

ALTERATIONS IN LIPID TRANSFER TO HIGH-DENSITY LIPOPROTEIN (HDL) AND ACTIVITY OF PARAOXONASE-1 IN HIV⁺ PATIENTS

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SUMMARY

HIV⁺ patients often develop alterations of the plasma lipids that may implicate in development of premature coronary artery disease. High-density lipoprotein (HDL) has an important role in preventing atherogenesis and the aim of this study was to investigate aspects of HDL function in HIV⁺ patients. HIV⁺ patients (n = 48) and healthy control subjects (n = 45) of both sexes with similar age were studied. Twenty-five were not being treated with antiretroviral agents, 13 were under reverse transcriptase inhibitor nucleosidic and non-nucleosidic (NRTI+NNRTI) and 10 were under NRTI + protease inhibitors (NRTI+PI) treatment. Paraoxonase 1 (PON1) activity and the transfer of free and esterified cholesterol, tryglicerides and phospholipids from a lipidic nanoemulsion to HDL were analyzed. In comparison with healthy controls, HIV⁺ patients presented low PON-1 activity and diminished transfer of free cholesterol and tryglicerides. In contrast, phospholipid transfer was increased in those patients, whereas the transfer of cholesteryl esters was unchanged. NRTI+NNRTI increases the transfer of cholesteryl esters and triglycerides but in NRTI+PI there was no difference in respect to non-treated HIV⁺ patients. HDL from HIV⁺ patients has smaller antioxidant properties, as shown by lower PON-1 activity, and the transfer of lipids to this lipoprotein fraction is also altered, suggesting that HDL function is defective in those patients.

KEYWORDS: High-density lipoproteins; Lipid Transfer Protein; Paraoxonase-1; Lipids; HIV; AIDS.

INTRODUCTION

In HIV⁺ and AIDS patients, dyslipidemias, including low levels of high-density lipoprotein (HDL) cholesterol, are often found. As the survival of those subjects is being increasingly prolonged by treatment, they are exposed to those important risk factors for coronary artery disease (CAD)¹³. Indeed, it has been described that in HIV⁺ patients the incidence of premature CAD increases. It has been reported that not only the HIV infection but also the antiretroviral treatment, especially with protease inhibitors, elicits dyslipidemias^{1,6,8,14}.

HDL cholesterol levels in the plasma inversely correlate with the risk of developing CAD. HDL has several actions that are associated with the atheroprotection such as the role in cholesterol esterification and in the reverse cholesterol transport that promotes the removal of the sterol from the body tissues to the liver for elimination in the bile^{2,15,23}. Furthermore, HDL has antioxidant properties that are mediated mainly by paraoxonase 1 (PON1) action. This enzyme is predominantly associated with the HDL fraction and catalyzes the degradation of oxidized LDL phospholipids¹⁸. Other actions of HDL are the antiadhesive, anti-inflammatory and improvement of the vascular reactivity^{2,3}.

In infection status HDL cholesterol levels are often decreased but the causes of this reduction are unknown. It had been previously found that HIV nef, a protein that enhances HIV replication and infectivity specifically inhibits the ABCA1 dependent cholesterol efflux and apo A1 lipidation that is linked with HDL production and role in reverse cholesterol transport. Inhibition of the ABCA1 protein complex leads to low HDL cholesterol levels^{7,22}. HDL may play a role in defense against infection and immunity²⁹.

HDL is constantly being remodeled and lipid transfers are essential for its role in the reverse cholesterol transport and in the esterification of cholesterol. Both processes are intertwined and are key for the cholesterol homeostasis in the organism²⁸. Lipid transfers between lipoprotein classes are bidirectional and depend on the structure and concentration in the plasma of the donor and the acceptor lipoprotein, as well as the action of the transfer proteins, namely cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP)¹⁶. Due to the fact that HDL is active in many antiatherogenic processes it has been recognized the importance of the systematic evaluation of the functional aspects of the lipoprotein, beyond the simple measurement of HDL cholesterol. In this study, the ability of HDL from HIV⁺ patients to receive lipids such as free cholesterol (FC),

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cholesteryl esters (CE), phospholipids (PL), and triglycerides (TG) as well as the PON1 activity were approached in HIV⁺ patients under different treatment regimens and in patients that were not being treated for the disease.

MATERIALS AND METHODS

Study population: Forty-eight HIV⁺ patients of both sexes and without diagnosed co-infections as hepatitis-B (HBV) and hepatitis-C (HCV) were studied and compared with 45 HIV serum negative healthy control subjects of similar age range and with total plasma cholesterol < 240 mg/dL and triglycerides < 200 mg/dL²⁷.

Exclusion criteria were history of diabetes mellitus or previous treatment with antidiabetic agents, hypocholesteremic agents, anti-hypertensive medications and antioxidants; reported use of testosterone, estrogen, growth hormone, or other steroids in the past six months. Women using oral contraceptives were also excluded.

Their physical characteristics and laboratorial data are shown in Table 1. The group of HIV⁺ patients was further separated in three distinct subgroups:

- 1) Non-treated, patients without antiretroviral treatment.
- 2) NRTI+NNRTI, patients who were being treated with nucleosidic reverse transcriptase inhibitors (NRTI) and non-nucleosidic reverse transcriptase inhibitors (NNRTI) (efavirenz, lamivudine, nevirapine, stavudine or zidovudine).
- 3) NRTI+PI, patients that were being treated with both nucleosidic reverse transcriptase inhibitors and protease inhibitors (PI) (atazanavir, lopinavir, nelfinavir, ritonavir or saquinavir).

Groups NRTI+NNRTI and NRTI+PI were being treated for at least the last six months. All the participants provided fully informed consent to participate in the study that was approved by the Ethics Committee of the Medical School Hospital of the Federal University of Santa Catarina.

Blood biochemical analysis: Blood samples were collected after a 12 hour fast and alcohol abstinence. Plasma total cholesterol (CHOD-PAP; Roche, Basel, SUI), triacylglycerols (Triglyceride Rapid; Roche, Basel, SUI) and glucose (Dimension[®] clinical chemistry system, Dade Behring Inc., Newark, USA) were determined by commercial enzymatic methods using a Cobas Mira analyzer (Roche). HDL cholesterol (HDL-C) was measured after precipitation of the very low density lipoproteins (VLDL) and LDL with HDL Reagent ROCHE (method phosphotungsten acid: MgCl₂) with automatic equipment. LDL-C was estimated by the Friedewald formula¹².

HIV virus load was determined by use of the Nuclisens HIV-1 QT test (Organon Teknika BV, Boxtel, Netherland) by methodology Nucleic Acid Sequence-based Amplification. CD4+, T cell and CD8+ T cell counts were determined by FACscan flow cytometry (Becton Dickinson, San Jose, CA), utilizing the assembly reactivate with monoclonal antibodies anti CD4/CD3 and anti CD8/CD3 (Becton Dickinson, San Jose, CA).

Paraoxonase (PON1) activity: PON1 activity was measured by adding serum to 1 mL Tris-HCl buffer (100 mmol/L, pH 8.0) containing 2 mmol/L CaCl₂ and 5.5 mmol/L paraoxon (Sigma Chemical Company, London, Eng). The generation of p-nitrophenol was measured at 405 nm, at 37 °C in a microplate reader (Bio-Rad, Benchmark, JPN)¹⁷.

Lipid transfer from a donor artificial nanoemulsion to HDL: The preparation of the nanoemulsion from a lipid mixture by prolonged ultrasonic irradiation followed by ultracentrifugation was performed as described elsewhere²¹.

Radioactive lipids were purchased from Amersham International (Amersham, Little Chalfont, Buckinghamshire, UK) and were added to the lipid mixtures. Two sets of nanoemulsions were prepared, one labeled with ³H-cholesteryl oleate and ¹⁴C-phosphatidylcholine and the other with ³H-triolein and ¹⁴C-cholesterol.

The assay consisted in the incubation of the radioactively labeled nanoemulsion with whole plasma followed by chemical precipitation of the apo B containing lipoproteins and the nanoemulsion. Finally, the radioactive counting for the lipids that shifted from the nanoemulsion to HDL was performed in a Packard 1600 TR model Liquid Scintillation Analyzer (California, USA) by addition of a scintillation solution (Packard BioScience, Groeningen, NED) to the HDL-containing supernatant.

To assay for the transfer of the nanoemulsion radioactive lipids to HDL, blood samples were collected from the subjects into 0.15% Na₂ EDTA containing glass tubes and plasma was obtained by 15 min centrifugation at 2,500 rpm at 4 °C. Test tubes with the plasma samples (0.2 mL) and 0.05 mL nanoemulsion labeled with ³H-cholesteryl oleate and ¹⁴C-phosphatidylcholine or with ³H-triolein and ¹⁴C-cholesterol were placed in a shaking bath and incubated for 60 min at 37 °C. Then, 0.250 mL solution with 0.02% dextran sulfate (50,000 M.W.) and 0.3 mol/L MgCl₂ was added to the tubes and vortexed by 30 s. Samples were centrifuged at 3,000 rpm for 10 min and 0.250 mL of the obtained supernatant containing the HDL plasma fraction were transferred to vials with scintillation solution (Packard BioScience, Groeningen, NED), vigorously shaken and left to stand for at least 45 min. Radioactivity was determined in a Packard 1600 TR model Liquid Scintillation Analyzer (California, USA). HDL acceptance of the nanoemulsion lipids was calculated as the % of a given labeled lipid in the nanoemulsion found in the HDL plasma fraction after the 60 min incubation period.

Statistical analyses: Comparison of all data was performed using the GraphPad Prism for Windows software (GraphPad, San Diego, CA). The comparison between the data from HIV⁺ patients and control subjects was performed by unpaired Student's t-test and the data of the three HIV⁺ subgroups were analyzed by Kruskal-Wallis nonparametric ANOVA test. Differences were considered significant when *p* value < 0.05. All data were expressed as mean ± standard deviation (SD).

RESULTS

Table 1 shows that the Body Mass Index (BMI) of the HIV⁺ patients was smaller than that of the control subjects. Regarding the plasma

Table 1
Individual physical characteristics and plasma lipids

Parameters	Controls	HIV+	<i>p</i>
No. of subjects (M/F)	45 (16/29)	48 (22/26)	
Age (years)	38 ± 9	37 ± 8	0.71
Weight (kg)	70.4 ± 14.8	63.6 ± 10.3	0.01
Height (m)	1.64 ± 0.1	1.70 ± 0.1	0.09
BMI (kg/m ²)	25.8 ± 3.7	22.7 ± 3.0	0.0001
Cholesterol (mg/dL)			
Total	191 ± 33	164 ± 30	0.0001
HDL	41 ± 10	43 ± 13	0.44
LDL	127 ± 30	101 ± 21	< 0.0001
Triglycerides(mg/dL)	116 ± 39	99 ± 32	0.03
PON1 (nmol.min ⁻¹ .mL ⁻¹)	71.8 ± 37.4	44.3 ± 38.6	0.001

BMI: Body Mass Index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PON1: paraoxonase 1. Results are expressed as mean ± SD, *p* < 0.05 (unpaired *t*-test).

lipids, the total and LDL cholesterol as well as the triglyceride values of the HIV+ patients were smaller than those of the controls.

HDL cholesterol did not differ between the two groups. Table 1 also shows that PON 1 activity was smaller in HIV+ than in controls.

Figure 1 shows the percentage of labeled lipids that was transferred from the nanoemulsion to HDL. HIV+ patients show an increase in the transfer of PL when compared control subjects (23.4 ± 1.6% and 17.5 ± 0.9, respectively), whereas the transfer of FC and TG in HIV+ patients

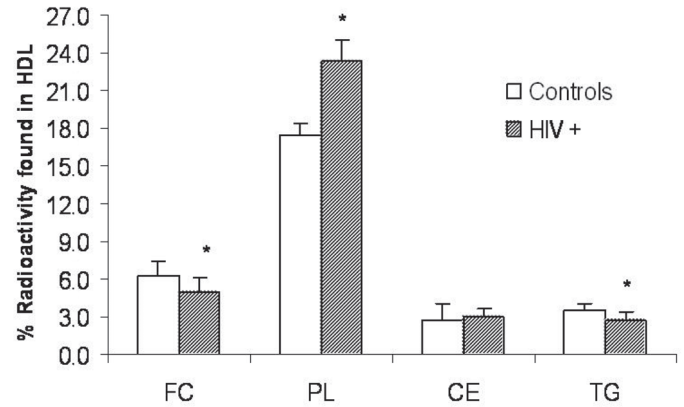


Fig. 1 - Percentage of the labeled lipids transferred from the lipidic nanoemulsion to the HDL fraction. Comparisons between HIV+ vs control groups: **p* < 0.0001 (unpaired *t*-test). Results are expressed as mean ± SD. FC = free cholesterol; PL = phospholipid; CE = cholesteryl esters, TG = triglycerides

was smaller (6.3 ± 1.1 vs. 5.0 ± 1.1% and 3.5 ± 0.6 vs. 2.7 ± 0.7%, respectively). On the other hand, no difference in CE transfer was observed between cases and controls.

Table 2 shows comparisons among the subgroups of HIV+ patients. HDL-cholesterol was greater in the NRTI+NNRTI than in non-treated and NRTI+PI subgroups and also greater than in the control HIV negative subjects. However, LDL cholesterol, triglycerides and PON1 were similar among the three subgroups of HIV+ patients. Regarding the data on lipid transfer to HDL, the PL and FC transfer were not

Table 2

BMI, glucose, blood lipids, PON1 activity and transfer of triglycerides (TG), free cholesterol (FC), cholesteryl esters (CE) and phospholipids (PL) from the lipidic nanoemulsion to the HDL fraction in patients without antiretroviral therapy (non-treated), with nucleosidic reverse transcriptase inhibitors (NRTI) and non-nucleosidic reverse transcriptase inhibitors (NNRTI) or with protease inhibitors (PI)

Parameters	Non-treated n = 25	NRTI with NNRTI n = 13	NRTI with PI n = 10
BMI (kg/m ²)	23.3 ± 3.5	22.4 ± 2.3	21.4 ± 2.0
Viral Load (RNA copies/mL)	25740 ± 57300	277 ± 610	23186 ± 65878
CD4 cell count (cells/mm ³)	435 ± 218	450 ± 190	429 ± 365
CD8 cell count (cells/mm ³)	1076 ± 873	802 ± 328	1091 ± 528
Glucose (mg/dL)	84 ± 9	102 ± 33 [§]	79 ± 11**
Cholesterol (mg/dL)			
Total	159 ± 27	180 ± 27	154 ± 34
HDL	39 ± 8	53 ± 16 [§]	38 ± 10*
LDL	100 ± 20	106 ± 19	97 ± 27
Triglycerides (mg/dL)	98 ± 33	103 ± 29	98 ± 37
PON1(nmol.min ⁻¹ .mL ⁻¹)	45.7 ± 36.9	54.8 ± 42.9	33.5 ± 37.9
Lipid transfers (%)			
Triglycerides	2.6 ± 0.8	3.1 ± 0.6 [§]	2.1 ± 0.3**
Free Cholesterol	5.0 ± 1.1	5.7 ± 1.0	4.3 ± 1.0**
Cholesteryl esters	2.9 ± 0.7	3.4 ± 0.6 [§]	2.8 ± 0.7*
Phospholipids	23.6 ± 1.6	23.8 ± 1.3	22.7 ± 1.6

BMI: Body Mass Index; PON1: paraoxonase 1. Results expressed as mean ± SD. **p* < 0.05, ***p* < 0.01 compared to NRTI with NNRTI (Kruskal-Wallis nonparametric ANOVA test); [§]*p* < 0.05 compared to non-treated (Kruskal-Wallis nonparametric ANOVA test).

different between non-treated and NRTI+NNRTI patients, but the CE and TG transfer were greater in the NRTI+NNRTI than in the non-treated group. However, when protease inhibitors were added to the treatment, in the NRTI+PI group, HDL cholesterol diminished and all the parameters of lipid transfer became altered, with the exception of PL transfer.

DISCUSSION

In this study, the HIV⁺ group of patients showed LDL cholesterol and triglyceride concentration in the plasma smaller than that of the control HIV negative subjects, whereas HDL cholesterol was equal. Indeed, HIV⁺ patients often show diminished LDL cholesterol^{10,25}, but triglycerides are generally described as increased in HIV^{9,10}, in contrast with the results of this study. However, increased triglyceride concentration leads to HDL cholesterol diminution⁵, and the fact that triglycerides were not increased in our HIV⁺ group ultimately facilitates the analysis of the HDL status.

The three subgroups of HIV⁺ patients did not differ among them in respect to LDL cholesterol. HDL cholesterol, however, was greater in the NRTI+NNRTI subgroup when compared with NRTI+PI, non-treated HIV⁺ patients and also with the values of the HIV negative group. It was also reported in other studies that treatment with NRTI+NNRTI increases HDL cholesterol whereas addition of PI in the treatment leads to decrease in this parameter^{4,26}.

PON 1 activity that is associated with the ability of HDL to prevent the accumulation of lipid peroxides on LDL and in the vessel wall¹⁹. The diminution of PON 1 in HIV⁺ confirms the findings of PARRA *et al.*²⁴, both treated and non-treated patients.

The ability to receive lipids is a fundamental property of HDL. HDL stabilizes the plasma cholesterol pool by promoting cholesterol esterification, a process that is catalyzed by LCAT using apo A1, that is mostly contained in the HDL fraction, as a co-factor. By producing a completely apolar molecule, esterification of the cholesterol localized in the particle surface monolayer results in shift of the compound to the particle core, where it is isolated from the contact with the aqueous medium. By receiving cholesterol from cells and other lipoproteins and sending esterified cholesterol to other lipoprotein classes and to hepatocytes for excretion in the bile, HDL plays a crucial role in the reverse cholesterol transport¹⁶. Transfer of esterified cholesterol from HDL to other lipoprotein classes is mediated by CETP. Reception of phospholipids is also important for the HDL formation and remodeling and triglycerides are also exchanged between triglyceride rich lipoproteins such as VLDL and HDL³⁰. This study shows that the ability of HDL to receive lipids, a fundamental aspect of the metabolism of this lipoprotein, is disturbed in HIV⁺ patients compared with the HIV negative subjects. Those alterations, characterized by smaller transfer of free cholesterol and triglycerides and increase in the transfer of phospholipids from the lipid nanoparticles to HDL may cause or be consequent of disturbances in the dynamics of the HDL metabolism and the function of the lipoprotein in the plasma cholesterol stabilization and reverse transport. On the other hand, compared to the HIV⁺ non-treated patients, treatment with NRTI+NNRTI increased the transfer to HDL of cholesteryl esters and triglyceride. In the group treated with

the NRTI+PI scheme, lipid transfer to HDL was unchanged. Those differences in lipid transfer to HDL in response to different treatment regimens are presumably related to the effect on lipid metabolism by those drugs. In this respect, compared with NRTI+NNRTI, PI treatment worsens the lipid profile^{4,20,26,31}.

The disturbances of HDL metabolism in HIV⁺ found in this study can be at least partially attributed to cytokine release consequent to the infectious and inflammatory process. Those cytokines can diminish HDL and modify the HDL composition and function, such as the antioxidant properties of the lipoprotein^{11,24,32}. Cytokine release in infectious and inflammatory processes also results in diminished HDL uptake by cells, by reducing the expression of ABCA1 system that helps in the removal of free cholesterol from the cells to the HDL particles¹¹. Those changes may elicit alterations in the ability of HDL to receive lipids, as observed in this study and in the shift of lipids from HDL to other lipoproteins.

In conclusion, in the HIV⁺ population sample studied here PON1 activity and the ability of HDL to receive lipids were altered. This suggests that functions of this uniquely protective lipoprotein can be disturbed in those patients.

RESUMO

Alterações na transferência de lipídeos para a lipoproteína de alta densidade (HDL) e atividade da paraoxonase 1 em pacientes HIV⁺

Pacientes HIV⁺ frequentemente desenvolvem alterações no metabolismo de lipídeos que podem influir no desenvolvimento de doença arterial coronária. A lipoproteína de alta densidade (HDL) tem papel importante na prevenção da aterogênese. Para investigar aspectos funcionais da HDL na doença, foram estudados 48 pacientes HIV⁺ e 45 indivíduos-controle saudáveis de ambos os sexos, com idade semelhantes. Vinte e cinco pacientes HIV⁺ não recebiam terapia antirretroviral, 13 estavam sob tratamento com inibidores nucleosídicos de transcriptase reversa e não-nucleosídicos (NRTI+NNRTI) e 10 sob tratamento com NRTI e inibidor de protease (NRTI+PI). Analisou-se a atividade da paraoxonase 1 e a transferência de colesterol livre e esterificado, triglicérides e fosfolipídios de uma nanoemulsão lipídica para a HDL. Pacientes HIV⁺ apresentaram menor atividade da paraoxonase 1 e menor transferência de colesterol livre e triglicérides em relação aos indivíduos saudáveis. A transferência de fosfolipídios foi maior nesses pacientes, mas a transferência de éster de colesterol foi similar. NRTI+NNRTI aumenta a transferência de éster de colesterol e triglicérides, mas em NRTI+PI não houve diferença comparando com os pacientes HIV⁺ não tratados. A HDL de pacientes HIV⁺ tem propriedades antioxidantes reduzidas, evidenciada pela menor atividade da paraoxonase 1, e transferência de lipídios alterada, sugerindo que a HDL apresenta função defeituosa nestes pacientes.

ACKNOWLEDGMENTS

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), São Paulo, Brazil. Dr. Maranhão is a Research Awardee of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brasília, Brazil.

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Received: 21 December 2007

Accepted: 15 July 2008