Lipid and Acute-Phase Protein Alterations in HIV-1 Infected Patients in the Early Stages of Infection: Correlation with CD_4^+ Lymphocytes

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Lipid and acute-phase protein alterations have been described in various infection diseases, and they have been recorded during the early stages of HIV infection. Lipid and acute-phase protein profiles also have been correlated with cellular immunological abnormalities. To document these correlations during HIV infection, we studied 75 HIV-infected patients and 26 HIV-negative controls. Patients were classified according to the criteria proposed by the Walter Reed Army Institute: as WR-1 (CD_4 lymphocytes, 1154 ± 268/mm^3), WR-2 (CD_4, 793 ± 348/mm^3) and WR3/4 (CD_4, 287±75 mm^3). Triglycerides, total cholesterol and HDL-cholesterol concentrations were measured by enzymatic methods. Immunoglobulins (IgA and IgG) and acute-phase proteins (haptoglobin, α_1-acid glycoprotein, C-reactive protein and transferrin) were determined by immunonephelometry. Haptoglobin levels were significantly increased in HIV-positive patients and correlated with the progression of HIV-infection (control<WR1<WR2<WR3/4). WR-2 and WR-3/4 patients had lower total cholesterol, HDL-cholesterol, and albumin concentrations, however, α_1-acid glycoprotein and IgA levels were higher, when compared to HIV-negative controls. Elevated triglyceride levels (1.51±0.75 mmol/L) were found only in WR3/4 patients, when compared to the control individuals (1.05±0.04 mmol/L). No differences were found in transferrin and C-reactive protein concentrations among the studied groups. CD_4^+ lymphocyte counts were inversely correlated with triglycerides, IgA, α_1-acid glycoprotein and haptoglobin, and they were positively correlated with albumin, total cholesterol and HDL-cholesterol. Multiple linear regression analysis showed that increased haptoglobin and IgA levels were the best predictive variables of a decreasing CD_4^+ lymphocyte count. In conclusion, our data showed that: 1) a decrease in total cholesterol, HDL-cholesterol and albumin levels occurred earlier than hypertriglyceridemia in the course of HIV infection; 2) increased levels of haptoglobin occurred earlier than that of α_1-acid glycoprotein and IgA; 3) haptoglobin and IgA were the best predictive variables of a decreasing CD_4^+ lymphocyte count. Decreases in HDL-cholesterol and albumin levels with increases in haptoglobin, α_1-acid glycoprotein, IgA, and triglycerides levels are indications of disease progression in HIV-infected patients.

Key Words: HIV, CD_4^+, triglycerides, IgA, α_1-acid glycoprotein, haptoglobin.

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Infection induces an acute phase response which is marked by changes in the plasma concentrations of a number of proteins. Lipid and protein abnormalities have been described in the early stages of HIV infection and become more evident with the disease's progression [1, 2]. Lipid alterations may be associated to the host's response to infection mediated by various cytokines [3]. A large number of cytokines including TNF, interleukines, and the interferon's increase serum triglyceride levels and decrease HDL-cholesterol [4]. Interferon-alpha is known to be elevated in AIDS and

HIV-positive individuals and has been shown to be positively correlated with plasma triglyceride concentrations [5, 6].

The acute-phase response to infection is also characterized by an increase in protein turnover plus an increased loss of protein [2]. Leukocyte proliferation and the synthesis of cytokines, immunoglobulins, and positive acute-phase proteins contribute to protein turnover [7]. Reports of increased protein turnover in humans with symptom-free Acquired Immunodeficiency Syndrome suggest that the infection by the virus, in the absence of clinical signs and symptoms, can induce changes in protein metabolism [2].

To evaluate the effect that Human Immunodeficiency Virus infection and the progression of AIDS have on lipids and acute-phase proteins, we measured the plasma concentrations of total cholesterol, LDL-cholesterol, triglycerides, immunoglobulins (IgG and IgA), and positive- (C-reactive protein, α_1-acid glycoprotein and haptoglobin) and negative- (albumin and transferrin) acute phase proteins in patients with HIV infection without secondary inflammatory acute disease, and then determined their relation with CD_4^+ and CD_8^+ lymphocyte counts as cellular immune markers.

Materials and Methods

Patients

Seventy-five HIV-seropositive outpatients, that attended at the Nereu Ramos Hospital and STD/AIDS Department of Health Center II (Florianópolis, Santa Catarina, Brasil) constituted the study group. Patients were classified according to the Walter Reed Army Institute system that is based on clinical criteria such as chronic lymphadenopathy and presence of other opportunistic infections and immune markers such as the CD_4^+ count (lymphocytes/mm^3) and delayed hypersensivity [8, 9]. The characteristics of the patients are given in Table 1. Only patients classified into the WR 3/4 group showed a significant weight loss when compared to the others. Blood samples were obtained from all patients before they engaged in antiviral therapy. Twenty-six randomly selected age-matched blood donors from the Blood Bank of the Federal University of Santa Catarina's Hospital (Florianópolis, SC, Brazil) served as a control group. These individuals showed no serological evidence for HIV and/or HCV-infection, and no abnormal laboratory findings (blood count, AST, ALT, g-GT, LD, amylase, glucose, urea, creatinine, blood lipids, total protein, albumin, globulins, acute phase proteins, iron, transferrin and ferritin were all within the normal range). All subjects gave their informed consent before participating in the study, and the project was approved by the local ethics committee and followed the guidelines of the 1975 Declaration of Helsinki.

CD_4^+ and CD_8^+ lymphocyte count

CD_4^+ and CD_8^+ counts were determined by immunofluorescence microscopy with the Dynabeadsâ T4-T8 kit (Dynal AS, Oslo, Norway) on an Olympus CBA microscope equipped with LH 50A and BH2-RFCA fluorescence accessories.

Lipid analysis

Peripheral blood from healthy subjects and HIV-infected patients were collected in EDTA containing tubes (Vacutainerâ , Becton-Dickinson) after 12h of fasting. Total serum cholesterol and triglycerides were determined enzymatically (Merck). HDL-cholesterol was measured (when triglycerides were <4 mmol/L) after precipitation of apoB-containing lipoproteins with phosphotungstic acid/manganese (Merck). LDL-cholesterol and VLDL-cholesterol were calculated according to Friedwald [10].

Acute-phase proteins and immunoglobulins

Albumin was determined by the bromocresol green method (Merckotest, Oslo, Norway). The concentrations of haptoglobin, α_1-acid glycoprotein, C-reactive protein, transferrin, IgA and IgG were determined by immunonefelometry (Behringwerke AG, Malburg, Germany).

Statistical analysis

All data are expressed as mean ± SD. The distribution of variables was tested for approximation

to the Gaussian distribution curve using the kurtosis and skewness tests. The categorical variables were tested by the chi-squared test. The comparison of the mean continuous numeric variables were tested by variance analysis (ANOVA) and Tukey HSD test. Correlations between two independent variables were calculated by the Pearson least-squares regression analysis. The association among continuous variables was assessed by the stepwise multiple regression analysis. *P* values < 0.05 were considered significant.

Results

Demographic features were similar among the 4 classification groups (control, WR1, WR2, WR3/4) (Table 1). As expected the CD_4^+ lymphocyte count was decreased significantly in the WR2 and WR3/4 groups compared to WR1 and controls (Table 1). A significant increase in triglyceride and VLDL-cholesterol concentrations were observed only in patients belonging to the WR3/4 group, in which CD_4^+ cell counts were $<400 \times 10^6$/ L (Table 2). In contrast, total cholesterol and LDL-cholesterol levels were decreased in this group (Table 2). HDL-cholesterol was lower in the WR2 and WR3/4 groups compared to the control and WR1 groups, indicating a continuous decrease during the progression of HIV-infection (Table 2).

Among the studied acute-phase proteins, haptoglobin was the most sensitive marker as it became progressively more enhanced in the HIV-positive sub-groups, with the highest values being found in WR3/4 patients (Table 2). α_1-acid glycoprotein increased in WR2 and WR3/4 groups, while C-reactive protein levels did not differ among the studied groups (Table 2). In relation to the negative acute-phase proteins, albumin concentrations were lower in the WR2 and WR3/4 groups, when compared to WR1 and control groups, although no difference was found in transferrin levels (Table 2). Regarding immunoglobulin levels, IgG and IgA levels were increased in the WR2 and WR3/4 groups, when compared to the WR1 and control groups (Table 2). CD_4^+ lymphocyte counts showed significant negative correlations with haptoglobin, IgA, α_1-acid glycoprotein, and triglyceride levels (Table 3). Haptoglobin ($R^2 = 0.4059$; P=0.0001) and IgA ($R^2 = 0.2842$; P=0.0001) were selected as the best predictive variables of a CD_4^+ lymphocyte decrease by stepwise multiple linear regression analysis.

Discussion

This study aimed to investigate the effect of infection by HIV alone on lipids and acute-phase proteins in HIV-positive patients who were in different stages of infection, including those free of signs and symptoms of secondary infections or any other AIDS-related complications, classified here as WR1 and WR2 sub-groups, and a subgroup of patients, classified as WR3/4, which showed initial signs of decreased cellular immune response [9].

The acute phase response is part of the host's reaction to infection [2]. It includes a multitude of changes in protein, lipid and lipoprotein metabolism. Hypertriglyceridemia has been reported as the first lipid alteration in HIV infection [11]. However, in the present study, hypertriglyceridemia was found only in HIV-infected patients with alteration of cellular immune response (WR3/4 group, $CD_4^+ < 400/mm^3$). In fact, the earliest lipid alterations, found in HIV-infected patients of the WR2 group, were the decreased levels of total cholesterol and HDL-cholesterol.

Decreases in total cholesterol and HDL-cholesterol have been reported in the early stages of HIV-infection, being more evident with decreasing CD_4^+ lymphocyte counts [12]. HDL-cholesterol has been considered as a marker of disease progression showing a negative correlation with TNFα, TNFα receptors, and IFNγ [12-14]. Our data show that lower plasma HDL-cholesterol levels occur in symptom-free HIV-infected patients, even in the absence of secondary infections, reinforcing previously reported data showing that disturbances in cholesterol metabolism precede hypertriglyceridemia during asymptomatic HIV infection [15]. This is important for HIV-infection pathogenesis as HDL provides cholesterol for peripheral cells involved in the immune response and tissue repair [12]. Moreover, apo A1, the main apolipoprotein of HDL, inhibits human immunodeficiency virus-induced CD_4^+ lymphocyte

Table 1. Characterisitics of HIV-positive patients and healthy control subjects

	Control	WR1 (n=26)	WR2 (n=28)	WR3/4 (n=31)	P (n=16)
Male (%)	62.5(16)	61.5(12)	42.9(22)	71.0(10)	0.171
Black (%)	3.9(1)	18.7(4)	16.1(5)	14.3(3)	0.403
Caucasian (%)	96.1(25)	81.2(24)	83.9(26)	85.7(13)	0.403
Age (years)	29.6±6.0	28.1±5.4	29.1±6.6	30.5±0.09	0.6243
Weight (kg)	67.47.7	65.1±13.1	65.0±6.6	57.9±6.4[a]	0.0371
Height (m)	1.70±0.08	1.66±0.1	1.69±0.1	1.66±0.08	0.2772
CD_4 lymphocytes/mm^3	1295±143.3	1153±268.2	793±348.3[b]	287±74.5[c]	0.0001
CD_8 lymphocytes/mm^3	767±137.5	870±222.4	762±221.3	663±210.4[d]	0.0130

Values are means ± SD, or number of cases (%); [a] $P<0.05$ as compared with control group; [b] $P<0.05$ as compared with control and WR1 groups; [c] $P<0.05$ as compared with control,WR1 and WR2 groups; [d] $P<0.05$ as compared with WR2 group.

Table 2. Lipids, immunoglobulins and acute-phase proteins in HIV-infected patients and healthy control subjects

	Control	WR1 (n=26)	WR2 (n=28)	WR3/4 (n=31)
Triglycerides (mmol/L)	1.05±0.039	1.30±0.44	1.17±0.43	1.51±0.75[a]
Total cholesterol (mmol/L)	4.50±0.66	4.22±0.66	3.99±0.87[a]	3.77±0.67[a]
LDL-cholesterol (mmol/L)	3.01±0.61	2.75±0.76	2.66±0.82	2.36±0.64[a]
VLDL-cholesterol (mmol/L)	0.48±0.18	0.60±0.20	0.53±0.19	0.69±0.34[a]
HDL-cholesterol (mmol/L)	1.02±0.21	0.93±0.25	0.83±0.25[a]	0.72±0.20[b]
Albumin (g/L)	40.7±2.3	40.0±2.3	38.8±2.6[a]	38.3±1.8[b]
Transferrin (mg/L)	2603±352	2576±516	2285±542	2567±595
a-1 acid glycoprotein (mg/L)	648±146	898±146	921±334[a]	1297±468[c]
Haptoglobin (mg/L)	1202±545	1645±613[a]	2189±841[b]	2506±1157[b]
IgG (mg/dL)	1422±257	2522±702[a]	2818±669[a]	3645±686[a]
IgA (mg/dL)	2177±800	2900±1481	3337±1899[a]	5975±3032[c]
C reactive protein (mg/L)	5.00±0.0	5.50±1.60	8.00±6.50	6.10±3.20

Mean ± SD; [a] $P<0.05$ as compared with control group; [b] $P<0.05$ as compared with control and WR1 groups; [c] $P<0.05$ as compared with control, WR1 and WR2 groups.

Table 3. Correlation of acute-phase proteins, lipids and CD_4^+ lymphocytes

	Triglycerides	Total cholesterol	HDL cholesterol	CD_4^+ lymphocytes
Albumin	-0.2384[a]	0.1613	-0.1614[a]	0.3112[b]
a-1 acid glycoprotein	0.4436[c]	-0.1741	-0.2362[a]	-0.4970[c]
Haptoglobin	0.3604[c]	-0.2108[a]	-0.2573[a]	-0.4876[c]
IgA	0.2110[a]	-0.2356[a]	-0.1615	-0.5334[c]
C reactive protein	-0.0435	-0.2354[a]	0.1532	-0.1556
Transferrin	-0.1486	0.0599	0.1137	0.0045
Triglycerides	-	-0.0705	-0.4404[c]	-0.2229[a]
Total Cholesterol	-0.0705	-	0.3473[c]	0.2271[a]
HDL-Cholesterol	-0.4404[c]	0.3473[c]	-	0.3247[b]

Pearson least-squares regression analysis. [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$.

syncytium formation [16]. A less efficient antioxidant activity of HDL may also be important for the impairment of immune function.

Paraoxonase is an HDL associated enzyme that metabolizes and detoxifies biologically active lipids in LDL [17]. Although paraoxonase activity has not been studied in HIV-infected patients, this enzyme is considered to be a negative acute-phase protein and its activity decreases during the acute phase response [17]. Increased lipid peroxidation is described in HIV-infected patients [18-20] and lipid hydroperoxides induce apoptosis in T-cells displaying an HIV-associated glutathione peroxidase deficiency [21]. TNFa also plays an important role on the lipid peroxidation of blood plasma as it induces the production of reactive oxygen species by polymorphonuclear leukocytes [22]. In addition to inducing lipid peroxidation, reactive oxygen species activate the nuclear transcription factor NF-kB, which is obligatory for HIV replication in CD_4^+ lymphocytes [23].

Hypertriglyceridemia has been described in HIV-infected patients, usually at the final stages of disease [24], and has been thought to be related with several factors, such as, the wasting syndrome, secondary acute infections, and impairment of the immune system [13, 24]. Our data show that increased triglyceride levels were found in HIV-infected patients of group WR3/4 who had significant weight loss (Table 1) and impairment of the cellular immune system (CD_4^+ lymphocyte < 400/mm^3), even in the absence of secondary infections. Cytokines, such as TNFa, IFNa, IFNg, and IL-6, mediate the acute phase response and promote an increase of triglyceride levels due to an increase in VLDL [1,3-6]. It has been reported that IFNa levels are correlated at a highly significant level to serum triglyceride concentrations in HIV-infected and AIDS patients [1]. Both hepatic overproduction of VLDL, due to increased hepatic lipogenesis, and delayed clearance, which is in part mediated by a decrease in lipoprotein lipase activity (LPL), contribute to hypertriglyceridemia [24-27]. Thus, our data confirm that hypertriglyceridemia is a marker of a less favourable disease evolution and that indicates a more severe impairment of the immune function.

Several studies have shown that HIV infection elicits an increase in the whole body's protein turnover; however, there are few reports on the alterations of the acute-phase protein profile in the very early stages of infection. The hepatic synthesis of certain proteins, such as the positive acute-phase proteins (i.e., C reactive protein, haptoglobin, a_1-acid glycoprotein), is increased, while the synthesis of other proteins, such as albumin and transferrin (negative acute-phase proteins), is inhibited in response to infections [1].

Previous reports have shown alterations of albumin, IgA, α_1-acid glycoprotein, C reactive protein, and transferrin in the final stages of HIV-infection, without changes in haptoglobin [2, 28].

In the present study, a significant increase in the positive acute-phase proteins haptoglobin, IgA, α_1-acid glycoprotein, as well as a decrease in albumin, were found in the symptom-free HIV-infected patients of the WR2 group. In contrast to previously described data [1, 2, 28], no significant differences were found for C reactive protein and transferrin among the studied groups. These alterations of acute-phase proteins may be associated to the enhanced production of IL-6 and IL-8 which modulate the synthesis of positive acute-phase proteins [29-31]. On the other hand, hypoalbuminemia is caused by an increased transcapillary escape rate and an increased catabolic rate promoted by infection, instead of decreased hepatic synthesis [32].

It has been reported that HIV-infection promotes an enhancement of the fractional and absolute synthesis rates of positive acute-phase proteins, including haptoglobin [2]. Previously reported data on acute-phase proteins in HIV infection are conflicting. Grunfeld, et al. [1], reported higher plasma concentrations of C reactive protein in a group of AIDS patients compared to the plasma concentrations of healthy controls; however, no difference in the plasma concentration of haptoglobin between the 2 groups was found. Monet, *et al*. [28], reported that 1 (β_2-microglobulin) of the 3 studied positive acute-phase proteins (C reactive protein, β_2-microglobulin and α_1-glycoprotein) had a higher plasma concentration in a group of AIDS patients. Jahoor, *et al*. [2], found that the symptom-free AIDS group had significantly higher plasma C reactive protein, fibrinogen and haptoglobin concentrations than the control group; in contrast, there was no difference in the plasma concentration of albumin between the 2 groups. The disagreement between these studies may be attributed to the different stages of HIV-infection of the AIDS patients broadly classified as symptom-free in each study, as well as to the inter-individual variation of the immune response among these patients. From these studies, and our data, it can be concluded that the HIV-induced acute phase response does not include all of the acute-phase proteins and is of a lesser magnitude than that observed in response to a bacterial infection [2].

In the present study, the CD_4^+ counts were negatively correlated to haptoglobin, IgA, α_1-acid glycoprotein and positively correlated to albumin. Among the acute-phase proteins, haptoglobin showed the earliest alteration in HIV-infection, as its levels were increased in the WR1 group of symptom-free HIV-infected patients in comparison to the other studied groups (Table 2). Haptoglobin has immunoregulatory and antioxidant properties, which vary among the different phenotypes [33], and may be important for the progression of HIV-infection. In fact, it has been described that HIV-infected patients carrying the Hp 2-2 phenotype show a worse prognosis, which is reflected by a more rapid rate of viral replication and a higher mortality in HIV patients [33]. IgA may neutralize *in vitro* primary strains of HIV-1 [35,36]. The HIV-1 specific IgA response is predominantly directed to the envelope proteins, including V4 and V3 regions within HIV-1 gp160 [37]. Protein kinase C activation by HIV+-IgA inhibits nitric oxide synthase [38]. Nitric oxide both inhibits HIV-1 replication in acutely infected cells and stimulates HIV-1 reactivation in chronically infected cells [39]. Moreover, this IgA-modulated inhibition of nitric oxide production may contribute to lymphocyte proliferation as endogenous nitric oxide inhibition rescues cells from apoptosis in AIDS patients with low circulating CD_4^+ [40].

These data show that the levels of HDL-cholesterol had a better correlation with the CD_4^+ count than with the triglyceride concentrations. Among the acute-phase proteins, haptoglobin, IgA and, α_1-acid glycoprotein were also correlated with CD_4^+ counts. However, haptoglobin and IgA had the best predictive values for the decrease in CD_4^+ lymphocyte counts. Decreases in HDL-cholesterol and the increases in haptoglobin and IgA are associated with the immunodeficiency and may be useful markers to indicate the progression of infection in HIV-seropositive subjects.

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