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Determination of the value of fetuin-A as a potential biomarker for early recognition of prognosis of fatality in patients with carbon monoxide poisoning

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ABSTRACT

Background: To investigate the role of fetuin-A as a potential biomarker for prognosis of fatality in patients with carbon monoxide (CO) poisoning.
Methods: In a prospective study, 60 poisoned patients with CO who were admitted to the department of emergency medicine between August 2017 and April 2018 were compared to 40 paired control subjects from the same department.
Results: Fetuin-A levels were significantly lower in the patients with CO poisoning, especially in those non-survive (68.9 ± 7.6 vs 59.5 ± 4.1, $p = 0.019$). The area under the curve in the ROC curve analysis for the fetuin-A was 0.914 with a cut off of 61.15 mmol/L.
Conclusions: The decrease of Fetuin-A may indicate an early signal for the progression of fatality due to CO poisoning.

1. Introduction

1.1. Background

Carbon monoxide (CO) poisoning which a significant cause of emergency department (ED) visits is associated with illness and death [1-4]. The toxic symptoms and signs of CO poisoning are often non-specific and are highly variable depending on the concentration and the length of exposure [2,5]. The symptoms in low-level exposure to CO including headache, dizziness, fatigue, malaise, nausea, confusion, visual disturbances, and disorientation, while severe symptoms comprise loss of consciousness, seizures, coma and death [6].

The most clearly established mechanisms for the CO toxicity associated with tissue hypoxia. Due to the affinity of CO to hemoglobin is 200 to 240-times greater than to oxygen [7] its inhalation increases the amount of carboxyhemoglobin (CO-Hb), which reduces the oxygen-carrying capacity of the blood. Thus, CO leads to increased extraction of oxygen from the blood by peripheral tissues and eventually to marked tissue hypoxia. However, tissue hypoxia is not the only processes for the toxic effects of CO were observed. CO causes severe detrimental effects by both oxidative stress and cellular damage by inflammatory processes [8,9]. Inflammatory response to CO poisoning triggers intravascular platelet-neutrophil interactions that leads to neutrophil degranulation and perivascular oxidative stress [10].

Fetuin-A, an anti-inflammatory reactant which is mainly synthesized by the liver is commonly involved in the reduction of the pro-inflammatory cytokines [11,12]. As a negative acute phase protein, fetuin-A is usually inhibited by pro-inflammatory cytokines, during the anti-inflammatory response [13]. Thus, decreased plasma concentrations of fetuin-A will limit and affect the actions of different anti-inflammatory mediators, enhancing amplification of pro-inflammatory mediators. Fetuin-A is a multifunnctional protein with metabolic disease biomarker capacity [14].

During the past decades, investigations have focused on fetuin-A due to its role as an independent prognostic factor for many conditions such as cardiovascular diseases, diabetes mellitus, renal dysfunction, and metabolic syndrome [7,15-17]. However, the fetuin-A level in patients with CO poisoning has not been investigated. Therefore, this study aimed to evaluate the relationship between laboratory parameters such as troponin, creatinine, pH,

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pO_2, CO-Hb and pCO_2 levels for providing evidence of adverse health effects of CO poisoning and to investigate the value of fetuin-A as a potential biomarker for early recognition of prognosis of fatality in patients with CO poisoning.

2. Methods

2.1. Study design and setting

This prospective case-control study includes patients (30 male, 30 female; mean age 39.1 ± 12.5 years) with acute CO poisoning which were admitted to the emergency department of Cumhuriyet University Hospital from February 2017 to August 2018. Each patient was matched with a control with respect to age and gender. The controls were selected from either relatives of the patients in the study group or from relatives of the other patients at the same department, if possible. The control group was comprised of 40 patients (18 female, 22 male) with a mean age 40.3 ± 10.8 years.

The inclusion criteria were patients >18 years of age with a diagnosis of acute CO poisoning CO poisoning at the time of ED admission. Patients with any of the following conditions were excluded: CO poisoning exposure for >24 h prior to presentation, <18 years of age. Also, patient who died prior to admission were not included. In this study, before weight management strategies such as caloric restriction, weight loss surgeries hematologic malignancy, chronic liver disease, diabetes mellitus, with acute or chronic inflammatory disease diagnosed patients were excluded from the study.

A patient history and physical examination, as well as blood CO-Hb levels (above 10% or 3% in smokers or nonsmokers, respectively) were used to establish the diagnosis of acute CO poisoning. The following parameters were evaluated with respect to differences in age, gender, laboratory data (level of initial, white blood cell count [WBC], plasma creatinine, albumin, calcium, plasma cardiac enzymes [creatine kinase, creatine kinase muscle and brain, troponin-I], C-reactive protein [CRP] levels), fetuin-A level and arterial blood gas analysis (pH, pO2, pCO2, and CO-Hb), as well as the outcome of patient (survival/non-survival). Generally, the blood of patients with CO poisoning were measured at the time of the ED admission. Computed tomography of the patients with neurological complaints was evaluated to determine the presence or absence of basal ganglion involvement due to acute CO intoxication.

The study protocol was approved by the institutional ethics committee of the Sivas Cumhuriyet University (2017-01/03) and consent was obtained from all patients or their relative ones.

Informed consent was received approval from the patient and his legal representatives.

2.2. Immunoassay analysis

Plasma fetuin-A levels were measured from peripheral venous blood samples which were collected from patients at the time of the ED admission. After receiving venous blood samples, the tubes were centrifuged for at 4000 rpm 4–5 min. Samples were stored at-80 °C. Plasma fetuin-A levels were measured using a human fetuin-A enzyme-linked immunosorbent assay Measurements with Elisa kit were in duplicate for each sample. (ELISA) kit (Cat no: EK-067-52, lot no: 603894; Phoenix Pharmaceuticals, Belmont, CA, USA).

Table 1
Demographic and clinical features of patients with CO positioning versus controls.

Variables	Patients (n = 60) (Mean ± SD)	Controls (n = 40) (Mean ± SD)	P value (Student's t test)
Age (years)	39.1 ± 12.5	40.3 ± 10.8	>0.05
Male/female	30/30	22/18	>0.05[a]
BMI	25.18 ± 1.76	24.76 ± 4.33	>0.05
Basal ganglia involvement	8/52	0/40	0.02[b]
Fetuin-A (mg/dL)	68.3 ± 7.8	228.4 ± 35.5	<0.001
Calcium (mg/dL)	9.1 ± 0.6	9.1 ± 0.5	>0.05
Albumin (mg/dL)	3.6 ± 0.5	4.5 ± 0.5	<0.001
White blood cell count ($x10^3/mm^3$)	10.3 ± 3.7	7.8 ± 2.3	<0.001
Troponin-I (ng/dL)	0.6 ± 2.2	0.1 ± 0.1	0.046
Creatinine (mg/dL)	0.8 ± 0.5	0.8 ± 0.2	>0.05
Carboxyhemoglobin (%)	20.3 ± 8.9	0.7 ± 0.1	<0.001
Platelet ($10^{x3}mm^3$)	251.7 ± 64.7	316.0 ± 73.1	<0.001
SaO_2 (%)	89. 2 ± 3.7	96.2 ± 1.3	<0.001
pH	7.3 ± 0.1	7.4 ± 0.0	<0.001
$PaCO_2$	31.1 ± 2.5	35.9 ± 5.6	<0.001
HCO3-	33.0 ± 9.0	39.2 ± 2.3	<0.001

Body mass index (BMI), arterial oxygen saturation (SaO_2), power of hydrogen(pH), partial pressure of carbon dioxide ($PaCO_2$), bicarbonate (HCO3-).
[a] Chi-square test.
[b] Fisher exact test.

2.3. Statistical analyses

Data were analyzed with the SPSS software version 22.0 for Windows (IBM corp. New-York, USA). Continuous variables were presented as mean ± standard deviation as appropriate, and categorical variables as numbers (%). The student's t-test or Mann–Whitney U test was used for continuous variables and categorical variables were compared with the chi-square test or Fisher exact test, to assess the significance of intergroup differences. The relationships between variables were calculated by Pearson's correlation coefficients. Receiver operating characteristic (ROC) curve was performed to determine the predictive value of fetuin-A as an independent variable for prognosis of mortality due to CO poisoning. A p value <0.05 was considered statistically significant.

3. Results

The general demographic features and laboratory findings in both patient and control groups are presented in Table 1. The number of basal ganglia involvement, WBC, Troponin-I, CO-Hb, and pCO2 levels were higher in patients than those in controls (8/52 vs. 0/40, p = 0.02; 10.3 ± 3.7 vs. 7.8 ± 2.3; 0.6 ± 2.2 vs. 0.1 ± 0.1, 20.3 ± 8.9 vs. 0.7 ± 0.1 and 31.1 ± 2.5 vs 35.9 ± 5.6, respectively; p < 0.001), however, fetuin-A, SaO2, pH and HCO3 levels were higher in controls than those in patients (68.3 ± 7.8 vs. 228.4 ± 35.5; 89. 2 ± 3.7 vs. 96.2 ± 1.3; 7.3 ± 0.1 vs. 7.4 ± 0.0 and 33.0 ± 9.0 vs. 39.2 ± 2.3, respectively; p < 0.001 for all comparisons) (Table 1).

Correlation between serum fetuin-A levels and variables in patients group are summarized in Table 2. Serum fetuin-A levels were positively correlated with albumin (r = 0.292 and p = 0.02), but it was negatively correlated with WBC, troponin-1, creatinine and CO-Hb levels (r = −0.289 and p = 0.02; r = −0.264, p = 0.04; r = −0.297, p = 0.02 and r = −0.383 and p = 0.01, respectively).

As presented in Table 3, fetuin-A, SaO2, pH and pO2 levels were found to be statistically significantly higher in survive than those

Table 2
Correlation between serum Fetuin-A levels and variables in both patients and control groups.

Variable	Patients (n = 60)		Controls (*n* = 40)	
	R	P Value	R	P Value
Calcium (mg/dL)	0.110	0.41	0.243	0.13
Albumin (mg/dL)	0.292	0.02	0123	0.45
White blood cell count (x10^3/mm^3)	−0.289	0.02	0.005	0.98
Troponin-I (ng/dL)	−0.264	0.04	−0.184	0.26
Creatinine (mg/dL)	−0.297	0.02	−0.066	0.69
Carboxyhemoglobin (%)	−0.383	0.01	−0.234	0.15
Platelet (10 x$3mm^3$)	0.125	0.34	−0.169	0.30
SaO_2(%)	0.210	0.10	0.066	0.69
pH	0.109	0.41	−0.021	0.90
PaCO2	0.028	0.84	−0.086	0.60
HCO_3-	0.051	0.70	−0.045	0.78

Arterial oxygen saturation (SaO2), power of hydrogen(pH), partial pressure of carbon dioxide (PaCO2), bicarbonate (HCO3-).

Table 3
Clinical features of patients with CO positioning admitted to the emergency medicine stratified by survival versus non-survival.

Variables	Survive *n* = 56	Non-Survive n = 4	P Value (Mann-Whitney U test)
Fetuin-A	68.9 ± 7.6	59.5 ± 4.1	0.019
Calcium (mg/dL)	9.1 ± 0.6	8.4 ± 0.4	0.027
Albumin (mg/dL)	3.6 ± 0.5	3.6 ± 0.2	>0.05
White blood cell count (x103/mm3)	10.0 ± 3.6	14.7 ± 3.5	0.014
Troponin-I (ng/dL)	0.2 ± 0.9	6.1 ± 6.2	0.002
Creatinine (mg/dL)	0.7 ± 0.4	1.9 ± 0.5	0.001
Carboxyhemoglobin (%)	19.3 ± 6.9	34.5 ± 19.8	>0.05
Platelet (10 x3mm3)	256.8 ± 62.6	179.5 ± 53.8	0.034
SaO_2(%)	90.0 ± 1.7	77.0 ± 3.5	<0.001
pH	7.4 ± 0.1	7.0 ± 0.1	0.001
PaO_2	97.0 ± 12.0	67.5 ± 26.6	0.009
$PaCO_2$	33.2 ± 9.2	29.9 ± 5.9	>0.05

Arterial oxygen saturation (SaO2), power of hydrogen(pH) partial pressure of oxygen (PaO2), partial pressure of carbon dioxide (PaCO2).

Table 4
Cut-off value, sensitivity, and specificity of serum fetuin-A level for predicting of fatality in prognosis of CO poisoning

	Fetuin-A level
Cut-off value	61,15
Sensitivity	0.75
Specificity	0.91
AUC (95% CI)[a]	0.914 (0,839–0,989)

[a] AUC, area under the curve; CI, confidence interval.

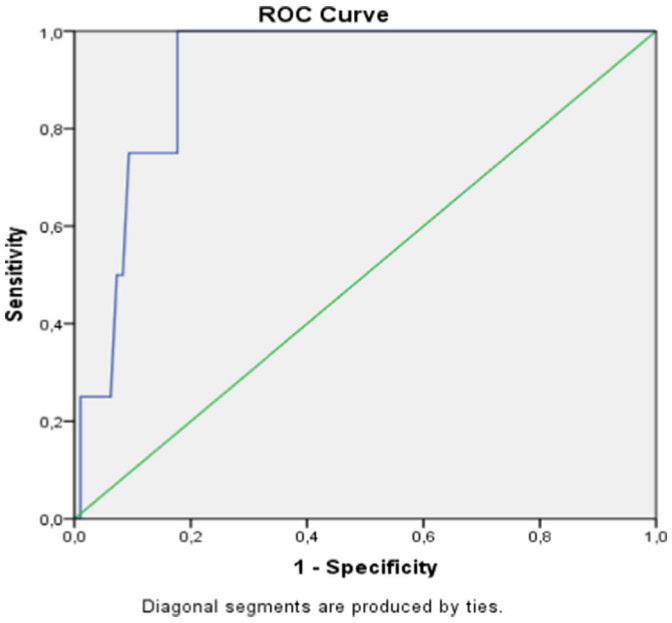

Fig. 1. Receiver operating characteristic curve of fetuin-A levels for the prediction of prognosis of mortality in patients with acute carbon monoxide poisoning.

non-survive (68.9 ± 7.6 vs. 59.5 ± 4.1, $p = 0.019$; 90.0 ± 1.7 vs. 77.0 ± 3.5, $p < 0.001$; 7.4 ± 0.1 vs. 7.0 ± 0.1, $p = 0.001$; 97.0 ± 12.0 vs. 67.5 ± 26.6, $p = 0.009$; 68.9 ± 7.6 vs. 59.5 ± 4.1, p = 0.019, respectively). Also, WBC count, troponin-1and creatinine levels were higher in non-survive than those survive (14.7 ± 3.5 vs. 10.0 ± 3.6, $p = 0.014$; 6.1 ± 6.2 vs. 0.2 ± 0.9, $p = 0.002$; 1.9 ± 0.5 vs. 0.7 ± 0.4, p = 0.001, respectively) (Table 3).

The cut-off value of fetuin-A levels to predict prognosis of fatality in CO poisoning is shown in Table 4. The ROC curve analysis that included the plasma fetuin-A that were significantly associated with fatality in bivariate analyses showed that the plasma fetuin-A had an area of 0.914 and a cut off of 61.15 mmol/L (sensitivity 75%, specificity 91%) ($p = 0.005$, respectively) (Fig. 1, Table 4).

4. Discussion

This case-control study revealed that levels of plasma fetuin-A were lower in patients with acute CO poisoning, which could potentially improve early recognition of fatality progression after acute CO poisoning. Furthermore, cut-off values of fetuin-A to predict the fatality in CO poisoning was also proposed in this current study. According to the literature reviews, this is the first study to demonstrate a significant association of higher fatality with lower plasma fetuin-A in patients with CO poisoning.

The outcomes of patients with CO poisoning admitted to the emergency department were evaluated in this study. Characteristics associated with fatality progression in CO poisoning includes high COHb level and pH values <7.20 [18]. The present study, similar to the findings from some recent studies, found that patients who succumbed to poisoning had lower SaO2, pH, PaCO2 and higher COHb levels as compared to those who survived [19,20].

There are a range of studies exist in the published literature examining fetuin-A levels and its' role in various diseases and/or conditions such as cardiovascular diseases, chronic kidney diseases, diabetes mellitus and metabolic syndrome [19-21]. However, there is no study, to date, exploring fetuin-A levels in patients with CO poisoning. In a recent study was reported that WBC count, CO-Hb and troponin levels were higher in patients with CO poisoning [22]. Inconsistent with the result of that recent research, this study found that the WBC count, as well as CO-Hb and troponin levels, were significantly higher in the patients with CO poisoning, but fetuin-A levels were lower at that patients. Furthermore, in similar to a research which conducted on patients with Chron's disease reported that fetuin-A levels negatively correlated with WBC counts [23], levels of troponin-1, creatinine, CO-Hb as well as WBC count in the study (in the patients group) were found to have negative correlation with fetuin-A levels.

In the present study, significant differences were observed in the baseline features of patients who survived and those who succumbed to the CO poisoning. Similar to a study which conducted on patients with chronic kidney diseases, this current study observed that higher fatality rates in patients with CO poisoning have been closely linked to low plasma fetuin-A level [19]. On the contrary, high levels of fetuin-A have been reported to increase various risk factors regarding disease [20]. The low-level concentration of fetuin-A, however, has shown to be protective against atherosclerosis [21]. In addition, as indicated in a large study, high plasma fetuin-A levels are associated with the metabolic syndrome and subclinical inflammation, suggesting fetuin-A that involved in the processes of these disease as a causal factor seems to be concentration-dependent [17].

4.1. Strength and limitations

The strength of this study is that it is first studied to represent a significant association of higher fatality with lower plasma fetuin-A in patients with CO poisoning. Nevertheless, some limitations should be mentioned in the current study. First, all the patients with acute CO poisoning were recruited from a single center and the results of this study are preliminary because the rate of fatality was 7.1% (4/56) and the total number of non-survive patients was relatively small for the further multivariate analysis. Second, because of the patients studied were comprised a relatively small number of the patients admitted to the emergency medicine, this study may not be representative of the clinical features of the CO poisoning patients elsewhere. Therefore, the results of this current study should be interpreted with caution. Finally, a large sample study is needed to confirm the results of this study with respect to CO toxicity in patients admitted to the emergency departments.

5. Conclusion

In conclusion, this prospective study was demonstrated a significant association of higher fatality with lower plasma fetuin-A in patients with CO poisoning. Therefore, the role of plasma fetuin-A as a potential biomarker for early recognition of fatality due to acute CO poisoning warrants more investigation.

Author contribution

The conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; and final approval of the manuscript was done by Yusuf Kenan Tekin.

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Declaration of Competing Interest

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