

Serum total antioxidant capacity status of HTLV-1 infected patients

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Summary. – Many aspects of the pathogenesis of Human T-cell lymphotropic virus type 1 (HTLV-1) still need further elucidations. Previous studies have indicated that oxidative stress occurs during infection with the other retrovirus, human immunodeficiency virus 1 (HIV-1). Similar results have been observed in some other chronic viral infections including hepatitis B (HBV) and hepatitis C (HCV). In order to reveal possible oxidative stress in HTLV-1-infected patients, we evaluated serum total antioxidant capacity (TAC) as an indicator of oxidative stress in these patients. Forty-four HTLV-1-seropositive individuals were included in this study, consisting of 12 symptomatic and 32 asymptomatic (carrier) cases. Controls consisted of 36 apparently healthy, HTLV-1-, HIV- and hepatitis-seronegative individuals. All symptomatic patients had HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Serum TAC levels in patients and healthy individuals were measured using a quantitative TAC assay. The antioxidant capacity in HTLV-1-seropositive cases was significantly reduced compared to control group ($P = 0.001$). In addition, TAC was lower in patients with more than 5 years history of HAM/TSP compared to those with ≤ 5 years duration of the myelopathy ($P = 0.03$). Our results show a depletion of TAC during HTLV-1 infection, which intensifies along with the disease progress. This finding indicates a role of the oxidative stress in pathogenesis of HTLV-1. These results may prompt further research to evaluate any possible therapeutic effect of antioxidant dietary supplements for HTLV-1 infected individuals.

Keywords: HTLV-1; oxidative stress; total antioxidant capacity (TAC)

Introduction

Under normal conditions, generated reactive oxygen species (ROS) become inactivated by the action of natural antioxidant system present in the body. This system consists of enzymatic antioxidants, such as superoxide dismutase

(SOD), glutathione peroxidase (GPX), and catalase, some macro-molecules, such as albumin and ceruloplasmin, as well as some micro-molecules, including ascorbic acid, α -tocopherol, and β -carotene (Ghiselli *et al.*, 2000). The system results in a natural balance between oxidant production and antioxidant defense under physiological conditions (Irshad and Chaudhuri, 2002).

However, various pathological conditions result in disruption of this normal balance. Under such conditions the imbalance might be the result of the overproduction of oxidants and/or the physiological defense might *per se* be insufficient or incapable to compensate the produced oxidants. Total antioxidant capacity is a marker of antioxidant status, which may serve as an indicator of oxidant/antioxidant imbalance (Suresh *et al.*, 2009).

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Abbreviations: HAM/TSP = HTLV-1-associated myelopathy/tropical spastic paraparesis; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV-1 = human T-lymphotropic virus type 1; ROS = reactive oxygen species; TAC = total antioxidant capacity

Different studies have addressed oxidative stress in malignancies (Rahal *et al.*, 2014), inflammatory conditions including autoimmune diseases (Kundu *et al.*, 2012; Norheim *et al.*, 2012; Wakamatsu *et al.*, 2013), as well as chronic infections such as HIV-1 (Oliveira *et al.*, 2011), HBV (Zhao *et al.*, 2013), and HCV (Paracha *et al.*, 2013).

Human T-lymphotropic virus type 1 (HTLV-1) is one of the first known retroviruses. Most individuals infected with HTLV-1 remain asymptomatic throughout their lifetime, however, in a minority of these patients the disease will progress to severe complications including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Yamano and Sato, 2012). This neurological complication is mainly believed to be due to HTLV-1-specific CTL responses and subsequent cytokine accumulation in the spinal cord, which in turn results in axonal degeneration/demyelination causing spastic paraplegia (Oliere *et al.*, 2011).

Despite several studies of HIV-1, little is known about the occurrence of oxidative stress during HTLV-1 infection. Given the inflammatory responses occurring during HTLV-1 infection, particularly in HAM/TSP cases, it is of interest to explore the oxidant/antioxidant status in these patients. The present study was, therefore, conducted to investigate the antioxidant status in these patients using a quantitative total antioxidant capacity assay.

Materials and Methods

Study groups. A total of 44 HTLV-1 seropositive cases and 36 healthy controls were included in this study. As shown in Table 1, HTLV-1 positive group consisted of 31 males and 13 females with the mean age of 39.8 (ranging from 22 to 58). The HTLV-1-positive patients were diagnosed by HTLV-1 antibody ELISA test and all were confirmed by western blot analysis. Among HTLV-1-positive individuals, 32 cases were asymptomatic (carrier group) with the mean age of 36.6 ± 8 and 12 patients were symptomatic HAM/TSP group (mean age of 43 ± 10). Control group consisted of 36 healthy blood donors with the mean age of 37 (ranging from 27 to 50). Controls were confirmed to be seronegative for HTLV-1, HIV, HBV and HCV. In addition, they filled a questionnaire to reveal any antioxidant regimen or dietary supplementation. Healthy and carrier samples were obtained from blood transfusion organization of Mashhad. HAM/TSP patient samples were taken from neurology department of Ghaem University Hospital in Mashhad. The collected sera were kept at -80°C until used for the TAC assay.

TAC measurement. Serum total antioxidant capacity (TAC) was measured by quantitative colorimetric assay, using an antioxidant assay kit (Cayman) according to manufacturer's instructions. Briefly, the antioxidants in samples could inhibit the oxidation of the radical ABTS (2,2'-azino-di (3-ethylbenzothiazoline-6-sulphonat) by met-myoglobin. The amount of produced ABTS⁺ was monitored by reading the absorbance of yellow color generated through the

reaction of chromogen with ABTS⁺ at 405 nm. The absorbance of the samples was plotted in standard curves based on Trolox equivalent antioxidant capacity (TEAC). The antioxidant capacity of a given sample is compared to the antioxidant function of defined amount (mM) of Trolox.

Statistical analysis. The statistical analysis was performed with SPSS software, version 11.5. Variables were expressed as mean and \pm standard deviation. Normal distribution of the variables was assessed with one-sample Kolmogorov-Smirnov Test. For comparison of the means between groups, independent samples t-test and ANOVA were used. Differences with $P \leq 0.05$ were considered significant in all calculations.

Ethical approval. The study was conducted in accordance with the Helsinki declaration on human research. The research proposal was approved by the ethics committee of Mashhad University of Medical Science (MUMS), Mashhad/Iran.

Results

In this study we measured serum total antioxidant capacity levels in HTLV-1 patients and healthy individuals using a quantitative assay. The mean age of healthy controls and HTLV-1-seropositive group was matched ($P = 0.07$) (Table 1). Table 2 shows the average of total antioxidant capacity in different study groups. TAC levels in the carrier group and in symptomatic HAM/TSP patients were comparable ($P = 0.2$). However, in both symptomatic and carrier groups, TAC was significantly lower than in the control group ($P = 0.001$, $P = 0.01$, respectively).

Similarly, a significantly reduced TAC was observed when symptomatic patients and carriers were grouped together as "HTLV-1-positive group" in comparison to the healthy controls ($P = 0.001$). Within HAM/TSP patient group, the TAC level was higher in patients with ≤ 5 years myelopathy compared to those with the duration of symptoms of more than 5 years ($P = 0.03$). No statistically significant difference in TAC levels between the two genders was observed ($P = 0.4$). More detailed information about the patients is presented in Table 3.

Discussion

The present research was performed in Mashhad, north-east of Iran, where HTLV-1 is endemic (Safai *et al.*, 1996; Rafatpanah *et al.*, 2011). The results indicate a depletion of serum total antioxidant capacity during HTLV-1 infection. To our knowledge this is the first report addressing serum antioxidant status in HTLV-1 patients.

The study groups were matched to exclude the effect of aging on total antioxidant capacity (Sims-Robinson *et al.*, 2013), and the samples were examined within two months

after collection to prevent any possible oxidative changes in the frozen sera.

The TAC was reduced in both carrier and symptomatic groups compared to healthy controls. We also found that TAC is further reduced sera of patients with more than 5 years of history of myelopathy. Such depletion indicates the increase of oxidative stress along with disease progress. It is reasonable to assume that oxidative stress *per se* might exacerbate the disease and the vicious cycle continues as the disease progresses; such pattern has been previously suggested in HIV-infected patients (Fuchs *et al.*, 1991).

Several studies have highlighted the oxidative stress in some chronic viral infections (Oliveira *et al.*, 2011; Paracha *et al.*, 2013; Zhao *et al.*, 2013), and different mechanisms for such oxidative stress have been suggested. In HIV, for example, decreased antioxidant defense and/or elevated serum levels of lipid peroxidation byproducts have been proposed (Dworkin *et al.*, 1986; Sonnerborg *et al.*, 1988; Revillard *et al.*, 1992; Coodley *et al.*, 1993; Dworkin, 1994; Favier *et al.*, 1994; Jarstrand and Akerlund, 1994; Schrauzer and Sacher, 1994). The resulting oxidant/antioxidant imbalance in turn enhances HIV replication and exacerbates the disease progression (Nabel and Baltimore, 1987; Baeuerle and Baltimore, 1988; Staal *et al.*, 1990; Fuchs *et al.*, 1991; Grunfeld *et al.*, 1992).

It has also been suggested that in HIV patients the decrease in antioxidants intake due to the loss of appetite or intestinal mal-absorption might be a reason for the reduction of antioxidants in the serum (Kotler, 1998). However, it seems that the infection-induced oxidative stress is the predominant factor affecting antioxidant levels in HIV-1 patients (Greenspan and Aruoma, 1994). Unlike HIV patients, HTLV-1 infected individuals do not generally suffer from loss of appetite or gastrointestinal manifestations. Therefore it is

Table 1. The age and sex distribution of groups

Group	Sex (F/ M)	Mean age (years)
Control	36 (5/ 31)	37± 8
Carrier	32 (6/ 26)	36.6±8
Symptomatic	12 (7/ 5)	43±10
Total	80 (18/ 62)	37.7±9

unlikely that low antioxidant intake is the main reason for depletion of antioxidants in these patients.

Several underlying mechanisms could explain impaired antioxidant status in HTLV-1 patients. One speculation is that HTLV-1 infection could disturb the oxidative balance through immune and inflammatory responses. Under such conditions, reduction of TAC might be due to overproduction of ROS. Moreover, virus replication might also promote the overproduction of ROS. Indeed, *in vitro* studies have suggested that the HTLV-1 tax protein induces the production of ROS (Silic-Benussi *et al.*, 2009; Chlichlia and Khazaie 2010; Kinjo *et al.*, 2010). The excessive ROS production results in excessive usage of available antioxidants leading to oxidative stress. We also observed that the duration of the symptomatic disease was associated with a higher reduction of TAC, which might be due to prolonged virus replication and thereby higher production of free radicals and/or less

Table 2. Total antioxidant capacity (mM/Trolox) in the three groups

	Control (n = 36)	HTLV-1* (n = 44)	
		Asymptomatic (n = 32)	Symptomatic (n = 12)
TAC (Mean ± S.D)	0.27 ± 0.03	0.25 ± 0.02	0.24 ± 0.03

Table 3. Characteristics of patients (HTLV-1 + with HAM/TSP)

Patient No.	Age (year)	Sex	Detection time (year)	Medications
p.1	29	F	3	α-Interferon, sodium valproate, corticosteroid
p.2	30	F	5	Calcium
p.3	30	F	15	ND
p.4	37	M	ND	ND
p.5	40	F	ND	ND
p.6	42	F	1	α-Interferon, sodium valproate, corticosteroid
p.7	44	F	13	Pregabalin, B ₁ Vitamin
p.8	45	M	ND	ND
p.9	52	M	20	α-Interferon, sodium valproate, corticosteroid, Folic Acid, baclofen, Tizanidine
p.10	52	M	ND	α-Interferon
p.11	58	F	ND	α-Interferon
p.12	58	M	2	α-Interferon, corticosteroid

ND not defined.

effective antioxidant responses over the long time of oxidative condition.

Moreover, as it was mentioned previously, there is a significant cytokine production and CTL response behind the pathogenesis of HAM/TSP (Oliere *et al.*, 2011). Thus, lower TAC in HAM/TSP group might be due to stronger disrupting immune responses in these patients.

The effect of green tea and vitamin C against HTLV-1 has been already reported (Kataoka *et al.*, 1993; Sonoda *et al.*, 2004). Such effect might be due to the powerful antioxidant properties of green tea and vitamin C, which lead to a corrected antioxidant status and thereby improved disease control. Our findings promote further research to examine more closely the effect of antioxidant dietary supplements in the management of HTLV-1-positive patients.

Although above assumptions seem reasonable, the exact mechanism of reduced TAC in HTLV-1 infection and its clinical relevancy remains to be more closely studied and many unanswered questions need to be further clarified.

Several limitations of the present study should be pointed out; first a higher participation rate would strengthen the findings. However due to a limited admissible time from sample collection to TAC measurement, it was infeasible to include higher number of participants. The other important limitation of the study is the possibility of missing some potential confounding factors, although, we considered the known major confounders and addressed them by a researcher-made questionnaire. Thus, it is unlikely that minor underlying confounding factors could greatly affect the results.

To summarize, we observed an impaired TAC in our HTLV-1-positive patients compared to controls. Our findings also indicated a lower TAC in HAM/TSP cases, which was related to the duration of symptoms. The imbalance of oxidants and antioxidants might serve as a clue for one of the aspects behind the HTLV-1 pathogenesis.

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