Early retinal vascular abnormalities in African-American cocaine users

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Abstract

Purpose—To evaluate early changes in the central retinal response in HIV positive patients without infectious retinitis using multifocal electroretinography (mfERG).

Design—The study was a case control study.

Methods—We evaluated three cohorts - HIV negative controls and two groups of HIV positive patients separated according to their nadir CD4 counts (≥ 100 and < 100 for a minimum of 6 months). MfERG first (FOK) and second order (SOK) kernels were analyzed separately by areas of rings, quadrants and individual hexagons for each cohort.

Results—Of 103 hexagon locations of FOK results there were no significant differences in amplitudes of P1 and N1 across the groups ($0.05 < p < 0.50$); although there was a trend for an overall reduction in the amplitudes. Similarly, latency N1 did not differ ($0.28 < p < 0.95$). There were significantly delayed latencies of P1 between cohorts across 103 hexagons in both kernels. SOK results also showed significant delay in latencies of P1 and a trend of reduced P1 amplitudes across studied locations among cohorts ($0.24 < p < 0.08$).

Conclusion—The results demonstrate widespread delay in latency in HIV positive patients, especially in those with prolonged low (below 100) CD4 nadir counts. These findings suggest early diffuse dysfunction of the inner retina resulted from severe HIV disease even in the era of HAART.

Keywords

cocaine use; African American; HIV infection; retinal vascular changes

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INTRODUCTION

Among the many different forms of drug abuse, cocaine addiction is the most common cause of drug-related death and drug-associated visits to emergency rooms of US hospitals¹. Although the global consumption of cocaine is declining, 2.3 million people in the United States are current cocaine users². Cocaine abuse leads to multiple serious medical complications including stroke, seizure, cerebral infarction, cerebral atrophy, arrhythmias, tachycardia, hypertension, and cardiomyopathy. These clinical diseases are usually related to systemic vascular changes induced by cocaine use. A recent study suggests the use of cocaine may also lead to subclinical atherosclerosis in those drug abusers³.

Changes in the caliber of retinal arterioles and venules have been found in persons with diabetes, stroke, systemic hypertension, and renal disease; and the microcirculation of many tissues, such as retina, is affected^{4,5}. Because the retinal arteries/arterioles share many common features in anatomy and physiology of similar-sized vessels in brain and kidney, the non-invasive visualization and measurement of retinal vasculature have been advocated for early detection of systemic diseases.

The bifurcation angle of a retinal artery is the geometric angle subtended between two branching arterioles. In an ideal configuration, the bifurcation of arteries will have an optimal branching arrangement to facilitate effective blood flow⁶. Some studies have shown that the bifurcation angle is narrowed in subjects with hypertension⁷ or with low birth weight⁸, but not in subjects suffering from a peripheral vascular disease with abnormally low ankle/brachial indices⁹.

Case reports^{10,11} have described ocular vascular changes, such as retinal hemorrhages, talc retinopathy, and central retinal artery occlusion, related to cocaine use. These clinical manifestations are not widely recognized, and the ocular features of cocaine-related complications have not been defined in detail. Because of the presence of cerebral vascular changes such as intracranial hemorrhage, cerebral infarction, and focal narrowing of cerebral arteries in cocaine users, we examined early retinal vascular changes in a group of subjects with a history of cocaine use. In this study, we investigated the association between cocaine use and both retinal vessel diameter and the bifurcation angle of the retinal arterioles. Because HIV infection was one of the major variables in this study population, we also examined its interaction with these ocular features

METHODS

Study Subjects

Seventy-four subjects for this study were recruited from an ongoing cohort study in which the relationships among cocaine abuse, HIV infection, and cardiovascular consequences are being evaluated¹². All were enrolled from inner-city neighborhoods in Baltimore, Maryland. For the ongoing cohort study, interviews about sociodemographics and drug-use behaviors, clinical examinations, lipid profiles, and 64-slice MDCT for coronary artery calcium (CAC) were performed. Information about medical history and medications was obtained from interviews and confirmed by medical chart reviews. Information about cocaine (powdered and crack forms) and other illegal drug (mainly, heroin) use was collected, including frequency, forms, administration mode (injection, smoking, etc.), and duration of drug use. Inclusion criteria were age between 25 and 54 years and African-American race. Exclusion criteria were 1) presence of hypertension (defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg), 2) ischemic heart disease based on clinical and hospitalization record of myocardial infarction, angina pectoris, and electrocardiographic and/or echocardiographic abnormalities, 3) other systemic symptoms related to cardiovascular diseases such as chest

pain or severe headache, and 4) pregnancy. Use of cocaine was defined as chronic use by any route for at least 6 months, administered at least 4 times a month. Nonuse of cocaine was defined as no use in the past 5 years.

Eye examination

In 74 participants, a comprehensive eye and retinal fundus examination through a dilated pupil was performed by a board-certified ophthalmologist at the Wilmer Eye Institute of the Johns Hopkins School of Medicine. After pupillary dilation, a digital fundus camera (Zeiss FF-series) was used to take a thirty degree retinal fundus photograph concentric with the optic disc for each eye (Figure 1).

Retinal images

The digital images were assessed by an optometrist, who did not have access to the personal data of participants. Retinal changes such as embolic phenomena, retinal hemorrhages, retinal necrosis, and the presence of cotton wool spots will be reported in a separate article.

Assessment of angle of arterial bifurcation

For each fundus image, the largest angle of arterial bifurcation (LAAB) was measured by means of computer software (Adobe Photoshop). The high resolution colored images (2540 dpi, 8 pits per pixel) were converted to grayscale images. The region of the LAAB was magnified 200%. Two 500- μ m bars, each with a width the same as the calibers of the intersecting blood vessels, were drawn parallel to the branched arterioles at the bifurcation. The center of the crossing of the two line bars was marked with the Pen Tool and extended to produce a line parallel to the line bars. The difference between the crossed lines was the angle of bifurcation. Sufficient measurements of branching angles in different quadrants were made, to ensure that the measured angle was the largest one seen in the images. Excluded from measurement were the branching angles inside the optic disk and branched arterioles with diameters smaller than 25 μ m. The technique of measurement is illustrated in Figure 2. Multiple measurements were taken to test the intergrader reliability of the method. The reproducibility of the LAAB measurement is shown in Figure 3. The correlation coefficient of repeated measurement was 0.76 ($p < 0.0001$).

Assessment of central retinal arterial or venous diameter

The high resolution images were also sent to the Wisconsin Fundus Photograph Reading Center for retinal vascular caliber measurement. The details of this measurement technique were previously described^{13,15}. In brief, a digitized grid was positioned over the image to locate the zone of measurement (Figure 4). The diameters of the largest six arteries or veins passing through the 0.5- to 1.0-disc diameter from the disc margin were measured by customized software (IVAN, Dept of Ophthalmology & Visual Science, University of Wisconsin-Madison, WI). These values were computed into the revised formulas to obtain the projected calibers of the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE)¹⁶. The examiner recognized the vessel as arteriole or venule according to the original color photo taken. Reproducibility of retinal vessel diameter measurements using similar software has been reported, and the correlation coefficients were 0.84 for intragrader and 0.79 for intergrader measurements¹⁷.

Statistical analyses

Because measurements made in the two eyes of each of the study subjects may be correlated, the statistical analyses were performed by using the GENMOD procedure in SAS 9.1 (SAS Institute Inc., Cary, NC) which fits models to correlate responses by the generalized estimation equations (GEE) method¹⁸. The GEE method, which extends generalized linear models

(GLMs) to a regression setting with correlated observations within subjects, was used by analyzing discrete and continuous longitudinal data¹⁹. Univariable GEE analysis was used to examine the associations between the independent variables such as age, sex, cigarette smoking, cocaine use, duration of cocaine use for 10 years or longer, route of drug administration (e.g., intravenous injection), HIV infection, the interaction between HIV and cocaine use, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum total cholesterol levels, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol, triglycerides, and abnormally high CAC. CAC was assessed by CT scan¹². The outcome variables were the LAAB, CRAE, and CRVE in any eye. Univariate GEE models were first fitted to evaluate the impact of age, sex, cocaine use, and other independent variables on each of the three outcome variables (LAAB, CRVE and CRAE). The independent variables that were significant ($p < 0.10$) in the univariate models were put into regression multivariate GEE model to identify the factors that were independently associated with the outcome variables. Those independent variables that ceased to make significant contributions (at the $p < 0.05$ level) to the models were deleted in a stepwise manner, yielding the final models. P-values reported are two-sided.

RESULTS

Seventy-four participants completed the eye examination and 147 retinal images were obtained. The characteristics of these participants by cocaine use status are presented in Table 1. Six participants with diabetes were excluded from statistical analysis because diabetes might affect the retinal vasculature and thereby could influence the results. Thus, data from 136 eyes of 68 subjects were included in the final data analysis. The average age of the study subjects was 39.8 ± 4.1 years (mean $\pm$ SD), and 22 (32.4 %) of them were female. Among the study subjects, 52 (76.5%) were cocaine users, 42 (61.8%) were HIV-positive, 53 (84.1%) smoked cigarettes, and 33 (62.3 %) were intravenous cocaine users.

Largest angle of arterial bifurcation (LAAB) was significantly larger in subjects with a history of cocaine use of over 10 years than in those with less than 10 years of cocaine use (Table 2). LAAB was positively associated with age, but it was also inversely associated with serum VLDL.

Larger CRVE was associated with a history of cocaine use in both univariate and multivariate analyses, but no association was found between CRVE and age, sex, cigarette smoking, BMI, SBP, DBP, triglycerides, cholesterol, CAC level, and intravenous (IV) injection (Table 3). CRVE was larger in cocaine users than in non-users ($p = 0.026$; Table 3).

Larger CRAE was significantly associated with younger age and a history of IV injection of cocaine in both univariate and multivariate analyses (Table 4).

DISCUSSION

In this study we focused on LAAB, CRVE, and CRAE as independent variables as observed in the ocular fundus images to detect early retinal vascular changes which we hypothesized may occur in relatively healthy subjects as a result of cocaine use. We found a positive association between a history of 10 years' cocaine use and larger LAAB. Increased CRVE was also significantly correlated with a history of cocaine use. However, CRAE was only positively associated with IV injection of cocaine and inversely associated with age. Although many subjects in this study were HIV-positive, we did not find any interaction between HIV status and the measured microvascular changes, supporting the hypothesis that cocaine use may cause potentially disease-inducing microvascular abnormalities.

The normal systemic arterial vascular networks are optimally designed to minimize energy loss and to maintain uniform levels of blood flow-induced shear stress²⁰. A change in blood flow or blood viscosity may induce a change of pressure gradient, resulting in a change of the vessel diameter and/or branching angle. In the retina, blood flow is autoregulated because the retinal circulation lacks autonomic innervations. The autoregulation of the retinal blood flow is determined by factors such as blood pressure, blood viscosity, local environmental factors in the retinal circulation (such as oxygen tension, pH), and mediators (such as nitric oxide, prostaglandins, endothelin-1) released locally from the retina²¹. In this study, we did not measure the blood flow or blood viscosity in the retina directly. However, the pharmacological effects of cocaine suggest potential pathologic mechanisms whereby cocaine abuse may affect the retinal circulation. For example, cocaine may act indirectly on the mediator-related functions by enhancing the production of endothelin and suppressing production of nitric oxide^{22,23}. Since largest angle of arterial bifurcation (LAAB) was found to be significantly larger in subjects with a history of cocaine use of over 10 years than in those with less than 10 years of cocaine use, such pharmacological actions may trigger focal arterial vasoconstriction, induce transient increase in blood pressure in the arterioles, and enlarge the branching angle in the arterioles subsequently.

Although we did not find any correlation between free triglycerides and retinal parameters in this study, we observed an inverse association between VLDL and LAAB. VLDL is the major carrier of triglycerides. Triglyceride concentration is correlated with blood viscosity and plasma viscosity^{24,25}. Cocaine may act on VLDL, indirectly changing the plasma viscosity by inducing the release of free triglycerides from the VLDL and thereby reducing the retinal blood flow. In this study we did not have enough samples to study the interaction between cocaine use and blood lipid levels. Cocaine-induced effects on triglycerides and VLDL should be further examined.

Blockade of dopamine transporter (DAT) is the major mechanism by which cocaine pharmacologically affects neurons²⁶. The chronic use of cocaine further blocks dopamine reuptake into the synaptic cleft. In the retina, dopamine is related to a number of physiological functions in the eye, including ocular growth, and light adaptation^{27,28}. Further research is needed to explore the potentially pathogenic effects of chronic cocaine use on dopamine receptors in the retina and its circulation.

On the other hand, ischemic lesions have been documented in the brain tissue of cocaine abusers²⁹. These lesions are related to increased permeability of the endothelial cells in blood vessels and thinning of the basal laminae of cerebral vessels³⁰. If a similar hypoxia occurs in the retina, it would be expected to induce hyperperfusion in the retina and vasodilatation in the venules, similar to what we observed in cocaine abuse subjects. Increased venular caliber may be due to retinal hypoxia³¹. Other studies have suggested that larger venular caliber is associated with systemic inflammatory markers such as elevated white blood cell count, elevated plasma fibrinogen, and metabolic disturbances such as obesity or hyperglycemia^{32,33,17}. Since frequent exposure to cocaine was reported to be associated with elevated C-reactive protein, a marker of inflammation³⁴, a potential explanation of the venular dilatation we observed could be that use of cocaine may lead to a chronic inflammatory process causing retinal hypoxia.

Retinal blood vessel caliber has been studied in several population-based observational studies, such as the ARIC, Blue Mountains, and Rotterdam studies^{35,15,36}. Aging, stroke, hypertension, and blood pressure were inversely associated with arteriolar caliber or AVR (arteriole-to-venule ratio)¹⁵. These studies showed that systemic diseases or systemic blood pressure were associated with vascular changes in the retinal arteries, even though the retinal circulation is autoregulated by local factors. Our study confirmed that age affects the CRAE

as in other studies^{15,37} even though our cohort was relatively young compared to earlier studies (mean age: 39.8 ± 4.1 ; age range 29–45 years).

Intravenous (IV) injection, a common administration method in chronic cocaine abusers, may affect blood flow in the capillary bed. Small undissolved particles in suspension, such as talc, may pass into the systemic circulation and emboli may present as tiny refractile dots and block the blood flow in the retinal capillary circulation. In this study, 29 (55.8%) of the cocaine abusers reported to have IV injection as a means to deliver the drug. The positive relation between injection and CRAE may be due to local blockage of capillaries leading to focal hypoxia, in turn leading to increased arterial calibers in response to hypoxia.

Several limitations in this study should be noted. First, the number of persons without HIV and cocaine use is relatively small. Second, selection bias could have obscured some relevant associations existing in the samples. The subjects in this study are in the lowest socioeconomic group, and so their lifestyles and physical activities may differ from those of the general population, although cocaine users commonly are in this segment of the population.

In conclusion, cocaine use appears to be associated with wider retinal venular caliber and increased arterial branching. These characteristics would be expected to reduce the efficiency of blood flow. Because the retina is part of the central nervous system, these abnormalities may be a sign heralding more widespread microvascular disease in the central nervous system induced by cocaine use. However, it is not clear whether similar changes are found in other organ systems of cocaine users. Further investigation to determine the potential substantial significance of these observations is warranted.

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C. Contributions of authors to each of these areas: Design of the study (IL, SL, JK, RK, MT, HL); Conduct of the Study (JK, RK, IL, SL, HL), Data Collection (IL, HL, JK, RK), Management and Analysis (SR, HL), Preparation (IL, HL), Review and Approval of the manuscript (RK, IL, SL, JK, SR, MT, HL)

D. Statement about conformity with Author Information: The Johns Hopkins School of Medicine IRB approved this study.

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Figure 1.
A Color stereoscopic fundus photograph, taken from an African-American cocaine user. A typical 30-degree image of the retina centered on the optic disk taken with a Zeiss fundus camera.

Figure 2.

Schematic illustration of measurement of branching angles in African American cocaine users. Two 500- μ m bars, each with a width the same as that of the calibers of the intersecting blood vessels, are drawn parallel to the branched arterioles at the bifurcation. The center of the crossing of the two line bars are marked with the pen tool and extended to produce a line parallel to the line bars. The difference between the crossed lines is the angle of bifurcation.

Largest angle of arterial bifurcation (LAAB)

Figure 3.

A Scatter plot showing the correlation between the first and second measurement of the largest angle of arterial bifurcation (LAAB) of retinal arterioles in African American cocaine users. The reproducibility of the LAAB measurements in this study is high ($r = 0.76$, $p < 0.001$).

Figure 4. Method for determining the reproducibility of the largest angle of arterial bifurcation (LAAB) measurements in African-American cocaine users. An overlying grid is centered on the optic disc. The color image is converted to a grayscale image. The color blue denotes venules; red denotes arterioles. All retinal vessels are measured in a circular ring starting from one-half disc diameter to one disc diameter from the optic disc. Only the largest six venules and arterioles are computed, using the Knudtson formula [23].

Table 1

Characteristics of 74 African American Study Participants by Cocaine Use Status *

Characteristics	Non-cocaine users (Mean $\pm$ SD, n = 24)	Cocaine users (Mean $\pm$ SD, n=50)	P-value
Age (years)	40.3 $\pm$ 5.0	43.0 $\pm$ 3.8	0.015
Female (%)	33	34	0.95
BMI (kg/m ²)	26.0 $\pm$ 5.2	24.3 $\pm$ 3.6	0.15
Heart rate (beats/min)	65.7 $\pm$ 13.9	63.8 $\pm$ 9.1	0.55
SBP (mm Hg)	109.8 $\pm$ 11.1	108.9 $\pm$ 12.2	0.76
DBP (mm Hg)	76.6 $\pm$ 7.3	77.4 $\pm$ 7.6	0.67
Total cholesterol (mg/dL)	164.9 $\pm$ 29.2	178.9 $\pm$ 40.5	0.13
HDL (mg/dL)	49.0 $\pm$ 14.0	54.5 $\pm$ 20.5	0.24
LDL (mg/dL)	94.5 $\pm$ 28.1	102.8 $\pm$ 33.1	0.29
VLDL (mg/dL)	20.5 $\pm$ 8.5	21.6 $\pm$ 13.3	0.67
Triglycerides (mg/dL)	121.8 $\pm$ 81.4	111.7 $\pm$ 78.7	0.61
Duration of cocaine use (years)	N/A	10.1 $\pm$ 7.5	N/A
HIV (%)	83	56	0.02
Cigarette smoking (%)	29	71	0.028
LAAB (degree)	88.4 $\pm$ 2.9	87.7 $\pm$ 1.6	0.88
CRAE (micron)	155.6 $\pm$ 2.8	158.3 $\pm$ 1.8	0.41
CRVE (micron)	233.9 $\pm$ 4.1	245.3 $\pm$ 3.0	0.024
AVR	0.67 $\pm$ 0.01	0.65 $\pm$ 0.01	0.21

* Abbreviations: SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; HIV, human immunodeficiency virus; LAAB, largest angle of arterial bifurcation; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; AVR, arteriole-to-venule ratio.

Table 2

Factors Associated with Largest Angle of Arterial Bifurcation (LAAB) in African American Study Participants*

Variable	Univariate		Multivariate	
	Regression Estimate (SE)	P-values	Regression Estimate (SE)	P-values
Age (years)	0.662 ± 0.316	0.036	0.739 ± 0.294	0.0119
Sex	0.350 ± 3.273	0.915		
BMI (kg/m ²)	0.239 ± 0.389	0.538		
Cigarette smoking	6.822 ± 3.299	0.039		
Cocaine use	4.296 ± 3.301	0.193		
Cocaine use >10 years	6.830 ± 2.749	0.013	6.586 ± 2.636	0.0125
HIV infection	1.231 ± 3.104	0.691		
Injection drug use	1.644 ± 3.717	0.658		
SBP (mm Hg)	-0.057 ± 0.129	0.659		
DBP (mm Hg)	0.0127 ± 0.176	0.942		
Total cholesterol (mg/dL)	-0.060 ± 0.039	0.125		
HDL (mg/dL)	-0.063 ± 0.060	0.294		
LDL (mg/dL)	-0.033 ± 0.046	0.467		
VLDL (mg/dL)	-0.257 ± 0.095	0.007	-0.2888 ± 0.094	0.0021
Triglycerides (mg/dL)	-0.025 ± 0.014	0.081		
CAC	-3.164 ± 2.840	0.265		

* Abbreviations: SE, standard error; BMI, body mass index; HIV= human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; CAC, coronary artery calcium.

Table 3
Factors Associated with Central Retinal Vein Equivalent (CRVE) in African American Study Participants

Variable	Univariate		Multivariate	
	Regression Estimate (SE)	P-values	Regression Estimate (SE)	P-values
Age (years)	-0.978 ± 0.578	0.091		
Sex	2.454 ± 5.381	0.65		
BMI (kg/m ²)	0.704 ± 0.532	0.19		
Cigarette smoking	2.461 ± 6.664	0.71		
Cocaine use	12.095 ± 5.419	0.026	12.095 ± 5.419	0.026
Cocaine use >10 years	6.561 ± 5.052	0.19		
HIV	-3.859 ± 5.282	0.46		
Injection drug use	9.475 ± 5.677	0.095		
SBP (mm Hg)	-0.005 ± 0.200	0.98		
DBP (mm Hg)	0.313 ± 0.329	0.34		
Total cholesterol (mg/dL)	0.006 ± 0.056	0.91		
HDL (mg/dL)	0.033 ± 0.123	0.78		
LDL (mg/dL)	0.006 ± 0.075	0.93		
VLDL (mg/dL)	-0.066 ± 0.171	0.70		
Triglycerides (mg/dL)	-0.018 ± 0.023	0.44		
CAC	5.520 ± 6.093	0.36		

* Abbreviations: SE, standard error; BMI, body mass index; HIV= human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; CAC, coronary artery calcium. .

Table 4
Factors Associated with Central Retinal Artery Equivalent (CRAE) in African American Study Participants

Variable	Univariate		Multivariate	
	Regression Estimate (SE)	P-values	Regression Estimate (SE)	P-values
Age	-0.915 ± 0.338	0.006	-1.019 ± 0.405	0.012
Sex	2.912 ± 2.904	0.316		
BMI (kg/m ²)	0.076 ± 0.255	0.76		
Cigarette smoking	2.059 ± 4.795	0.67		
Cocaine use	1.613 ± 4.239	0.70		
Cocaine use >10 years	2.962 ± 3.108	0.34		
HIV	0.614 ± 3.399	0.85		
Injection drug use	7.352 ± 3.764	0.05	8.216 ± 3.629	0.024
SBP (mm Hg)	-0.184 ± 0.085	0.03		
DBP (mm Hg)	-0.211 ± 0.172	0.22		
Cholesterol (mg/dL)	0.002 ± 0.043	0.96		
HDL (mg/dL)	0.009 ± 0.106	0.93		
LDL (mg/dL)	-0.003 ± 0.048	0.95		
VLDL (mg/dL)	0.025 ± 0.114	0.83		
Triglycerides (mg/dL)	-0.002 ± 0.015	0.91		
CAC	-1.912 ± 4.076	0.64		

* Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; CAC, coronary artery calcium.