

Changes in ceruloplasmin levels in chronic heart failure in patients with HIV Infection

Goryacheva O.G.¹, Terekhina N.A.¹, Zubarev M.A.¹, Ponomarev S.B.²

¹ Federal State Budgetary Educational Institution of Higher Education "Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of Russia, Perm, Russia.

² Federal State Institution "Research Institute of the Federal Penitentiary Service of Russia", Moscow, Russia.

AUTHORS

Olga G. Goryacheva*, PhD, MD, Associate Professor, Department of Outpatient Therapy, Federal State Budgetary Educational Institution of Higher Education "Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of Russia, Perm, Russia. ORCID: 0000-0002-3336-229X

Natalya A. Terekhina, Doctor of Medical Sciences, Professor, Head of the Department of Biochemistry, Federal State Budgetary Educational Institution of Higher Education "Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of Russia, Perm, Russia. ORCID: 0000-0003-0780-3116

Mikhail A. Zubarev, PhD, MD, Honorary Professor, Department of Propedeutics of Internal Diseases, Federal State Budgetary Educational Institution of Higher Education "Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of Russia, Perm, Russia. ORCID: 0009-0002-0909-742X

Sergey B. Ponomarev, PhD, MD, Federal State Institution "Research Institute of the Federal Penitentiary Service of Russia", Moscow, Russia. ORCID: 0000-0002-9936-0107

Ceruloplasmin (CP) is an important plasma antioxidant and a weak acute-phase reactant, and this is why its assessment allows evaluation of the level of antioxidant defence and the activity of the inflammatory process in the body.

Objective. To evaluate the effect of chronic heart failure (CHF) on ceruloplasmin plasma levels in HIV-infected patients.

Methods. A total of 240 HIV-infected patients were examined, 160 of them had signs of CHF. CP levels were measured in the plasma of all CHF patients and 30 healthy volunteers using RANDOX reagent kits on a biochemical

analyser. The diagnosis of CHF was confirmed in accordance with the 2020 Clinical Guidelines of the Russian Society of Cardiology.

Results. The CP plasma level in healthy volunteers was 388.9 ± 18.7 mg/L. The CP level in HIV-infected patients with CHF was significantly below the reference range: 137.0 [102.0; 155.5] mg/L. CP levels increased in the presence of chronic kidney disease and anaemia. The threshold CP level for the development of CHF with reduced ejection fraction was 233.5 mg/L (sensitivity 99%, specificity 90%).

Conclusion. CP plasma levels are significantly reduced in HIV-infected patients with CHF. Even against a background of low CP values, a tendency for CP to increase with worsening CHF severity is preserved. A plasma CP level of 233.5 mg/L increases the probability of CHF with Ejection Fraction (EF) < 40%. In patients with reduced left ventricular ejection fraction or NT-proBNP \geq 1500 pg/mL, CP levels are somewhat elevated but remain below the reference limits. CP levels increase in the presence of chronic kidney disease and anaemia.

Keywords: HIV infection, chronic heart failure, ceruloplasmin, chronic kidney disease, anaemia, inflammation.

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Introduction

Ceruloplasmin (CP) is a copper-containing glycoprotein with ferroxidase activity, particularly essential for iron metabolism, as it facilitates the conversion of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), enabling its binding to transferrin [1]. Elevated CP levels following clinical recovery of patients with inflammatory diseases indicate an incomplete resolution of the inflammatory process [2]. The Human Immunodeficiency Virus (HIV) causes a multitude of metabolic disorders, including significant alterations in iron metabolism, which contributes to the development of complications including anaemia and oxidative stress [1].

Oxidative stress poses a serious problem in HIV infection, as it promotes cell and tissue damage, inflammation, and disease progression. CP neutralises free radicals, thereby protecting against oxidative stress and demonstrating its potent antioxidant properties [3].

Objective

The aim of the study was to evaluate the effect of CP levels on the clinical and functional status of HIV-infected patients.

Methods.

A total of 240 HIV-infected patients were examined at the State Budgetary Healthcare Institution "City Clinical Hospital named after M.A. Tverie" in Perm, 160 of them were diagnosed with chronic heart failure (CHF). To establish the normal CP plasma concentrations, its levels were measured in 30 healthy volunteers (donors at the blood transfusion station). CP plasma levels were analysed in 160 HIV-infected CHF patients. Plasma CP concentrations were deter-

mined using RANDOX (United Kingdom) reagent kits on the Clima MC-15 biochemical analyser.

To confirm the diagnosis of CHF, all patients underwent echocardiography using the VIVID T8 system (USA), plasma N-terminal pro-natriuretic peptide (NT-proBNP) levels were measured, and clinical assessment was performed using the Clinical Status Assessment Scale modified by V.Yu. Mareev (SHOKS) [4] and the Six-Minute Walk Test (6MWT). NT-proBNP was determined using Vektor-Best (Russia) reagent kits on the Immulite 1000 immunoassay analyser (USA). A total peripheral resistance (TPR) level of 210 kPa·s/L or higher was considered elevated, as it was previously established by our group [5]. Alcohol dependence was diagnosed using the AUDIT questionnaire, with a score of 20 or more [6].

Inclusion criteria: diagnosis of CHF in an HIV-infected patient and signed voluntary informed consent to participate in the study. Patients with oncological pathology, severe valvular heart disease, pregnant women, individuals under 18 years of age, and patients with tuberculosis were excluded.

The study design complied with the requirements of the Declaration of Helsinki and GCP, and was approved by the Ethics Committee of Perm State Medical University named after Academician E.A. Wagner.

Statistical analysis

Statistical analysis was performed using Statistica 13 (Russia) and SPSS 26 (USA) software. The normality of distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In all of cases, quantitative variables had a non-normal distribution and are presented as median with upper and lower quartiles. Binary variables are presented as absolute

numbers and percentages. The Mann–Whitney test, chi-squared (χ^2) test, and ROC analysis were used.

Results

The CP level in healthy volunteers was 388.9 ± 18.7 mg/L [Patent No. 2362998]. According to reference materials, the normal plasma CP value is 200–600 mg/L [7]. CP serum levels were analysed in CHF patients infected with HIV ($n=160$). The mean CP level was 137.0 [102.0; 155.5] mg/L, which is substantially below the reference values.

CP levels were analysed in the group of HIV-infected CHF patients across subgroups defined by key features determining CHF severity (table 1).

It was found that CP levels were significantly reduced in CHF with reduced EF and at plasma NT-proBNP levels ≥ 1500 pg/mL. An interesting association was found between elevated CP serum levels and subsequent death within 2 months of study enrolment. No significant differences were found for the remaining parameters.

ROC analysis was performed between serum CP levels and the presence of CHF with reduced EF $< 40\%$, and significant results were obtained ($p=0.036$), with an area under the ROC curve of 0.940 ± 0.034 [95% CI: 0.874–1.000]. The threshold CP value for the development of CHF with reduced EF was 233.5 mg/L (sensitivity 99%, specificity 90%). Thus, a serum CP level of 233.5 mg/L might indicate a very high probability of CHF with reduced EF in an HIV-infected patient. A search was conducted for differences between features depending on the presence of a threshold CP value of 233.5 mg/L.

Group 1 comprised patients with CP levels at or above the threshold. Group 2 comprised patients who did not reach the threshold CP level (table 2).

At threshold and above CP levels, fewer steps were completed during the 6MWT, which may indicate a greater clinically significant reduction in exercise tolerance. Left ventricular end-diastolic volume (EDV) was higher, and LVH was more frequent in the group with threshold and above CP values.

The ratio of peak velocities of early transmitral blood flow and early diastolic mitral annular motion (E/e') was higher in the group with threshold CP values. This group also had a higher prevalence of patients with reduced LVEF, PAH, and enlarged LA volume. TPR was higher in Group 1 patients.

At threshold and above CP levels, higher serum cystatin C concentrations and lower GFR values were observed. The latter indicates an association between CP and renal glomerular function. The level of growth stimulation expressed gene 2 (ST2), encoded by the ST2 gene (also known as suppression of tumorigenicity 2), differed significantly between groups, with higher values in the higher-CP group. ST2 is a modern, highly sensitive CHF biomarker, and its concentration increase is associated with worsening CHF severity [8]. The proportion of patients with elevated NT-proBNP ≥ 1500 pg/mL was higher in the group with threshold and elevated CP, while NT-proBNP plasma levels did not differ significantly between groups.

Discussion

CP is the main copper-containing glycoprotein of the blood, binding up to 95% of plasma copper and ap-

Table 1. Plasma CP levels (mg/L) compared by features determining CHF severity in HIV-infected patients

Comparison parameter	CP level in subgroup with feature present	CP level in subgroup with feature absent	p
Male sex, n (%)	135.5 [102.0; 146.0]	143.0 [102.5; 237.5]	0.131
LVEF $< 40\%$, n (%)	272.0 [267.0; 277.0]	130.0 [97.0; 143.0]	0.038
Diastolic dysfunction of LV (DDL), n (%)	139.0 [110.5; 132.5]	115.5 [95.5; 138.0]	0.083
\uparrow TPR, n (%)	161.0 [101.0; 186.0]	110.5 [99.0; 139.0]	0.887
\uparrow Left atrial volume index, n (%)	126.0 [105.0; 147.0]	138.0 [97.0; 139.0]	0.650
Pulmonary arterial hypertension (PAH), n (%)	137.0 [115.0; 147.0]	113.0 [99.0; 139.0]	0.756
Smoking, n (%)	134.0 [95.0; 153.0]	137.0 [134.0; 158.0]	0.126
Alcohol dependence, n (%)	115.0 [90.0; 153.0]	137.0 [106.0; 158.0]	0.291
Coronary heart disease, n (%)	142.0 [128.5; 150.0]	135.5 [97.0; 161.0]	0.229
NT-proBNP > 1500 pg/mL, n (%)	193.5 [150.0; 250.5]	155.0 [108.0; 190.0]	0.048
Death within 2 months of study inclusion, n (%)	267.0 [153.0; 277.0]	134.0 [99.0; 147.0]	0.031
Chronic kidney disease, n (%)	212.0 [147.0; 277.0]	123.0 [97.0; 128.0]	0.044
Antiretroviral therapy, n (%)	110.5 [90.0; 139.0]	138.0 [105.0; 164.0]	0.123
Anaemia, n (%)	139.0 [117.5; 161.0]	73.5 [42.3; 97.0]	0.025
Thrombocytopaenia, n (%)	135.5 [97.0; 150.0]	133.5 [105.0; 164.0]	0.223

Table 2. Differences in characteristics by threshold CP level of 233.5 mg/L in HIV-infected CHF

Parameter	CP ≥233.5 mg/L, n=36	CP < 233.5 mg/L, n=124	p
Clinical and anamnestic parameters			
Age, years	35.5 [30.0; 44.0]	36.0 [32.0; 40.0]	0.886
CHF functional class	2 [1; 3]	1 [1; 2]	0.055
6MWT, m	300.0 [250.0; 320.0]	440.0 [350.0; 500.0]	<0.001
SHOKS score	5.0 [4.0; 7.5]	5.0 [4.0; 7.0]	0.361
Viral hepatitis B, C, or both, n (%)			
Echocardiographic parameters			
LVEF < 40%, n (%)	11 [30.5]	1 [0.8]	<0.001
LVEF, %	49.0 [37.0; 63.0]	54.0 [46.0; 64.0]	0.432
DDL, n (%)	16 [100]	63 [34.7]	0.501
LV myocardial mass index, g/m ²	89.0 [77.0; 120.5]	119.0 [99.0; 105.0]	0.067
LVH, n (%)	13 [36.1]	71 [57.2]	0.025
LV end-diastolic volume, mL	79.0 [44.0; 92.0]	102.0 [83.0; 113.0]	0.038
LV end-systolic volume, mL	30.0 [23.0; 47.0]	38.0 [32.0; 54.0]	0.383
Left atrial (LA) volume, mL	30.8 [24.7; 61.9]	31.6 [26.0; 45.4]	0.834
TPR, kPa·s/L	442.3 [321.4; 552.9]	238.3 [173.7; 355.2]	0.033
Enlarged LA volume, n (%)	22 [61.1]	49 [39.5]	0.021
PAH, n (%)	25 [69.4]	53 [42.7]	0.004
Mean pulmonary artery pressure, mmHg	17.0 [11.0; 33.0]	16.0 [14.0; 33.0]	0.922
E/e'	3.8 [2.6; 5.6]	6.9 [5.2; 9.9]	0.031
Laboratory parameters			
Transferrin, mg/dL	138.4 [83.8; 172]	92.1 [48.7; 127.0]	0.136
Ferritin, µg/L	152.0 [85.0; 256.0]	119.9 [65.9; 325.2]	0.559
Uric acid, µmol/L	87.2 [45.3; 184.7]	106.3 [61.1; 178.7]	0.799
Cystatin C, mg/L	4.97 [4.0; 5.2]	1.7 [1.27; 4.0]	<0.001
GFR, mL/min/1.73m ²	32.0 [10.0; 38.0]	41.0 [12.0; 59.0]	<0.001
NT-proBNP, pg/mL	392.0 [159.1; 1635.7]	364.8 [256.1; 801.9]	0.885
NT-proBNP > 1500 pg/mL; n (%)	19 [52.8]	15 [12.1]	<0.001
CP, mg/L	257.5 [239.0; 285.0]	135.5 [101.0; 162.0]	<0.001
ST2, pg/mL	104.6 [100.0; 110.2]	91.4 [77.9; 148.4]	<0.001

proximately 3% of total body copper. It functions as a “scavenger” of superoxide radicals, serving as an important antioxidant and acute-phase protein [9].

CP exhibits significant antioxidant properties, protecting cells from oxidative stress. It scavenges reactive oxygen species free radicals, including superoxide radicals, thereby preventing oxidative damage to cellular components. This is particularly important in inflammatory processes, where elevated free radical levels cause extensive tissue damage [1]. CP reduces platelet pro-aggregant properties, decreasing the activity of the inflammatory process [10].

The majority of CP is synthesised by hepatocytes, and a smaller fraction is made by lung epithelial cells [11]. In our study, many patients had hepatocellular insufficiency with frequent comorbidity with viral hepatitis, which explains the reduced CP levels observed across almost the entire patient cohort. Hepatocellular insufficiency, particularly in the context of hepatic fibrosis, is known to be accompanied by a marked decrease in CP levels [12]. In CHF, and

especially CHF with reduced EF, CP concentrations increase [13], which was also observed in our study — even against a background of initially low values, a rise in CP was noted with reduced EF.

We previously developed a non-invasive method for diagnosing the completion of the inflammatory process in the necrosis zone in myocardial infarction, and identified a link between CP concentration and CHF severity in myocardial infarction [14], where the relationship between CP and heart failure, as well as the increase in CP concentration with worsening CHF, were first demonstrated. In the present study, CP levels were reduced below reference values in all HIV-infected patients with CHF, however, a rise in CP was noted with reduced LVEF, as well as with elevated NT-proBNP ≥ 1500 pg/mL. Severe CHF with NT-proBNP ≥ 1500 pg/mL is accompanied by more intense inflammatory activity in HIV-infected patients [15].

CP is a contradictory agent. On the one hand, the ferroxidase properties of CP manifest as antioxidant activity through inhibition of free radicals, the abil-

ity to “capture and quench” superoxide anion radicals, and prevention of erythrocyte haemolysis. On the other hand, oxidative stress may substantially enhance the oxidase properties of CP as an acute-phase reactant [10]. According to the literature, CP levels exhibit divergent trends in various viral infections. An increase in CP activity has been described in post-COVID syndrome, explained by deficiency of copper and iron required for oxidative phosphorylation and cellular respiration [16]. Severe herpesvirus infection in the acute and remission stages is accompanied by a slight elevation in blood CP levels [17]. Severe influenza is associated with CP suppression, explained by a marked reduction in antioxidant defence. CP concentrations in plasma and cerebrospinal fluid were studied in HIV-infected patients in the context of cerebral disorders, when high CP levels were associated with pronounced cognitive impairment [18]. In unstable atherosclerotic plaques, outside of acute coronary syndrome, blood CP concentrations were reduced [19]. There are data indicating elevated blood CP concentrations in atherosclerosis, angina pectoris, and aortic aneurysm [20]. CP plasma levels may decrease following coronary artery bypass grafting [21]. The complexity of

evaluating the role of CP in mechanisms of oxidative stress lies in the possible manifestation of both its ferroxidase and oxidase properties. CP is an extracellular antioxidant and under normal conditions inhibits approximately 50% of blood lipid peroxidation products [22].

Thus, the obtained data demonstrate the complex and ambiguous role of CP in the pathogenesis of CHF in HIV-infected patients, where its level reflects the interplay between oxidative stress, inflammation, hepatic and renal dysfunction.

Conclusion

Plasma CP levels are markedly reduced in HIV-infected patients with CHF. This is attributable to suppression of antioxidant defence in the context of HIV infection, tissue hypoxia promoted by CHF, and hepatocellular insufficiency. Even against a background of low CP values, a tendency for CP to increase with worsening CHF severity is preserved. A plasma CP level ≥ 233.5 mg/L increases the probability of CHF with EF $< 40\%$ and NT-proBNP > 1500 pg/mL.

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References

- Obeagu EI, Chukwu PH. Ceruloplasmin and Iron Metabolism in HIV: A Review. *Elite Journal of HIV*, 2024; 2(6): 1-12.
- Deshmukh HM, Bhivapure RV, Patil VW et al. Serum Ceruloplasmin/Albumin ratio in HIV patients with anti retroviral therapy. *MedPulse International Journal of Biochemistry*, 2018; 8(1): 11-13.
- Ivanov AV, Valuev-Elliston VT, Ivanova ON et al. Oxidative Stress during HIV Infection: Mechanisms and Consequences. *Oxidative Medicine and Cellular Longevity*, 2016; 8 (91), 1-18.
- Tereshchenko SN, Galyavich AS, Uskach TM et al. Chronic heart failure. *Clinical guidelines 2020*. *Russian Journal of Cardiology*. 2020. 25(11): 311-374. Russian. DOI: 10.15829/1560-4071-2020-4083
- Goryacheva OG, Zubarev MA Arterial stiffness in patients with chronic heart failure infected with human immunodeficiency virus — clinical and prognostic relationships. *Medical Alliance*. 2025. 13(1): 71-77. Russian. DOI: 10.36422/23076348-2025-13-1-71-77
- Goryacheva OG, Terekhina NA, Terekhin GA The effect of alcohol dependence on the course of chronic heart failure in patients with HIV infection. *Ural Medical Journal*. 2023; 22(6): 104-111. Russian. DOI: 10.52420/2071-5943-2023-22-6-104-112
- Kishkun AA *Clinical laboratory diagnostics: textbook*. 2nd ed., revision and supplement. M.: GEOTAR-Media, 2019. 837 p. Russian
- Riccardi M, Myhre PL, Zelniker TA et al. Soluble ST2 in Heart Failure: A Clinical Role beyond B-Type Natriuretic Peptide. *J Cardiovasc Dev Dis*. 2023;10(11):468. DOI: 10.3390/jcdd10110468
- Terekhina NA, Goryacheva OG The Role of Oxidative Stress and Antioxidants in Occurrence of Myocardial Infarction and Chronic Heart Failure. *Medical University*. 2020; 3(4): 155-164. DOI: 10.2478/medu-2020-0019
- Obeagu EI Ceruloplasmin and Oxidative Stress in HIV: A Review. *Elite Journal of HIV*, 2023; 1(1): 29-42.
- Romuk E, Jacheć W, Zbrojkiewicz E et al. Ceruloplasmin, NT-proBNP, and Clinical Data as Risk Factors of Death or Heart Transplantation in a 1-Year Follow-Up of Heart Failure Patients. *J Clin Med*. 2020; 9(1): 137. DOI: 10.3390/jcm9010137
- Zeng DW, Dong J, Jiang JJ, Zhu YY, Liu YR. Ceruloplasmin, a reliable marker of fibrosis in chronic hepatitis B virus patients with normal or minimally raised alanine aminotransferase. *World J Gastroenterol*. 2016;22(43):9586-9594. DOI: 10.3748/wjg.v22.i43.9586

13. Lazar-Poloczek E, Romuk E, Rozentryt P et al. Ceruloplasmin as Redox Marker Related to Heart Failure Severity. *International Journal of Molecular Sciences*, 2021. 22(18): 10074. DOI: 10.3390/ijms221810074
14. Terekhina NA, Zubarev MA, Goryacheva OG, Reuk SE Patent No. 2362998 C1 Russian Federation, MPC G01N 33/50. Method of diagnostics of the end of the process of acute inflammation in the necrosis zone in myocardial infarction: No. 2008126367/15: applied for on 27.06.2008: published 27.07.2009. Russian
15. Goryacheva OG, Koziolova NA Risk factors for the development of severe chronic heart failure in patients infected with human immunodeficiency virus. *Russian Cardiological Journal*. 2021. 26(1): 65-72. Russian. DOI: 10.15829/1560-4071-2021-4275
16. Mikashinovich ZI, Telesmanich NR, Smirnova OB et al. Diagnostic significance of antioxidant defense indicators to assess the course of postcovidian syndrome. *Molecular Medicine*. 2023. 21(6): 48-53. Russian. DOI: 10.29296/24999490-2023-06-07
17. Reuk SE, Terekhina NA. Development of a method for evaluating the effectiveness of treatment of children with herpetic stomatitis. *Klin Lab Diagn*. 2020;65(5):269-274. Russian. DOI: 10.18821/0869-2084-2020-65-5-269-274
18. Kallianpur AR, Gittleman H, Letendre S et al.; CHARTER Study Group. Cerebrospinal Fluid Ceruloplasmin, Haptoglobin, and Vascular Endothelial Growth Factor Are Associated with Neurocognitive Impairment in Adults with HIV Infection. *Mol Neurobiol*. 2019; 56(5):3808-3818. DOI: 10.1007/s12035-018-1329-9
19. Stakhneva EM, Kashtanova EV, Polonskaya YaV et al. Correlation of proteins of the acute phase of inflammation in blood with the presence of unstable atherosclerotic plaques in coronary atherosclerosis. *Preventive Medicine*. 2023; 26(8): 76-81. Russian. DOI: 10.17116/profmed20232608176
20. Lazar-Poloczek E, Romuk E, Rozentryt P et al. Ceruloplasmin as Redox Marker Related to Heart Failure Severity. *Int J Mol Sci*. 2021; 22(18):10074. DOI: 10.3390/ijms221810074
21. Milyutina NP, Sidorov RV, Doltmurzieva NS et al. Assessment of patients who underwent aortocoronary bypass. *Actual issues of biological physics and chemistry*. 2021; 6(2): 300-305.
22. Puchkova LV, Kiseleva IV, Polishchuk EV et al. The Crossroads between Host Copper Metabolism and Influenza Infection. *Int J Mol Sci*. 2021; 22(11): e:5498. DOI: 10.3390/ijms22115498
23. Zeng DW, Dong J, Jiang JJ et al. Ceruloplasmin, a reliable marker of fibrosis in chronic hepatitis B virus patients with normal or minimally raised alanine aminotransferase. *World J Gastroenterol*. 2016; 22(43): 9586-9594. DOI: 10.3748/wjg.v22.i43.9586