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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

Nisha I. Parikh [a, b, *], Mariana Gerschenson [c], Kara Bennett [a], Louie Mar M. Gangcuangco [a], Mary S. Lopez [c], Nehal N. Mehta [d], Martin P. Playford [d], Beau K. Nakamoto [a, f], Todd B. Seto [e], Dominic C. Chow [a], Cecilia M. Shikuma [a]

[a] Hawaii Center for AIDS, Department of Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA
[b] Cardiovascular Division, Department of Medicine, University of California San Francisco, CA, USA
[c] Department of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA
[d] Section of Inflammation and Cardiometabolic Diseases, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[e] Cardiovascular Division, The Queens Medical Center, Honolulu, HI, USA
[f] Department of Neurology, Straub Clinics and Hospital, Honolulu, HI, USA

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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, 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.

1. 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

* Corresponding author. Cardiovascular Division, Department of Medicine, University of California San Francisco, CA, USA.
E-mail address: nparikh@medicine.uscf.edu (N.I. Parikh).

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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 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.

2. Methods

2.1. 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.

2.2. 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.

2.3. Laboratory measurements

The lipid, glucose and insulin measurements were performed after a 12 h 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.

2.4. 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

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/mm^3) (%)	85
CD4 count, cell/mm^3	524
Nadir CD4 count, cell/mm^3	167
HAART (%)	100
NRTI[a]	96
NNRTI[a]	51
PI[a]	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
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.
[a] Not mutually exclusive, participants could be on more than one class.