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Lipoprotein Concentration, Particle Number, Size and Cholesterol Efflux Capacity are associated with Mitochondrial Oxidative Stress and Function in an HIV Positive Cohort

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Abstract

Background—Association of lipoprotein particle size/number and HDL function with mitochondrial oxidative stress and function may underlie the excess cardiovascular (CVD) risk in HIV.

Methods and Results—Among HIV infected individuals on stable highly active antiretroviral therapy, we related standard and novel lipid measures [plasma total cholesterol, triglycerides, HDL-C, LDL-C, lipoprotein particle (-P) subclass size and number and HDL function (via cholesterol-efflux capacity)] with oxidative stress [peripheral blood mononuclear cell's mitochondrial-specific 8-oxo-deoxyguanine (8-oxo-dG)] and function markers [oxidative phosphorylation (OXPHOS) NADH dehydrogenase (Complex I) and cytochrome *c* oxidase (Complex IV) enzyme activities]. Multivariable-adjusted logistic and linear regression analyses were employed adjusting for age, gender, CD4 nadir, viral load, smoking, diabetes, HOMA-IR,

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hypertension and lipid medications. Among 150 HIV-infected persons (mean age 52 years, 12% women, median CD4 count 524 cell/mm3), low HDL-C and high total cholesterol/HDL-C ratio were related to PBMC 8-oxo-deoxyguanine (p=0.01 and 0.02 respectively). Large HDL-P and HDL-P size were inversely related to PBMC 8-oxo-deoxyguanine (p=0.04). Small LDL-P (p=0.01) and total LDL-P (p=0.01) were related to decreased OXPHOS Complex I activity. LDL-P was related to decreased OXPHOS Complex IV activity (p=0.02). Cholesterol efflux capacity was associated with increased OXPHOS Complex IV activity.

Conclusions—HDL concentration and particle size and number are related to decreased PBMC mitochondrial oxidative stress whereas HDL function is positively related to mitochondrial oxidative function. The association we find between atherogenic lipoprotein profile and increased oxidative stress and function suggests these pathways may be important in the pathogenesis of cardiometabolic disease in HIV disease.

Keywords

atherosclerosis; cardiovascular disease; lipids; NMR spectroscopy; oxidative phosphorylation; cholesterol efflux capacity; HDL

Introduction

Mitochondrial oxidative stress and function, which relate to HIV treatment, metabolic disease and atherosclerosis, represents a potential key pathophysiologic mechanism by which HIV infection confers excess cardiometabolic risk. Dyslipidemia, an important component of cardiometabolic risk in HIV, is etiologically associated with viral infection and antiretroviral treatment.[1] However, a traditional clinical lipid profile may not fully capture atherogenic risk and lipid particle size and number [as measured by nuclear magnetic resonance (NMR) spectroscopy] may provide more meaningful information with regards to cardiometabolic risk. In the general population, small LDL size with a high LDL particle number are linked with the metabolic syndrome.[2] In persons with HIV on antiretroviral therapy, HDL particle size has a demonstrated inverse association with clinical coronary disease.[3] Cholesterol efflux capacity, a biomarker of HDL function and reverse cholesterol transport, has not been studied in HIV positive individuals.

Glycosylated or oxidized LDL affects mitochondrial function, specifically oxidative phosphorylation in vascular endothelial cells and may increase reactive oxygen species resulting in mitochondrial specific oxidative stress, 8-oxo-deoxyguanine (8-oxo-dG).[4] Reactive oxygen species have also been shown to result in preferential mtDNA damage and dysfunction in vascular cells and with the extent of atherosclerosis in both mice and human aortas.[5] LDL and in particular, small LDL is susceptible to oxidation whereas HDL can prevent oxidation. These differences are due to fatty acid and protein composition of the specific cholesterol particles.[6, 7]

Whether or not and NMR spectroscopic lipid profiles and HDL efflux capacity are related to mitochondrial oxidative function and/or stress in HIV is uncertain. Thus, we sought to better characterize the association between NMR lipid profile, cholesterol efflux capacity and

peripheral blood mononuclear cells' (PBMC) mitochondrial function and oxidative stress in a cohort of men and women with HIV on stable HAART therapy.

Methods

Study Sample

Our study is a cross-sectional examination of baseline data from the Hawaii Aging with HIV - Cardiovascular Study cohort, a longitudinal natural history study of the role of oxidative stress and inflammation in cardiovascular risk among individuals with chronic stable HIV. Inclusion criteria for participation consisted of a documented HIV-positive status and having been on stable antiretroviral therapy for at least six months. The cohort was not selected based on CVD history or risk factors. Our study sample includes 150 HIV infected men and women residing in the state of Hawaii, aged > 40 years who had oxidative stress measurements. A subset of 129 persons who had cholesterol efflux capacity information were included in the analysis of cholesterol efflux and mitochondrial oxidative stress. A signed consent for participation in the study was obtained from each person, and IRB approval was obtained from the University of Hawaii.

Clinical covariate measurements

Medical and medication history was obtained through chart review and self-report. Current and past smoking status was taken from patient report as yes or no responses.

Height, weight, systolic and diastolic blood pressure, waist-hip ratio, ankle-brachial index, and EKG were measured. Patients had blood drawn for fasting lipids, NMR lipid measurements and oxidative stress measurements.

Laboratory measurements

The lipid, glucose and insulin measurements were performed after a 12 hour fast. The standard lipid profile measured included directly measured LDL, HDL, triglycerides and total cholesterol assays (via enzymatic colorimetric method). The Liposcience assay employs NMR spectroscopic analysis to report lipoprotein size and particle number from serum and has been previously described.[8] Mitochondrial oxidative stress and function assays were performed on viable PBMC's as previously described.[9] Briefly, mitochondrial oxidative stress was measured as 8-oxo-dG, which reflects DNA break frequencies. Mitochondrial oxidative function was assessed via activity of two key enzymes along PBMC's mitochondrial inner membrane's oxidative phosphorylation pathway or electron transport chain, Complexes I and IV.

The cholesterol efflux capacity assay was performed by the Mehta laboratory using the method previously described.[10, 11] Briefly, the total efflux mediated by pathways of known relevance in cholesterol efflux from macrophages is quantified via liquid scintillation counting and is a reflection of HDL function. Each sample was run in duplicate. Values were normalized by dividing the efflux capacity of individual patients by the efflux capacity of a serum pool run with each assay.

Statistical Methods

Descriptive statistics (n, mean, medians, standard deviations, percentages) were performed for baseline characteristics. Multivariable-adjusted logistic and linear regression analyses were employed to relate mitochondrial oxidative stress function respectively with lipid parameters (standard lipid panel, lipid subclass and lipid subclass size). The mitochondrial oxidative stress measure 8-oxo-dG was considered categorically due to skewed distribution with a high number of zero values (≤ 0 or > 0). The mitochondrial oxidative function measures OXPHOS Complex I and IV activities were both normal distributed and therefore were analyzed as continuous variables. Cholesterol efflux capacity was log transformed due to the sewed distribution of this data. Covariates included in multivariable models included age, gender, medical diagnosis of diabetes, hypertension (defined as systolic BP > 140 mmHg, diastolic BP > 90 mmHg or on hypertension medications), homeostatic model of assessment – insulin resistance (HOMA-IR) [serum glucose (mg/dL)/plasma insulin (uM/mL) * 450], current smoking (1 or more cigarettes per day currently), use of lipid medications, viral load and CD4 nadir (per laboratory record/medical records). A p-value of <0.05 was considered significant. All data analysis was performed using SAS version 9.2.

Results

The mean age of the study participants was 52 years, 12% were female. The majority of participants reported past smoking (66%) whereas 25% were current smokers (Table 1). Fifty eight percent of our participants were white, 24% reported mixed ethnicity and 8% were or Asian ethnicity. Nearly one third of participants had hypertension and nearly one third of participants were on lipid lowering medication. Mean body mass index was in the overweight range (26.5 kg/m2) and mean measured blood pressure was normal (123/76 mmHg). Mean values of the NMR derived lipoproteins and oxidative stress and function measures in our study sample, by lipid lowering medication, are given in Table 2.

HDL-C was inversely associated with PBMC 8-oxo-dG and total/HDL-C ratio was positively associated with 8-oxo-dG (Table 3). No other standard lipid parameters were statistically significantly associated with any other the oxidative stress or function measures. Results for the analysis of NMR derived lipoproteins and oxidative stress and function measures are shown in Table 4. Large HDL-P and HDL-P size were both inversely associated with 8-oxo-dG (Table 4). Small LDL-P were associated with decreased Complex I activity. Total LDL-P was associated with both decreased Complex I and IV activities (Table 4).

Cholesterol efflux capacity demonstrated significant correlation with HDL parameters including HDL-C (r=0.33), HDL size (r=0.30) and particle number (r=0.38) (all p values < 0.001). Cholesterol efflux capacity was related to increased Complex IV activity (β=0.21, p=0.04) but not to Complex I activity. Cholesterol efflux capacity was not related to PBMC 8-oxo-dG.

Secondary Analysis

We additionally adjusted models relating LDL lipid parameters with 8-oxo-dG and Complex I and IV activity for triglyceride level. Upon additional adjustment for triglycerides, beta and p values for these models did not materially change (data not shown).

Discussion

Principal findings

Low HDL-C, high total/HDL-C ratio and decreased large HDL particle size and number were related to increased mitochondrial oxidative stress as measured by PBMC 8-oxo-dG. HDL function as measured by cholesterol efflux capacity was positively associated with mitochondrial oxidative function as measured by increased PBMC Complex IV activity. Small LDL-P was associated with decreased mitochondrial oxidative function as measured by diminished PBMC Complex I activity. Total LDL-P was significantly related to diminished mitochondrial oxidative function as measured by PBMC Complex I and Complex IV activities. These associations were not explained by age, gender, CD4 nadir, HIV viral load diabetes, insulin resistance, hypertension, smoking, or use of lipid lowering medications.

Prior data

HDL-C and oxidative stress and function

HDL-C has several demonstrated and hypothesized mechanisms through which it exerts antioxidant effects including 1) Reduction of phospholipid hydroperoxides by Met residues of a major component of HDL-C, apoA-I, 2) relative fluidity of the surface phospholipid monolayer in HDL-C effecting transfer efficiency of phospholipid hydroperoxides from LDL-C to HDL-C and 3) direct oxidative effects of the antioxidant tocopherols present on the surface of the HDL molecule.[12] Furthermore, the HDL component PON-1 (a glycoprotein in the paraoxonase family) has been demonstrated to be protective against the formation of oxidized LDL-C.[13] Prior research suggests that age-related changes in HDL-C (ie. lowering of HDL-C) are accompanied by increased oxidative stress (plasma oxidized LDL-C and malondialdehyde) and vascular stiffness[14] which in turn are established CVD pathways. In a nested case control study of lipoprotein subclass and CVD mortality and morbidity within an HIV antiretroviral therapy clinical trial, investigators demonstrated that small, medium and large HDL-P were all inversely related to CVD.[3] A prospective study of lipid particle size in the Women's Health Study demonstrated that only large HDL-C was inversely related to CVD.[15] Our findings that low serum HDL-C, large HDL-P and HDL-P size were inversely related to increased PBMC 8-oxo-dG suggest that mitochondrial oxidative stress may mediate the association between low HDL-C and low large HDL-P with CVD that has been reported in the prior studies.

Cholesterol efflux capacity provides an estimation of the dynamic function of HDL with regards to cholesterol reverse transport.[10] Our findings that cholesterol efflux capacity is related to increased mitochondrial oxidative function is interesting in light of our findings that HDL concentration and HDL particle size and number were related to mitochondrial

oxidative stress rather than oxidative function. Indeed, prior investigations have demonstrated that HDL efflux is only partly explained by differences in HDL-C level.[10] Determining specific pathways that link HDL function and mitochondrial oxidative function versus oxidative stress may help us elucidate potential atheroprotective strategies and targets in persons living with HIV.

LDL-C and mitochondrial oxidative function

In prior studies among 27,673 women in a vitamin clinical trial[15] and in a nested case control study within the cardiovascular health study cohort of elderly men and women,[16] small LDL-P and increased LDL-P number were related to incident cardiovascular disease. We extend these findings in our current study and demonstrate that small LDL-P and increased LDL-P number were associated with a key CVD pathway of decreased oxidative function[17] in our sample of men and women with HIV on stable HAART. Our findings demonstrate that within an HIV positive population on stable HAART, small LDL-P and increased LDL-P number are associated with decreased PBMC Complex I activity (small LDL and particle number) and Complex IV Complex I activities (LDL-P number). The role of LDL in impairing mitochondrial respiratory chain complex enzymes in vascular endothelial cells has been previously reviewed.[4] Our data, therefore suggests atherogenic LDL cholesterol including small LDL-P in high particle numbers may lead to CVD via decreased mitochondrial oxidative phosphorylation.

Lipid modifying medications in HIV

Prior data suggests that the CVD protective, LDL lowering medication atorvastatin has been demonstrated to decrease LDL-P number, to increase LDL-P size, and to decrease markers of inflammation in the general population.[18] In the ACTG A5087 randomized, multi-center, 48 week open-label non-inferiority study of two lipid-lowering agents in HIV-infected persons with combined hyperlipidemia, pravastatin and fenofibrate improved lipid profile but did not alter markers of glucose homeostasis, thrombogenesis, endothelial function, and inflammation.[19] In this prior study, effect of statins on mitochondrial oxidative stress in HIV infection was not evaluated. Furthermore, i*n vitro* studies with human coronary artery endothelial cells treated with protease inhibitors have shown increased ROS production, via the oxidation of CMH2DCFDA, that is reduced with statins.[20] Our findings suggest that small LDL and increased LDL particles are related to PBMC mitochondrial specific oxidative stress and OXPHOS function independently of statin usage. Prior data has shown that statins do lead to decreased OXPHOS activity in the mitochondria of skeletal muscle.[21] The efficacy of prospective statin therapy intervention on LDL and particle size number, in the context of PBMC mitochondrial oxidative stress and OXPHOS function in patients with HIV, would therefore be an important area for further investigation.

The medication niacin has been demonstrated to decrease levels of the oxidative stress biomarkers including thiobarbituric acid reactive substances, lipid peroxides and paraoxonase activity in persons with low HDL.[22] A prior study of dietary niacin in a study of middle-aged healthy men, demonstrated decreased levels of oxidative stress.[23] To our knowledge, no study of niacin of other HDL-modifying medications in HIV has specifically measured effects on oxidative stress but this would be an important area for future research.

Strengths and Limitations

The strengths of our study are the careful covariate phenotyping of our study population including lipoprotein NMR measures and novel mitochondrial oxidative stress, oxidative function and cholesterol efflux capacity measurements. However, there are limitations that also deserve mention. Our study is cross-sectional and therefore causality cannot be assessed. Given that we had a relatively small study sample we did not therefore account for multiple testing in terms of adjusting our alpha level. We were unable to fully assess extent of HIV infection severity upon the lipoprotein-oxidative stress association as all participants were on stable HAART therapy with relatively low viral load and high CD4 counts. Indeed, it would be important to better understand the impact that HAART therapy has on mitochondrial oxidative stress and function measurements.

Conclusions and Implications

HDL-P and LDL-P size and number are related to PBMC mitochondrial oxidative stress and OXPHOS function in men and women with HIV on stable HAART, independent of CVD risk factors and lipid lowering medications. HDL function as measured by cholesterol efflux capacity is positively related to increased mitochondrial oxidative function. Further studies of lifestyle modification and lipid medications upon lipoprotein profiles, mitochondrial oxidative stress and OXPHOS activities in the population living with HIV may be considered in order to determine treatment efficacy and to elucidate pathways underlying dyslipidemia and CVD in HIV. Confirming these findings in persons without HIV infection would also constitute an important next step.

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- We related novel biomarkers of lipoprotein particle size, number and function with mitochondrial oxidative stress and function in an HIV positive cohort, adjusted for age, gender, CD4 nadir, HIV viral load diabetes, insulin resistance, hypertension, smoking, or use of lipid lowering medications.
- Low HDL-C, high total/HDL-C ratio and decreased large HDL particle size and number were related to increased mitochondrial oxidative stress as measured by PBMC 8-oxo-dG.
- HDL function as measured by cholesterol efflux capacity was positively associated with mitochondrial oxidative function as measured by increased PBMC Complex IV activity.
- Small LDL-P was associated with decreased mitochondrial oxidative function as measured by diminished PBMC Complex I activity.
- Total LDL-P was significantly related to diminished mitochondrial oxidative function as measured by PBMC Complex I and Complex IV activities.

Table 1

Characteristics of Participants (n=150) from the Hawaii Aging with HIV - Cardiovascular Study Cohort

Characteristic	% or mean ± STD/median [IQR]where indicated
Age, mean (yrs)	52
Female (%)	12
Tobacco-past (%)	66
Tobacco-current (%)	25
Viral load undetectable (< 48 copies/mm3) (%)	85
CD4 count, cell/mm3	524
Nadir CD4 count, cell/mm3	167
HAART (%)	100
NRTI*	96
NNRTI*	51
PI*	47
Ethnicity (%)	
White	58
African American/Black	4
Native American/Native Alaskan	2
Pacific Islander	1
Asian	8
More than one race	24
Unknown	3
Hypertension (%)	
Total	67
On medications	76 (among total hypertensives)
Diet controlled	54 (among total hypertensives)
On lipid lowering medication	31
Diabetes (%)	7
HOMA-IR, mean ± STD	2.53 ± 3.77
Body Mass Index, kg/m2, mean ± STD	26.5 ± 4.6
Systolic blood pressure, mmHg, mean ± STD	123 ± 16
Diastolic blood pressure, mmHg, mean ± STD	76 ± 10
Total cholesterol, mg/dL, mean ± STD	179.9 ± 40.3

Characteristic	% or mean ± STD/median [IQR]where indicated
HDL cholesterol, mg/dL, mean ± STD	44.5 ± 17.4
LDL cholesterol, mg/dL, mean ± STD	110 ± 35
Triglycerides, mg/dL: median[IQR]	117.5[87–168[

STD=Standard deviation

IQR=interquartile range

HOMA-IR- homeostasis model assessment of insulin resistance

NRTI=nucleoside/nucleotide reverse transcriptase inhibitor, NNRTI= non-nucleoside/nucleotide reverse transcriptase inhibitor, PI=protease inhibitor

* not mutually exclusive, participants could be on more than one class

Table 2

Lipoprotein and Cholesterol Efflux Capacity and Oxidative Stress Measures

	Mean ± STD or %	
	On lipid lowering meds?	
	Yes (30%)	**No (70%)**
VLDL & Chylomicron Particles (total)nmol/L	90.2+/−59.3	70.3+/−42.4
Large VLDL & Chylomicrons Particles nmol/L	6.7+/−7.6	5.1+/−6.9
Medium VLDL Particles nmol/L	43.2+/−39.8	30.2+/−23.5
Small VLDL Particles nmol/L	40.2+/−23.7	35+/−24.8
LDL Particles (total) nmol/L	1139.6+/−301.3	1255.5+/−393.4
IDL Particles nmol/L	97.5+/−77.5	120.4+/−83.5
Large LDL Particles nmol/L	365.6+/−268.2	396+/−246.1
Small LDL Particles nmol/L	676.3+/−362.7	739.2+/−404.9
HDL Particles (total) umol/L	34.1+/−7.7	32.5+/−6.8
Large HDL Particles umol/L	4.8+/−3.7	4+/−2.8
Medium HDL Particles umol/L	11.5+/−5.4	11.9+/−6.5
Small HDL Particles umol/L	17.8+/−6.6	16.6+/−5.5
VLDL Size nm	50+/−7	48.6+/−8.1
LDL Size nm	20.4+/−0.6	20.5+/−0.6
HDL Size nm	9+/−0.5	8.9+/−0.5
Triglyceride (total) mg/dL	170.4+/−95.7	140.1+/−75.5
VLDL & Chylomicron Triglyceride (total) mg/dL	137.6+/−98.4	105.3+/−75.6
HDL Cholesterol (total) mg/dL	48.6+/−15.2	44.7+/−12.5
Cholesterol Efflux Capacity	1+/−0.2	1+/−0.2
8-oxo-deoxyguanine [break frequency (BF)]	0.12+/−0.23	0.08+/−0.12
8-oxo-dG(BF) <=0	37%	45%
>0	63%	55%
8-oxo-dG(BF) <=0.1	70%	75%
>0.1	30%	25%
OXPHOS Complex I activity (optical density (O.D.)/mg protein x 10^3)	67.81+/−27.4	68.99+/−27.05
OXPHOS Complex IV activity (O.D./mg protein x 10^3)	49.66+/−17.53	49.85+/−17.78

Table 3

Mitochondrial Oxidative Stress and Function and Clinical Lipid Panel in Men and Women with HIV infection on stable HAART (adjusted for age, gender, nadir CD4, CD4, viral load, high blood pressure, diabetes, HOMA, smoking, and lipid lowering medications)

	8-Oxo-dG (BF) OR, (p value)	**Complex I Activity (O.D.)/μg protein x 10^3) β, (p value)**	**Complex IV Activity (O.D.)/μg protein x 10^3) β, (p value)**
Total Cholesterol (mg/dL)	OR=0.99 (p=0.16)	β =−0.1 (p=0.09)	β =−0.05 (p=0.21)
LDL Cholesterol (mg/dL)	OR=0.99 (p=0.31)	β =−0.12 (p=0.07)	β =−0.07 (p=0.11)
HDL Cholesterol (mg/dL)	**OR=0.96 (p<0.01)**	β =−0.07 (p=0.65)	β =−0.08 (p=0.41)
Triglycerides (mg/dL)	OR=1.00 (p=0.28)	β =−0.01 (p=0.64)	β =0.00 (p=0.95)
Total/HDL Cholesterol Ratio	**OR=1.42 (p=0.02)**	β <0.01 (p=1.0)	β =0.4 (p=0.67)

Table 4

Mitochondrial Oxidative Stress and Lipoprotein Size and Number in Men and Women with HIV infection of Stable HAART (adjusted for age, gender, nadir CD4, CD4, viral load, high blood pressure, diabetes, HOMA, smoking, and lipid lowering medications)

	Mitochondrial Oxidative Stress and Function		
Type of Particle	**8-oxo-dG (BF)**	**Complex I (O.D.)/μg protein x 10^3)**	**Complex IV (O.D.)/μg protein x 10^3)**
	HDL		
Small HDL Particles (umol/L)	OR=0.99 (p=0.7)	β =−0.06 (p=0.89)	β =−0.3 (p=0.29)
Medium HDL Particles (umol/L)	OR=1.00 (p=0.95)	β =0.2 (p=0.61)	β =0.26 (p=0.32)
Large HDL Particles (umol/L)	**OR=0.87 (p=0.04)**	β =−0.29 (p=0.73)	β =−0.3 (p=0.59)
HDL Particles (umol/L) (total)	OR=0.97 (p=0.27)	β =0.06 (p=0.85)	β =−0.05 (p=0.83)
HDL Size (nm)	**OR=0.41 (p=0.04)**	β =−4.55 (p=0.4)	β =−2.4 (p=0.5)
	LDL		
Small LDL Particles (total) (nmol/L)	OR=1.00 (p=0.67)	**β =−0.02 (p=0.01)**	β =−0.01 (p=0.11)
Large LDL Particles (nmol/L)	OR=1.00 (p=0.48)	β =0 (p=0.69)	β =0 (p=0.5)
LDL Particles (nmol/L) (total)	OR=1.00 (p=0.71)	**β =−0.02 (p=0.01)**	**β =−0.01 (p=0.02)**
LDL Size (nm)	OR=0.84 (p=0.59)	β =4.32 (p=0.3)	β =−0.42 (p=0.88)
	VLDL		
Small VLDL Particles (nmol/L)	OR=1.00 (p=0.62)	β =−0.13 (p=0.17)	β =−0.05 (p=0.44)
Medium VLDL Particles (nmol/L)	OR=1.00 (p=0.89)	β =−0.03 (p=0.72)	β =0.02 (p=0.75)
Large VLDL & Chylomicrons Particles (nmol/L)	OR=1.04 (p=0.24)	β =0.14 (p=0.7)	β =0.12 (p=0.62)
VLDL & Chylomicrons Particles (nmol/L) (total)	OR=1.00 (p=1.0)	β =−0.04 (p=0.39)	β =0 (p=0.89)
VLDL Size (nm)	OR=1.04 (p=0.19)	β =0.51 (p=0.12)	β =0.31 (p=0.15)