

Original Article

Serum resistin levels may be new prognostic factor of crimean-congo hemorrhagic fever

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Abstract: Crimean-Congo hemorrhagic fever (CCHF) virus can cause potentially fatal infections in humans. During this disease, cytokines are intensive released. Resistin which is a good marker of inflammation is an adipocytokine released from adipose tissue. We aimed to investigate whether serum resistin level in patients with CCHF has a prognostic value in predicting recovery time. Twenty men and 22 women (a total of 42 CCHF patients) and a similar age group of 40 healthy individuals (16 men and 24 women) were included in the study. Hematologic tests, serum resistin level, C-reactive protein (CRP) and others biochemical values of all the two group subjects were evaluated. Multivariate logistic regression analysis was performed. Resistin level of patients with CCHF was higher than the controls (1252.6±864.7 ng/ml vs. 824.1±224.6 ng/ml, $p=0.003$). There was strongly association among recovery time, increased resistin level ($p < 0.001$), prothrombin time (PT) ($p < 0.001$), INR ($p < 0.001$), decreased white blood cell count (WBC) ($p=0.012$) and lower platelet counts ($p=0.007$). Serum resistin level is significantly elevated in CCHF patients. Resistin level may be a good prognostic factor to predict recovery time in patients with CCHF.

Keywords: Crimean-Congo hemorrhagic fever, resistin, cytokines, C-reactive protein

Introduction

Crimean-Congo hemorrhagic fever (CCHF) virus can bring about potentially fatal infections in humans. Its symptoms include sudden onset of high fever, chills, severe headache, dizziness, fatigue, myalgia, back and abdomen pain, nausea, vomiting, bloody diarrhea, mucosal-skin hemorrhagic lesion, neuropsychiatric and cardiovascular changes [1]. In drastic cases it may advance to organ failures and disseminated intravascular coagulation. During the infection the deterioration of endothelial cell function may change vascular permeability leading to the hemorrhage [2]. Elevated levels of pro-inflammatory cytokines such as interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) with interleukin (IL)-10 which inhibits cell-mediated immunity by down regulating IL-12 expression may be important in CCHF pathogenesis [1, 3].

Resistin is adipocytokine that is found in adipocytes, muscles cells, pancreatic islet cells,

mononuclear cells, macrophages, neutrophils, and the placenta [4]. Resistin is a member of the cysteine-rich secretory protein family it is 12.5-kDa peptide with a 108-amino-acid, the other members of this family referred to as resistin-like molecules [5]. It competes with lipopolysaccharides to bind Toll-like receptor and may act as a pro-inflammatory cytokine in the monocytes [6]. Serum resistin level has a strong correlation with serum CRP level and pro-inflammatory cytokines such as TNF- α and IL-6 [7-9]. In addition, it is known to be elevated in severe bacterial and viral infections such as sepsis and chronic viral hepatitis [10-12]. Studies conducted on patients with sepsis have demonstrated resistin level to be correlated with infection severity and have reported resistin level to be a prognostic factor in patients with sepsis [13-15].

In this study, we aimed to investigate whether serum resistin level in patients with CCHF has a prognostic value in predicting recovery time.

Material and methods

Patient selection

This study was carried out according to the guidelines of the Helsinki Declaration and was approved by the local ethics committees. Forty-two patients diagnosed with CCHF (22 females, 20 males) who had admitted to the Infectious Disease Department of Ataturk University Medical School Hospital were enrolled in the study. All the patients with tick bite were called every day for follow up. During the follow up patients who showed the disease symptoms such as high fever, chills, severe headache, dizziness, fatigue, myalgia, back and abdomen pain, nausea, vomiting, bloody diarrhea, mucosal-skin hemorrhagic lesion and/or those with impaired laboratory parameters were considered as CCHF and were hospitalized.

A blood sample of 1.5 ml was drawn from each patient and was sent according to the rules of cold chain to Refik Saydam Hygiene Institute (RS HM, CCHF reference center), Ankara, Turkey a reference laboratory of CCHF. At this center the diagnosis was confirmed by detecting the nucleic acids via real-time reverse transcriptase polymerase chain reaction (PCR) [16]. According to PCR results patients with positive viral RNA were accepted to have CCHF and were included in the study. The first day of the disease was accepted to be the day in which the blood samples were drawn.

Additionally, specific immunoglobulin (Ig) M antibodies were checked from the serum on the 6th day after drawing the samples. IgM level was measured via Elisa test (anti-CCHFV IgM, ELISA IgM capture assay) and IgM > 1/128 titer was accepted to be positive. The reagents used for IgM tests were kindly provided by the Centers for Diseases Control and Prevention (CDC), USA [16]. The reason is that IgM starts to be positive after 4-6 days [17]. IgM results confirmed the accuracy of PCR.

Recovery time

The recovery from CCHF was considered when the patient's complaints and symptoms were disappeared or when the laboratory parameters became normal. PCR test was repeated for all the patients and when the viral RNA was not detected the day in which the sample was drawn was considered as the recovery day. The

interval between the day in which viral RNA was detected and the day in which it disappeared was considered as the recovery time. IgM measurement was not repeated and IgG was not measured as they turn positive from the 6th day and lasts for 1 year for IgM and 5 years for IgG [17].

Control group

A total of 40 healthy subjects (24 females, 16 males) were included in the control group. The patients included in the control group were not definitely exposed to tick bite, had not acute or chronic inflammatory disease or any other infectious disease. Additionally, subjects with history of diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, cirrhosis, portal hypertension, hematological disorders and malignancies were excluded from the patients and the control group. All the subjects were non-smokers and were not consuming alcohol or using drugs. As the patients in the control group were not exposed to tick bite PCR and IgM were not measured.

Biochemical and hematological parameters

The biochemical parameters were measured after 12 hours of fasting. The serum samples were stored at -30°C. Serum fasting plasma glucose (FPG), urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and other biochemical parameter levels were measured using *photometric* assays and an Abbott Architect C16000 analyzer (Abbott Diagnostics, USA). C reactive protein (CRP) levels were measured using the nephelometric method of the Coulter Image 800 device (Beckman, USA). The hematological tests like white blood cell (WBC), platelets, and hemoglobin (Hb) were checked using the Abbott Cell-Dyn Ruby analyzer (Abbott Diagnostics, USA). Coagulation parameters were measured with Diagnostica Stago kit in STA Compact Coagulation analyzer.

Resistin measurement

Serum resistin levels were quantified by enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (RayBiotech, Inc., USA). The procedure for ELISA method was performed according to the manufacturer instructions. Absorbance was measured at

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Table 1. The main characteristics and hematologic parameters for the 2 groups

| | Control (mean±SD) | CCHF (mean±SD) | P value |
|-----------------------------------|-------------------|----------------|---------|
| Age (years) | 39.0±11.2 | 43.8±13.8 | 0.115 |
| Gender (M/F) (n) | 16/24 | 20/22 | 0.156 |
| Recovery time (days) | | 12.8±2.5 | |
| WBC (×10 ⁹ /L) | 7.4±2.5 | 2.5±1.0 | 0.001 |
| Neutrophils (×10 ⁹ /L) | 4.5±2.0 | 1.4±0.8 | 0.001 |
| Lymphocytes (×10 ⁹ /L) | 2.0±0.8 | 0.7±0.4 | 0.001 |
| Hb (g/dL) | 13.8±1.8 | 13.3±2.0 | 0.109 |
| Platelets (×10 ⁹ /L) | 255.3±54.5 | 78.8±43.8 | 0.001 |
| PT (sec) | 13.0±1.0 | 14.7±2.5 | 0.001 |
| aPTT (sec) | 30.2±3.3 | 32.1±5.4 | 0.068 |
| INR | 1.0±0.1 | 1.8±0.2 | 0.001 |

Abbreviations: CCHF, Crimean Congo hemorrhagic fever; M, male; F, female; WBC, white blood cell counts; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

Table 2. Results of biochemical parameters for the 2 groups

| | Control (mean±SD) | CCHF (mean±SD) | P value |
|--------------------|-------------------|----------------|---------|
| Resistin (ng/ml) | 1252.6±864.7 | 824.1±224.6 | 0.003 |
| FPG (mg/dl) | 107.6±24.2 | 98.1±9.6 | 0.158 |
| Urea (mg/dl) | 34.6±6.4 | 30.0±8.0 | 0.700 |
| Creatinine (mg/dl) | 1.0±0.2 | 0.8±0.2 | 0.001 |
| AST (IU/L) | 157.6±162.1 | 23.1±10.0 | 0.001 |
| ALT (IU/L) | 99.5±88.5 | 21.4±13.9 | 0.001 |
| GGT (IU/L) | 68.8±86.1 | 36.8±16.1 | 0.559 |
| Tbil (mg/dl) | 1.2±0.5 | 0.8±0.3 | 0.001 |
| Ibil (mg/dl) | 0.8±0.4 | 0.3±0.1 | 0.001 |
| LDH (IU/L) | 463.7±257.0 | 195.8±33.6 | 0.001 |
| CPK (IU/L) | 448.3±528.4 | 70.3±17.7 | 0.001 |
| CRP (mg/dl) | 3.2±6.5 | 0.7±0.6 | 0.019 |
| ESR (mm/hr) | 19.9±14.6 | 16.5±13.7 | 0.290 |

Abbreviation: CCHF, Crimean Congo hemorrhagic fever; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; Tbil, total bilirubin; Ibil, direct bilirubin; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

450 nm wavelength using an ELISA reader. Resistin levels were presented as ng/mL. The intra-assay and inter-assay coefficients of variation (CV) were < 10% and < 12%, respectively. The sensitivity was 2 pg/mL.

Statistical analysis

SPSS for Windows (ver. 13.0; SPSS, Chicago, IL, USA) was used for data analysis. All the results were analyzed using the Kolmogorov Smirnov to determine normal and non-normal data distribution. The statistical significance of

the differences among all the parameters between the CCHF and the control groups were analyzed using independent sample t-tests for normal distribution parameters and Mann-Whitney U test for non-normal distribution parameters. The relationship between the variables was analyzed using Pearson's correlation. Stepwise multivariate (MVA) logistic regression analyses were performed also for them. The results are given as odds ratio (OR), 95% confidence interval (CI). The differences were considered significant at $p < 0.05$.

Results

Main characteristic and hematological and biochemical parameters

The mean age of CCHF patients was 43.8±13.8 years and the mean age of the control group subjects was 39.0±11.2 years. WBC (2.5±1.0 ×10⁹/L), neutrophils (1.4±0.8 ×10⁹/L), lymphocytes (0.7±0.4 ×10⁹/L) and platelets (78.8±43.8 ×10⁹/L) counts of CCHF patients were significantly lower than WBC (7.4±2.5 ×10⁹/L, $p < 0.001$), neutrophils (4.5±2.0 ×10⁹/L, $p < 0.001$), lymphocytes (2.0±0.8 ×10⁹/L, $p < 0.001$) and platelets (255.3±54.5 ×10⁹/L, $p < 0.001$) counts of the control group.

Prothrombin time (PT) (14.7±2.5 sec), international normalized ratio (INR) (1.8±0.2), resistin (1252.6±864.7 ng/mL), creatinine (1.0±0.2 mg/dl), AST (157.6±162.1 IU/L), ALT (99.5±88.5 IU/L) and CRP (3.2±6.5 mg/dl) levels of CCHF patients were significantly higher than control group's PT (13.0±1.0 sec, $p < 0.001$), INR (1.0±0.1, $p < 0.001$), resistin (824.1±224.6 ng/ml, $p = 0.003$), creatinine (0.8±0.2 mg/dl, $p < 0.001$), AST (23.1±10.0 IU/L, $p < 0.001$), ALT (21.4±13.9 IU/L, $p < 0.001$) and CRP (0.7±0.6 mg/dl, $p = 0.019$) levels. The results of patients' sociodemographic characteristics, hematological and biochemical parameters are shown in **Tables 1, 2.**

Pearson correlation analyses

There was a negative correlation between recovery time and WBC ($r=-0.775$, $p < 0.001$), neutrophils ($r=-0.699$, $p < 0.001$), lymphocytes ($r=-0.698$, $p < 0.001$) and platelets counts ($r=-0.844$, $p < 0.001$). There was a positive correlation between recovery time and resistin ($r=0.386$, $p < 0.001$), PT ($r=0.342$, $p=0.002$), INR ($r=0.848$, $p < 0.001$), CRP ($r=0.234$, $p=0.037$), FPG ($r=0.269$, $p=0.016$), creatinine ($r=0.355$, $p < 0.001$), total bilirubin ($r=0.319$, $p=0.004$), indirect bilirubin ($r=0.505$, $p < 0.001$), AST ($r=0.494$, $p < 0.001$), ALT ($r=0.519$, $p < 0.001$), lactate dehydrogenase (LDH) ($r=0.551$, $p < 0.001$), and creatinine phosphokinase (CPK) ($r=0.405$, $p < 0.001$).

MVA

The effects of resistin and the other independent parameters on recovery time were investigated by performing stepwise logistic regression analysis. WBC counts (OR -0.01, 95% CI -0.01--0.1, $p < 0.001$), platelet numbers (OR -0.014, 95% CI -0.007--0.004, $p=0.007$), PT (OR -0.726, 95% CI -1.145-0.306, $p < 0.001$), INR (OR 10.0, 95% CI 7.11-12.97, $p < 0.001$), and resistin (OR 0.2, 95% CI 0.11-0.24, $p < 0.001$) levels were found to be strongly predictor of recovery time. Other parameters were not statistically significant.

Discussion

Depending upon the results of our study the count of WBC, neutrophils, lymphocytes and platelets of the patients with non-fatal CCHF was quite lower than the healthy control group. PT and INR of these patients were higher than the control group. In addition, serum resistin, glucose, AST, ALT, urea, creatinine, LDH, bilirubin, CPK and CRP levels of CCHF patient group was significantly higher than the control. When the recovery time of the patients group was evaluated using MVA, resistin level, PT and INR, the count of WBC and platelets were found to be predictors of the recovery time. Our results have shown also CRP and ESR levels to be unpredicted of the recovery time for patients with CCHF.

Extensive proinflammatory cytokines such as TNF- α and IL-6 are released in response to the viral infection in CCHF patients. It is known that

the release of TNF- α and IL-6 increase serum resistin level [3, 18, 19]. Many studies have shown resistin being a good predictor of inflammation [20, 21]. Also, resistin enhanced the secretion of pro-inflammatory cytokines, such as TNF- α and other pro-inflammatory cytokines [14]. Resistin may probably plays an important role in acute inflammatory in CCHF due to excessive and sustained cytokines circulation. Our results have shown serum resistin level of CCHF group to be significantly higher than the control group. This elevation may indicate the release of an adipocytokine resistin secondary to the release of pro-inflammatory cytokines such as TNF- α and IL-6. Cytokine and resistin release will continue as long as there is the viral infection, thus resistin may be a strong prognostic factor to demonstrate the severity of the disease and the possible recovery time.

There was no correlation found between CRP level of the patients and the recovery time. CRP is a good marker for systemic infection [22]. However, as it can increase in non-infectious situations with chronic inflammation it is considered as a nonspecific marker [23]. Although procalcitonin is available for usage in bacterial infections, specific marker for viral infections is not available [24, 25]. While CRP is a good marker for bacterial infections it is not good for viral infections. The reason this inadequate elevation of CRP is that viral infections lead relatively to low acute phase reactions [26]. There is a strong correlation between the leukocytes counts and CRP level; however, it has been reported that CRP level increases mildly or does not increase at all in leucopenia [27]. On the other hand, CRP release from liver tissue is stimulated by cytokines such as TNF- α and IL-6. CRP synthesis has been reported to be decreased in acute liver failure [28]. In our study, CRP level has been found to be not prognostic in the patients with CCHF. In addition, the higher levels of AST, ALT, PT and INR than the control group may show the presence of liver tissue damage via hemophagocytosis related to the release of intensive cytokines in CCHF patients. Being the viral infection with manifestations of leucopenia and acute liver failure explains why CRP is not a prognostic factor in CCHF patients. Additionally even though there is no liver failure CRP does not increase enough in viral infections so it is not a suitable parameter to be show CCHF prognosis.

During CCHF infection pro-inflammatory cytokines like IL-6 and TNF- α is released excessively from macrophages and T-lymphocytes [29, 30]. These cytokines leads to the development of pancytopenia and acute organ damage via both endothelial damage and reactive hemophagocytosis [31]. In our study, there was a strong correlation among recovery time and WBC, platelet counts, creatinine, FPG, LDH, CPK, AST, ALT PT and INR. Factors that demonstrate CCHF disease course to be sever include Low WBC and platelet numbers, high levels of AST, ALT, creatinine, LDH and CPK and prolonged PT and INR CCHF patients of this study had a mild course of the disease so there was no organ failure. Our study suggests that resistin level may be a prognostic factor for recovery time and mortality as it directly estimates the recovery time especially in sever patients with organ failure including liver, kidney and pancytopenia. The reason is that release from adipose tissue may be increased secondary to excessive release of cytokines in CCHF patients. Excessive release of cytokines in CCHF patients affects the course of the disease. Thus unlike CRP serum resistin level may be a good prognostic factor in CCHF.

In our study, the results might be influenced by the absence of mortality and the selected patients being mild cases. In more severe CCHF cases further resistin may be released secondary to further cytokines release so it may be a good marker to estimate some organ failure and mortality. In our country fatal cases of CCHF are seen in Central Anatolia and Western Black Sea regions. However, we performed this study in Eastern Anatolia region that has frequently non-fatal cases. Another probability may be that on the contrary to other regions of our country this region has tick strains with lower viral load. Different tick strains with different RNA percentages have been reported to be present even in the same region [32]. Additionally, despite the frequent tick bite cases CCHF cases are 5-10/100000 and the reason may be low viral load in our region [33]. Due to infrequent fatal CCHF cases in our region we could not investigate whether serum resistin level is a prognostic factor of mortality. In this study, we compare CCHF patients with healthy controls. However, we did not investigate CCHF infected and non-infected patients after tick bites. In fact resistin may help in the

diagnosis CCHF. Our study is a pilot study so further studies are needed for the mortality estimation and the possibility to be a diagnostic factor.

Conclusion

Resistin may excessively release from adipose tissue secondary to intensive cytokine release during the course of CCHF. Despite the absence of adequate CRP response in these patients excessive elevation of resistin level indicates that it is a good prognostic factor of the recovery time of patients with CCHF.

Disclosure of conflict of interest

None.

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