

Oxidative, nitrosative and glycosative stress levels in Crimean-Congo hemorrhagic fever disease

Oxidative stress biomarkers in Crimean-Congo fever

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Abstract

Aim: This study aimed to investigate Oxidative/Nitrosative/Glycosative stress (OS/NS/GS) biomarkers levels in CCHF disease, their levels in the course of the disease, and to benefit from the results obtained in the pathogenesis and treatment of the disease.

Material and Methods: In the study, serum OS, NS, and GS biomarkers levels of the participants in the CCHF (n = 60) and control (n = 35) groups were compared. In addition, the participants with CCHF were classified as mild, moderate, and severe infection subgroups according to the Severity Grading Score (SGS). A commercial enzyme-linked immunosorbent test kit was used to measure the levels of 8-OHdG, 3-NT, 8-NG, NO, CML, 8-iso-PGF2 α in serum samples obtained from the participants in the CCHF and control groups. MDA levels were measured in serum samples by a spectrophotometric method. Total Antioxidant Status and Total Oxidant Status levels were determined using commercial kits.

Results: On the whole, the mean OS/NS/GS biomarkers levels in the participants in the CCHF group were significantly higher than were those in the control group (p <0.005). Accordingly, it was found that in the participants with CCHF, as the severity of the disease increased so did the biomarker levels.

Discussion: Consequently, in addition to routine laboratory tests, the presence of unbalanced OS/NS/GS in CCHF should be taken into account in the follow-up of patients. Considering that the main factor in CCHF treatment is supportive therapy, adding antioxidant agents to the treatment can contribute to the improvement of the prognosis.

Keywords

Oxidative stress; Nitrosative stress; Glycosative stress; Crimean-Congo; Hemorrhagic fever

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Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a Viral Hemorrhagic Fever (VHF). VHF occurs when a person is infected with the CCHF virus, a member of the genus *Nairovirus* of the family *Bunyaviridae*. CCHF is endemic in a wide geographic area including Europe, Asia and Africa [1]. Therefore, studies focusing on the clarification of the pathogenesis of CCHF are of great importance.

As with other VHA, one of the main features of CCHF is endothelial cell dysfunction, leading to changes in vascular permeability and bleeding. Endothelial damage is not a direct effect of virus replication, but it is a consequence of multiple mechanisms of host origin, which includes cytokines [2].

Endothelial cells are both the potential targets of ROS and the source of ROS production. Reactive oxygen/nitrogen types that develop as a result of endothelial damage cause various structural and functional changes in hemostatic elements. In various inflammatory diseases associated with vascular complications, modifications of the components of the hemostatic system such as oxidation and nitration have been observed [3].

CML is the predominant AGE found in tissue proteins and blood circulation and a commonly used AGE biomarker. AGEs can bind to receptors in endothelial cells and activate an intracellular cascade resulting in OS, inflammation, thrombosis, and WBC uptake [4]. These factors are accepted to increase the risk of endothelial dysfunction and chronic diseases [5]. In addition, the number of studies conducted to investigate the effects of AGEs on viral infections is very small.

Although endogenous antioxidant systems, which are important in the inactivation of ROS, are well researched, "regulation of NS", which is critical for the survival of the organism, has gained importance recently because in severe sepsis with high mortality rates as in CCHF, intense NS occurs [6].

OS/NS/GS biomarkers are characteristic of a common mechanism of many diseases rather than being diagnostic for a particular disease. It can be effective in determining the severity of the disease, in determining patients who may benefit from certain treatments (especially antioxidant therapy).

The primary aim of the present study is to determine the levels of OS biomarkers such as Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidative Stress Index (OSI), 8-isoprostaglandinF2 α (8-isoPGF2 α), 8-OHdeoxyguanosine (8-OHdG) and MDA Malondialdehyde (MDA), the levels of NS biomarkers such as 8-nitroguanine (8-NG), nitric oxide (NO) and 3-nitrotyrosine (3-NT), and the levels of GS biomarkers such as Carboxymethyl-lysine (CML), and to investigate the pathogenesis and prognosis of CCHF.

Material and Methods

Study Population

The current study included 60 individuals who were pre-diagnosed with CCHF in the Clinic of Infectious Diseases and Clinical Microbiology Clinic of the Cumhuriyet University Medical Faculty Research and Practice Hospital. Their final diagnosis was established in the Ankara National Reference Virology Laboratory of Refik Saydam Hygiene Center using the PCR and ELISA methods. Their mean age was 45.73 \pm 14.02

years. Twenty-three of the patients (38.3%) were women. The patients were randomly selected without considering age and sex.

These patients, diagnosed with CCHF, were later assigned into three subgroups as mild, moderate, and severe depending on the severity of the disease to determine the course of the disease and mortality risk using the Severity Grading Score (SGS) system developed by Bakır et al. [7].

In our study, the group with low or no risk which included patients whose SGS was ≤ 4 was called the "mild" subgroup. Patients with an SGS ranging between 5 and 8 comprised the "moderate" subgroup. The third subgroup (severe group) consisted of 10 patients. Their SGS was 9 or above. The severity of the disease and the mortality risk in this group were high. Two of the patients in this group died. In the mild and moderate subgroups, no patients died.

The control group of the study included 35 healthy people who presented to the hospital for routine controls and volunteered to participate in the study. Their mean age was 45.97 \pm 11.95 years; 13 of them (37.1%) were women. They had common lab tests (routine biochemistry analysis, complete blood count and coagulation tests) and physical examinations and did not have any pathological features of CCHF (of any disease).

Ethical considerations

Written informed consent was obtained from all the participants (including the participants in the control group) or their relatives. The study was approved by the local ethics committee (Sivas Cumhuriyet University Clinical Research Ethics Committee) and carried out in accordance with the ethical principles of the Helsinki Declaration.

Analysis

All measurements were performed on 10 ml venous blood samples taken from the patients with CCHF and the participants in the control group on the first morning when they presented to the hospital. The blood samples were centrifuged at 3000 rpm for 10 minutes. Two tubes containing gel were used for 8-OHdG, 3-NT, 8-NG, NO, CML, 8-isoPGF2 α , TAS, TOS, MDA and for routine biochemistry analyses, a citrated tube was used for coagulation test analysis and a tube containing K2EDTA was used for a complete blood count. All tubes were produced by Beckon Dickinson, Franklin Lakes, NJ, USA. After the blood samples were centrifuged, plasma and serum samples were portioned. Routine biochemistry analysis, complete blood count and clotting tests were performed on the samples. Serum samples to be used for 8-OHdG, 3-NT, 8-NG, NO, CML, 8-isoPGF2 α , TAS, TOS, and MDA analyses were stored at -80°C until the analysis day.

The levels of 8-OHdG, 3-NT, 8-NG, NO, CML, 8-isoPGF2 α in serum samples were determined in the Triturus Analyzer (Diagnostics Grifols, Barcelona, Spain), using the enzyme-linked immunosorbent assay (ELISA) kit (Yehua, Shanghai, China).

MDA levels were measured by a method based on the spectrophotometric measurement of the color formed during the reaction between thiobarbituric acid (TBA) and MDA in serum samples obtained from the patients with CCHF and the participants in the control group.

The levels of TAS and TOS in the samples were measured using the Rel Assay commercial kits developed by Erel [8, 9] (Assay

Kit Rel Diagnostics, Turkey). OSI was determined by dividing the total oxidant capacity by the total antioxidant capacity. The concentration of thiobarbituric acid reactive substances (TBARS) was calculated by the absorption coefficient of the MDA-TBA complex and expressed as nmol/mL. A standard MDA bis (dimethyl acetal)-TBA complex was used [10].

Statistical analysis

The SPSS Statistics 22.00 for Windows was used to perform all the analyses. Continuous variables were presented as mean \pm standard deviation (SD). The Kolmogorov-Smirnov test was used to check whether the distribution was normal. In the intergroup comparisons, the Student t-test, one-way variance analysis (ANOVA), the Tukey range test, and the parametric test were used. P-values less than 0.05 were considered statistically significant.

Results

There was no statistically significant difference between the patients with CCHF and the participants in the control group in terms of variables such as mean age ($p = -0.084$; $t = 0.933$) and sex ($X^2 = 0.908$).

There were statistically significant differences between the patients with CCHF and the participants in the control group in terms of the mean values for OSI, OS biomarkers (8-isoPGF2 α , 8-OHdG, MDA), NS biomarkers (8-NG, 3-NT, NO), and the NS biomarker (CML) (Table 1) ($p < 0.005$).

In the present study, the patients with CCHF were assigned into three subgroups as mild, moderate, and severe based on their SGSs. The levels of OS, NS, and GS biomarkers were determined in these subgroups (Table 2).

Discussion

The production of free radicals is an important immunological defense mechanism and occurs against viral infections. There is a delicate balance between pro-oxidants and antioxidants in the body, which limits possible macromolecule damage caused by free radicals. Disruption of this balance leads to a wide variety of diseases, including complications of viral diseases [11]. Taking these studies into consideration, the present study aimed to determine the OS, NS, and GS biomarker levels in patients with CCHF and examine the pathogenesis and prognosis of CCHF.

Our investigation demonstrated that OSI values increased in patients with CCHF compared to the participants in the control group. Similar to the findings in our study, Güner et al. found that TOS levels were significantly higher in patients with CCHF than those in the control group [12].

In our study, the analysis of the TOS levels determined in the CCHF subgroups (mild, moderate, and severe) demonstrated that TOS levels increased as the severity of the disease increased. On the other hand, TAS levels were highest in the mild group and close to each other in the moderate and severe groups. Our findings are consistent with those in the literature. The CCHF virus may have altered the oxidative balance either by increasing the formation of free radicals or by inhibiting the synthesis of enzymes involved in oxidative defense within the host cells.

In their controlled study conducted with patients with CCHF, Aydın et al. found that MDA, an OS lipid biomarker, was

Table 1. Comparison of the patients with CCHF and the participants in the control group in terms of their mean biomarker values

Biomarkers	Patient (n=60)	Control (n=35)	p
TOS ($\mu\text{mol H}_2\text{O}_2$ Eq/L)	45,91 \pm 16,96	29,66 \pm 13,24	<0,05
TAS ($\mu\text{mol Trolox}$ Eq/L)	0,99 \pm 0,21	1,16 \pm 0,12	<0,05
OSI	4,99 \pm 2,39	2,55 \pm 1,09	<0,05
MDA (nmol/mL)	0,34 \pm 0,17	0,07 \pm 0,04	<0,05
8-isoPGF2 α (pg/mL)	73,86 \pm 30,78	31,81 \pm 16,08	<0,05
8-OHdG (ng/mL)	32,19 \pm 10,48	11,40 \pm 5,88	<0,05
NO ($\mu\text{mol/L}$)	21,72 \pm 7,51	15,43 \pm 4,80	<0,05
3-NT (nmol/L)	265,51 \pm 84,87	165,09 \pm 52,48	<0,05
8-NG (ng/mL)	71,49 \pm 13,47	27,47 \pm 9,53	<0,05
CML (ng/mL)	106,72 \pm 67,12	39,70 \pm 15,16	<0,05

The results are shown as mean \pm SD (Standard deviation). TOS: Total Oxidant Status, TAS: Total Antioxidant Status, OSI: Oxidative Stress Index, MDA: Malondialdehyde, 8-isoPGF2 α : 8-isoprostaglandinF2 α , 8-OHdG: 8-OHdeoxyguanosine, NO: Nitric oxide, 3-NT: 3-nitrotyrosine, 8-NG: 8-nitroguanine, CML: Carboxymethyl-lysine, p: difference between patient and control

Table 2. Levels of biomarkers in the patients in the subgroups and in the control group

Biomarkers	Control	Mild CCHF	Middle CCHF	Severe CCHF
TOS ($\mu\text{mol H}_2\text{O}_2$ Eq/L)	29,66 \pm 13,24	30,53 \pm 8,05	55,44 \pm 12,90	60,51 \pm 11,06
TAS ($\mu\text{mol Trolox}$ Eq/L)	1,16 \pm 0,12	1,13 \pm 0,19	0,87 \pm 0,17	0,94 \pm 0,12
OSI	2,55 \pm 1,09	2,77 \pm 0,86	6,64 \pm 2,03	6,45 \pm 1,01
MDA (nmol/mL)	0,07 \pm 0,040	0,29 \pm 0,15	0,32 \pm 0,14	0,53 \pm 0,19
8-isoPGF2 α (pg/ml)	31,81 \pm 33,23	88,12 \pm 39,10	64,76 \pm 17,77	59,95 \pm 17,99
8-OHdG (ng/mL)	11,40 \pm 5,88	29,93 \pm 9,82	30,29 \pm 9,77	42,58 \pm 8,01
NO ($\mu\text{mol/L}$)	15,43 \pm 4,80	21,94 \pm 3,5	25,78 \pm 7,26	11,01 \pm 4,8
3-NT (nmol/L)	165,10 \pm 52,48	216,10 \pm 67,51	287,43 \pm 84,82	334,25 \pm 50,14
8-NG (ng/ml)	27,47 \pm 9,53	61,81 \pm 11,12	75,89 \pm 10,41	84,70 \pm 7,96
CML (ng/mL)	39,70 \pm 15,16	81,32 \pm 56,13	114,59 \pm 69,44	150,53 \pm 64,68

The results are shown as mean \pm SD (Standard deviation). TOS: Total Oxidant Status, TAS: Total Antioxidant Status, OSI: Oxidative Stress Index, MDA: Malondialdehyde, 8-isoPGF2 α : 8-isoprostaglandinF2 α , 8-OHdG: 8-OHdeoxyguanosine, NO: Nitric oxide, 3-NT: 3-nitrotyrosine, 8-NG: 8-nitroguanine, CML: Carboxymethyl-lysine, p: difference between patient and control.

elevated in the patients with CCHF [13]. In our study, MDA levels increased significantly in the patients with CCHF compared to the participants in the control group. In addition, in the subgroups, the increase in the MDA levels was proportional to the severity of the disease, which suggests that the CCHF attacked polyunsaturated fatty acids and eventually initiated lipid peroxidation, which can lead to membrane dysfunction and disruption of the membrane integrity by inducing ROS production.

8-isoPGF2 α is one of the most abundant F2-isoprostane stereoisomers. Therefore, it is most frequently measured in biological samples [14]. In the present study, levels of 8-isoPGF2 α increased in the patients with CCHF more than in the participants in the control group. However, 8-isoPGF2 α levels gradually decreased in the patients in the mild, moderate, and severe subgroups respectively. There is evidence that the formation and metabolism of F2-isoprostanes are complex. Platelet activating factor acetylhydrolase (PAF-AH) catalyzes the hydrolysis of an inflammatory mediator PAF and other

biologically active oxidized phospholipids. PAF-AH activity is variable in some diseases and may affect free F2-isoprostane levels in plasma [15].

Our study revealed that NO values were higher in the patients with CCHF than in the control group. In a study conducted with patients with viral infectious diseases, NO levels were higher in the patient group than in the control group, similar to our study [16]. The high NO levels in the patients with CCHF in the present study can be explained with intense inflammation in these patients. NO plays a role in many stages of inflammation. With the stimulation of different agents, monocytes, mast cells, macrophages, and neutrophils can synthesize NO [17]. In patients with CCHF, such agents could be viruses and their products. These products can also increase NO production by inducing iNOS.

In a study conducted by Tütüncü et al., investigating the role of NO in infection control in patients with CCHF and healthy controls, serum NO levels were significantly higher in patients with CCHF in healthy controls. Tütüncü et al. also compared NO levels of terminally and non-terminally ill patients with CCHF and determined that NO levels were higher in terminally ill patients than in non-terminally ill patients [18]. In our study, in the mild and moderate subgroup patients, as the severity of the disease increased, so did the NO levels. However, NO levels decreased in the severe subgroup patients.

Downregulation of iNOS expression has been reported for some cytokines [19]. However, these suppressive cytokines have been reported to indirectly reduce NO production through arginase induction, which reduces the supply of L-arginine, the substrate for iNOS [20]. The reduction in the severe group, including terminally ill cases, may result from a lack of NO synthesis due to arginine deficiency caused by cytokines induced by the virus in patients with CCHF.

In a study conducted on the cerebrospinal fluid (CSF) of HIV-infected patients, 3-NT levels were significantly higher in the patient group [16]. Although the patients in the present study did not have the same virus, the findings of our study are consistent with that study conducted with patients infected with HIV, which causes severe infection. In the current study, 3-NT levels in all the patients with CCHF may have increased in relation to other parameters we studied because with the increase in NO, the formation of peroxynitrite, the primary mediating molecule of tyrosine nitration, is stimulated. Inflammatory events can provide the appropriate medium for the nitration of tyrosine residues in proteins.

8-nitroguanine, a typical DNA nucleobase product of nitrosative damage [21], increased in the patients with CCHF compared to the control group. In this case, we can say that the high level of NO in the patients with CCHF was rapidly converted to peroxynitrite of superoxide radical above the basal level. Consequently, high levels of 8-NG in our patients with CCHF indicates that this marker which cannot be detected in normal tissues causes intense NS and thus DNA damage.

We determined that levels of 8-OHdG, a biomarker of DNA oxidative damage, increased more in the patients with CCHF than in the healthy controls. In a study investigating 8-OHdG levels, it was reported that 8-OHdG levels increased in patients with HCV and HBV infection [22]. Due to the increase in Ca²⁺

concentration resulting from excessive stimulation of cells in pathological conditions such as infection, binding of these ions with high affinity to the guanine bases in DNA may trigger OS-induced DNA damage.

AGEs are compounds produced by non-enzymatic glycation of proteins, lipids, and nucleic acids, and are thought to play a role in the pathogenesis of diseases in many organ systems.

In the present study, we also investigated CML levels as the last parameter in patients with CCHF and healthy controls. Our results showed that CML levels increased more in patients with CCHF than in the participants in the control group, and the increase in CML levels was proportional to the severity of the disease in the patient subgroups. In a prospective cohort study conducted to investigate the role of AGEs in HIV infection in recent years, it was determined that the accumulation of AGE in the skin was higher in HIV-1-infected patients than in healthy age-matched controls [23]. In another study, the plasma levels of AGEs in HIV/AIDS patients decreased 6 months after the administration of the combined antiretroviral therapy (cART) [24].

High CML levels in patients with CCHF are said to stem from events such as the endothelial damage targeting the capillary endothelium which occurs in this disease, the activation of cellular signaling pathways due to their interaction with the receptors of AGEs (RAGEs) leading to the induction of the release of cytokines, and the existence of RAGEs, which are the AGE receptors, especially in phagocytes [25].

The results of the current study expand our understanding of the role of OS/NS/GS in the pathogenesis of CCHF and thus draw attention to the relationship between CCHF and the formation of OS/NS/GS. Although there are studies investigating OS, the present study is the first study in the literature in which OS/NS/GS in CCHF were investigated.

The greatest strength of the present study is that Oxidative OS/NS/GS were investigated with several biomarkers. In CCHF, which has a high mortality rate, the assignment of patients into subgroups based on their SGSs determined in the acute period also facilitated the investigation of biomarkers in the pathogenesis of the disease. Therefore, the data obtained revealed that in the subgroups of patients with CCHF, the levels of biomarkers increased as did the SGS, the predictor of mortality rates. In the current study, the control group consisted of healthy individuals; therefore, the fact that the third group of patients with fever of different origin was not included in the study could be considered as the limitation of the study.

Consequently, the presence of unbalanced OS/NS/GS in CCHF should be taken into account in the follow-ups of patients in addition to the routine laboratory tests. Considering that the main factor in the treatment of CCHF is supportive therapy, adding antioxidant agents to the treatment might contribute to the improvement of the prognosis. To reveal the positive aspects of adding antioxidant agents to the treatment, more detailed and long-term clinical studies should be conducted.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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