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Oxidative Stress Parameters in Women with HIV and HIV/hepatitis B and/or C Co-infection

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Abstract

The pathogenesis of HIV/hepatitis B and/or C co-infection is far from being understood; yet, some studies have shown its relationship with oxidative stress. Because of oxidative stress (conjugated dienes and thiobarbituric acid reactants) and antioxidant defense systems (superoxide dismutase activity, α-tocopherol, reduced and oxidized glutathione) had different parameters in 26 women with HIV-monoinfection and 27 women with HIV/hepatitis B and/or C co-infection (with no signs of AIDS), they were evaluated. Spectral fluorofotometric methods were used. Statistical analysis was performed by parametric and non-parametric methods. The evaluation found that while conjugated dienes levels were significantly higher, superoxide dismutase (SOD) activity and α-tocopherol levels were significantly lower in women with HIV/hepatitis B and/or C co-infection than in those with HIV-monoinfection. Concurrently, during the highly active antiretroviral therapy (HAART), conjugated dienes, thiobarbituric acid reactants mean levels were lower; SOD activity and α-tocopherol levels were higher in HIV-monoinfected patients than in those with HIV/hepatitis B and/or C co-infection (with no signs of AIDS). This outcome was characterized by more expressed oxidative stress.

Keywords: HIV/hepatitis B and/or C co-infection; HAART therapy; Oxidative stress; Antioxidative defense

Background

According to data from the Russian Federation Ministry of Health, more than 600,000 HIV-infected people are presently registered in Russia. Thus, the majority of newly registered cases (60%) are diagnosed among women at ages of 20-30 years old. Among the routes of HIV expansion among the population, drug use (63.4%) and heterosexual contacts (20.3%) prevail. The numbers of new cases of infection, including unprotected sexual acts and HIV transmission from mother to the child, have increased annually. The Irkutsk region shows a particularly unfavorable epidemiological situation of HIV infection: there are more than 30 thousand people currently infected and 1300 new cases with HIV were registered by the end of year 2013. A sexual route of infection prevails in 73.4% of cases.

An increase in the number of patients with HIV/hepatitis B and/or C co-infection during the past decade has seen [1]. Viral hepatitis taking the prominent place in the list of death causes of HIV-infected patients however, this influence on HIV infection course has been insufficiently studied even though there is an opinion that hepatitis leads to rapid HIV infection and AIDS progression [2,3]. The possibility of extra hepatic virus replication has been proved, in particular, in immune competent cells which may become a reservoir of infection, and the hepatocyte source of reinfection causes persistent immune deficiency. Faster reduction of CD4+ cells which impedes the achievement of sustainable response for viruses in patients with hepatitis have been registered [2]. The most important sequel of chronic HIV/hepatitis C infection is progressive liver fibrosis leading to cirrhosis as liver disease end-stage and in some cases for hepatic carcinoma [4].

Antimicrobial protection is provided through the combined impact of cellular and humoral factors [5-7]. Non-specific resistance of the organism largely determines the development and outcome of any infectious process [8].

Several studies have attributed oxidants as playing critical roles in the genesis of AIDS [9]. A number of researches have suggested that the mechanisms responsible for AIDS progression could be reversed through the administration of antioxidant reducing agents [10]. Oxidative stress development usually can be measured by relationship between antioxidant parameters (superoxide dismutase, reduced and oxidized glutathione, α-tocoferol) and parameters of lipids peroxidation (conjugated dienes and thiobarbituric acid reactants [11]. Of great interest are data on oxidative stress (OS) development and antioxidant defense (AOD) level in patients with HIV/hepatitis B and/or C [12-14]. It is probable, that these patients will experience more severe violations in their antioxidant defense system than in patients with HIV monoinfection. These studies are required to assign an adequate antioxidant therapy to patients.

Objective

To reveal of oxidative stress parameters in reproductive age women with monoinfection (HIV) and co-infection (HIV/hepatitis B and/or C) with or without HAART therapy

Methods

The study was conducted at the Scientific Centre for Family Health and Human Reproduction Problems, Russian Academy of Medical Sciences *(Irkutsk, Russia), in Irkutsk infections hospital and in Irkutsk regional AIDS Center* in 2012-2014 according to ethical standards of Helsinki Declaration (2008). This study was approved by the Ethic

Committee of Scientific Centre of Family Health and Human Reproduction Problems (Siberian Branch of RAMS), and all involved patients signed the Informed Consent agreement for participation in our study. The comparative analyses included HIV-monoinfected and HIV/hepatitis B and/or C co-infected 18-40 years old women with no signs of AIDS. The inclusion criteria were: 18-40 years of age, confirmed HIV carriers, and informed consent of this research. Exclusion criteria were: excessive weight, the presence of tuberculosis, and/or diabetes mellitus.

Patients underwent interviews that included demographic, medical, nutritional and recreational drug-related questions. A physical examination was completed and anthropometrics were measured. After overnight fasting, blood samples were obtained to confirm HIV status, hepatitis B virus (HBV) status, and hepatitis C virus (HCV) status, and to determine CD4+ cell count, HIV viral load, plus complete blood cell count and blood biochemistry, including the plasma concentrations of antioxidant parameters (superoxide dismutase (SOD), reduced (GSH) and oxidized (GSSG) glutathione, α-tocoferol) and parameters of oxidative stress (plasma conjugated dienes (CDs) and thiobarbituric acid reactants (TBARs)). Lymphocyte phenotype was determined with a four-colored monoclonal antibodies immunephenotyping panel. Differential counts were determined with a cytometry method using a FacsCount (Becton Dickinson, USA). HIV viral load was obtained by reverse transcriptase-polymerase chain reaction. Information about HIV infection and hepatitis B, C was obtained from the interviews, and then confirmed serologically, including using medical charts.

Patient's blood samples centrifuged for 5 min at 1.500 g at 4°C; and erythrocytes were rinsed three times with NaCI 0.9% (wt/vol). Aliquots of ethylene diaminetetra acetic acid plasma and washed erythrocytes were used immediately or kept frozen in -40°C, not exceeding one month.

The concentration of CDs absorbance detected on plasma heptanes extracts at 232 nm [15]. The coefficient of molar absorption ($K = 2.2 \cdot 10^5\ M^{-1}\ C^{-1}$) for conversion of absorption units to m mol/l was used. TBARs levels were detected by fluorometry end estimated in mmol/l. SOD activity was measured in erythrocytes using a commercially available kit (Ransel; Randox Lab, Crumlin, U.K.) [16]. Fluorometry for GSH and GSSG levels in hemolysate were been used. And, α-tocopherol levels were detected in plasma by fluorometry [17,18].

Body mass index (BMI) was calculated using the standard formula that divides weight in kilograms by the square of height in meters (kg/m2).

Statistical analysis was performed by STATISTICA 6.1 software (Stat-Soft Inc., USA). Means and standard deviation (SD) of means were calculated and significance of differences between values was evaluated by Student (T-test) and Mann-Whitney (U-test) tests. Since the distribution of most of the indicators corresponds to normal, the mean ± SD, was used. The level of significance was set at $p<0.05$.

Results

Group's characteristics are shown in a Table 1. There were no significant differences between the HIV-monoinfected and HIV/hepatitis B and/or C co-infected in ages (30.58 ± 5.35 years vs. 31.67 ± 3.51 years; p>0.05), BMI (19.19 ± 3.27 kg/m^2 vs. 20.19 ± 3.04 kg/m^2; p>0.05), alcohol consumption (30.8% vs. 22%; p>0.05), cigarette smoking (65.4% vs. 40.7%; p>0.05), illicit drugs (19.2% vs. 25.9%; p>0.05). There were no significant differences in those who received highly active antiretroviral therapy (HAART) (38.5% vs. 40.74; p>0.05).

Parameters	HIV-monoinfected (n=26)	HIV/hepatitis B and C co-infected (n=27)	P-value
Age (years) (mean ± SD)	30.58 ± 5.35	31.67 ± 3.51	0.352
Receiving HAART (% (n))	38.5% (10)	40.74% (11)	0.911
BMI (kg/m^2) (mean ± SD)	19.19 ± 3.27	20.19 ± 3.04	0.258
Frequent alcohol use (>2 drinks daily) (% (n))	30.8% (8)	22.% (6)	0.694
Frequent cigarette use (>1 pack daily) (% (n))	65.4% (17)	40.7% (11)	0.128
Injecting illicit drug use (% (n))	(9.2% (5)	25.9% (7)	0.800

Table 1: Characteristics of Patients of HIV-monoinfected and HIV/hepatitis B and/or C co-infected Groups. All values are mean ± SD. * - significant.

The HIV/hepatitis B and/or C co-infected group consisted of women with HIV/hepatitis B - 6 (22.2%), HIV/hepatitis C – 10 (37.1%), HIV/hepatitis B+C – 11 (40.7%). Clinical manifestations in patients with HIV co-infection presented more severe signs of the main symptoms and syndromes: weaknesses, fatigues, pains in the right upper quadrant, lymphadenopathy, and hepato splenomegaly. Patients who had no clinical symptoms significantly more often belonged to a group of HIV-mono infected patients.

Laboratory data are shown in a Table 2. CD4+ cell counts and HIV viral loads were not significantly different between the HIV-mono infected and HIV/hepatitis B and/or C co-infected group (CD4+ counts 217.5 ± 99.3 vs. 177.3 ± 89.1 cells/ml (p>0.05); viral loads 2.5 ± 0.31 vs. 5.85 ± 1.53 log10 HIV-1 RNA copies/ml (p>0.05)). There were no statistically significant differences between the HIV-mono infected and HIV/hepatitis B and/or C co-infected in their levels of alanine aminotransferase (ALT) (45.6 ± 39.1 vs. 59.4 ± 62.1 U/L; p>0.05), aspartate aminotransferase (AST) (55.7 ± 47.9 vs. 79.4 ± 67.8 U/L; p>0.05), albumin (40.6 ± 3.3 vs. 41.8 ± 13 g/dl; p>0.05), hemoglobin (111.2 10.0 vs. 111.5 ± 16.0 U/L; p>0.05). However, plasma bilurubin was significantly higher in HIV/hepatitis B and/or C co-infected group (27.3 ± 6.3 mg/dL) than in those who were HIV-mono infected (8.2 ± 2.8 mg/dL) (p<0.05).

Plasma levels of CDs and TBARs prove the presence of oxidative stress. Table 3 demonstrates that the CDs level mean is significantly higher (1.9 ± 1.00; p<0.05) in patients with HIV/hepatitis B and/or C co-infected than in those who were HIV-mono infected (1.4 ± 0.9 μmol/l). There were no TBARs levels differences between the HIV-mono infected and HIV/hepatitis B and/or C co-infected group in (0.9 ± 0.5 vs. 1.1 ± 1.0 μmol/l) (Table 3). HIV/hepatitis B and/or C co-infected group also had significantly lower levels of antioxidants, including SOD (1.6 ± 0.04 U/mg Hb) and α-tocoferol (7.7 ± 3.1 μmol/l), than the HIV-mono infected group (1.8 ± 0.2 U/mg Hb and

9.7 ± 2.9 μmol/l, respectively ($p<0.05$)) (Table 3). However, there were no differences in GSH and GSSG levels between mono infected and HIV/hepatitis B and/or C co-infected groups, respectively ($p>0.05$).

Laboratory value	HIV-monoinfected (n=26)	HIV/hepatitis B and/or C co-infected (n=27)	P-value
Viralload (log10 copies/ml) (mean ± SD)	2.5 ± 0.31	5.85 ± 1.53	0.278
CD4+ count (cells/ml) (mean ± SD)	217.5 ± 99.3	177.3 ± 89.1	0.127
AST (IU/L) (mean ± SD)	55.7 ± 47.9	79.4 ± 67.8	0.146
ALT (IU/L) (mean ± SD)	45.6 ± 39.1	59.4 ± 62.1	0.442
Albumin (g/dl) (mean ± SD)	40.6 ± 3.3	41.8 ± 13	0.665
Bilirubin (mg/dl (mean ± SD)	8.2 ± 2.8	27 ± 6.3	0.006*
Hgb (g/dl) (mean ± SD)	111.2 ± 10.0	111.5 ± 16.0	0.928

Table 2: Laboratory Parameters Value in Patients of HIV-monoinfected and HIV/hepatitis B and/or C co-infected Groups. All values are mean ± SD. * - Significant.

Blood value	HIV-monoinfected (n=26)	HIV/hepatitis B and/or C co-infected (n=27)	P-value
CDs (μmol/l)	1.4 ± 0.9	1.9 ± 1.00	0.027*
TBARs (μmol/l)	0.9 ± 0.5	1.1 ± 1.0	0.378
SOD (U/mg Hb)	1.8 ± 0.2	1.6 ± 0.04	0.003*
GSH (μmol/l)	2.2 ± 0.3	2.2 ± 0.4	0.742
GSSG (μmol/l)	2.1 ± 0.4	2.2 ± 1.2	0.406
α-tocoferol (μmol/l)	9.7 ± 2.9	7.7 ± 3.1	0.012*

Table 3: Differences in Oxidative Stress and AOD Parameters between the HIV-monoinfected and HIV/hepatitis B and C co-infected Groups All values are mean ± SD. * - Significant.

Notably, the HAART treatment outcomes (Table 4) show statistically significant differences between groups of patients who received this treatment. The CDs and TBARs mean levels were significantly lower (1.1 ± 0.41 μmol/l and 0.7 ± 0.4 μmol/l, respectively) in HIV-monoinfected patients than in HIV/hepatitis B and/or C co-infected patients (2.2 ± 1.3 μmol/l and 1.5 ± 1.1 μmol/l, respectively; $p<0.05$). AOD system changes were registered by 2 indicators – the raised SOD values (1.9 ± 0.1 U/mg Hb) and α-tocoferol (11.7 ± 2.5 μmol/l) in comparison with HIV/hepatitis B and/or C co-infected group of women (1.6 ± 0.2 U/mg Hb and 8.1 ± 2.1 μmol/l, respectively; $p<0.05$). There were no differences in GSH and GSSG levels in the HIV-monoinfected and HIV/hepatitis B and/or C co-infected groups with HAART, respectively ($p>0.05$).

Discussion

It has been reported that HIVs induces OS by disturbing cellular antioxidant defense and initiating oxidative reactions. OS is associated with impaired balance of intracellular reactive oxygen species (ROS)/antioxidants and cellular redox status along with activation of ROS, growth and free radical peroxidation processes, degradation of cellular structures [19,20]. Viral exposure, depending on the strength and duration, can cause OS and cell death, or the initiation of adaptive defense mechanisms that lead to the growth of cellular redox status and new balance of ROS/antioxidants appearance.

Blood value	HIV-monoinfected with HAART (n=10)	HIV/hepatitis B and/or C with HAART (n=11)	P-value
CDs (μmol/l)	1.1 ± 0.41	2.2 ± 1.3	0.007*
TBARs (μmol/l)	0.7 ± 0.4	1.5 ± 1.1	0.041*
SOD (U/mg Hb)	1.9 ± 0.1	1.6 ± 0.2	0.001*
GSH (μmol/l)	2.2 ± 0.3	2.1 ± 0.4	0.667
GSSG (μmol/l)	2.1 ± 0.4	2.4 ± 1.2	0.174
α-tocoferol (μmol/l)	11.7 ± 2.5	8.1 ± 2.1	0.002*

Table 4: Differences in Oxidative Stress and AOD Parameters in HIV-monoinfected and HIV/hepatitis B and/or C co-infected Groups with HAART. All values are mean ± SD. * - Significant.

Many reports suggest that OS is a principal mechanism in the AIDS progression [21]. Since OS can induce apoptosis, ROS may trigger apoptotic pathways responsible for the initial T-cell depletion during HIV-infection. Investigation of CD4+ T-cell count, spontaneous apoptosis and Fas expression in HIV-infected patients revealed both Fas expression and apoptosis, which were consistent with CD4+ depletion [9].

Obviously, both viruses have a concurrent, combined effect on the human body, and cause a number of serious pathological disorders [22]. We found downward trend CD4+ cells in co-infected patients and high bilirubin level due to the presence of hepatitis. The study also shows a tendency to viral load increase in HIV/hepatitis B and/or C co-infected patients, probably due to the presence of hepatitis. In our study, we demonstrated an increase in the CDs content in HIV/hepatitis B and/or C co-infected women compared to HIV-monoinfected. The formation of compounds with conjugated double bonds (CDs) occurs in the first stage of lipid peroxidation in the separation of the hydrogen atom from polyunsaturated fatty acid molecules [23]. Formation and accumulation of conjugated dienes increases the polarity of the hydrophobic hydrocarbon tails of fatty acids. Land hydrocarbon tails, whose polarity increased, were ousted from the thickness of the membrane to the surface, which affects the permeability of membranes, and membrane-associated activity of enzymes and ion transport [7]. This effect is the loss of membrane barrier functions which is the basis of the pathogenesis of many diseases, including HIV. Both HIV and hepatitis infections have been recognized as conditions of oxidative stress elevation which contributes to liver fibrosis, and may be one of the mechanisms involved in the pathogenesis of hepatitis [22]. Similar data have been obtained in other studies of HIV/hepatitis B and/or C co-infected [24,25]. Development of oxidative stress often occurs due to the

reduction of AOD system buffer capacity, compromising its mobilization to the increased activity of prooxidant system [26].

In our study, changes in the content of some antioxidant factors have been shown. Thus, in HIV/hepatitis B and/or C co-infected patients compared to monoinfected women, there was a significant decrease of the average levels of the main enzyme - SOD. It is believed that SOD dismute superoxide anions to hydrogen peroxide and plays a central role in the antioxidant defense [23,27]. Vitamin E deficiencies and OS have been associated with HIV-seropositive patients [28,29]. Vitamin E has been suggested to have a protective role in cell membranes by preventing lipid peroxidation due to its lipophilic nature, as well as elevating the activity of other antioxidants to aid in the scavenging of free radicals [30]. It is known that α-tocopherol, as a structural antioxidant, affects various parts of the reproductive system, stimulating steroidogenesis in the ovaries, protein biosynthesis in the endometrium and other target organs of steroid hormones. And, its deficiency certainly has pathogenetic importance in the development of infertility [27]. Thus, reduced levels of SOD and α-tocopherol may contribute to the development of reproductive disorders in HIV/hepatitis B and/or C co-infected. Marked activation of phagocyte cells and, accordingly, enhanced cytotoxic effects of free radicals on cell membranes may underlie the deficit of antioxidant protection in viral hepatitis [31]. The absence of differences in GSH and GSSG can likely be associated with the low activity of enzymes that use glutathione as a substrate.

The majority of our investigations were focused on the use of HAART to suppress HIV viral replication and the progression of HIV disease. Use of HAART does not improve the condition of patients with HIV/hepatitis B and/or C co-infected. We found lipids peroxidation products increased levels and SOD and α-tocopherol reduced levels in HIV/hepatitis B and/or C co-infected patients compared with monoinfected patients. Increased SOD activity can be interpreted as an adaptive response, but it is not an adequate conclusion.

Conclusions

Women with HIV/hepatitis B and/or C co-infection demonstrate more pronounced imbalance between the pro-oxidants and antioxidant factors compared to monoinfected women. HIV/hepatitis B and/or C co-infection is associated with increased oxidative stress and decreased antioxidant concentrations compared with HIV-monoinfection (both with and without HAART). This fact may indicate increased intake of antioxidants in cell damaged by hepatitis in the human liver or HIV infection. Therefore, the focus of future research should be placed on antioxidants as additional agents for treatment of HIV and AIDS patients. In this respect, further research is needed.

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