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A THROMBOSPONDIN TYPE-1 MOTIF, MEMBER 13 (ADAMTS13) LEVELS DECREASE IN COVID-19 PATIENTS

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Abstract

Aim: Thrombotic pathologies develop at an increasing rate in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Understanding the pathologies that cause thrombosis in SARS-CoV-2 infection is important for developing prophylaxis strategies for the development of thrombosis and regulating treatment in cases of thrombosis. For all these reasons, we aimed to evaluate the levels of A disintegrin and metalloproteinase with a Thrombospondin Type-1 Motif Member 13 (ADAMTS13), in SARS-CoV-2 patients.

Material and Methods: The data of patients who were followed up in the intensive care unit due to coronavirus disease of 2019 (COVID-19) with lung involvement, who received respiratory support and pulse steroid therapy, and those who were followed up as outpatients without lung involvement were analyzed. Demographic data, laboratory results, and serum ADAMTS13 levels were recorded. These results were compared with those of the control group.

Results: ADAMTS13 levels were significantly lower in the COVID-19 group without lung involvement than in the control group (p=0.037). ADAMTS13 levels were significantly lower in the COVID-19 group with lung involvement than in the control group (p=0.016). There was no difference in ADAMTS13 levels between COVID-19 patients with and without lung involvement (p=0.797). There was no significant difference in ADAMTS13 levels between patients with and without chronic diseases in the COVID-19 group (p=0.40 for those without lung involvement; p=0.573 for those with lung involvement).

Conclusion: SARS-CoV-2 caused a decrease in ADAMTS13 levels. ADAMTS13 levels were decreased more in patients with lung involvement than in those without lung involvement. Decreased ADAMTS13 levels in COVID-19 may be a cause of the prothrombotic process.

Keywords: COVID-19, ADAMTS13, SARS-CoV-2, trombosis

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INTRODUCTION

In 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a novel coronavirus. In 2020, SARS-Cov-2 was declared a pandemic by the World Health Organization. The disease has spread rapidly worldwide, causing over 1.1 million deaths, and the number of cases and deaths is steadily increasing (1). The clinical presentation of patients with coronavirus disease of 2019 (COVID-19) may be asymptomatic, or some patients may progress to a more serious and systemic disease characterized by treatment-resistant fever, acute respiratory distress syndrome (ARDS) and acute lung injury. In addition, shock and multiple organ dysfunction are associated with significant mortality may develop (2-4).

Infections can trigger the development of autoimmune diseases. Therefore, it is important to understand the interaction between viral infections and immunogenic events. Rheumatologists are often involved in COVID-19 treatment management. The incidence of thrombosis increases in systemic inflammation and infectious diseases.

However, Helms et al. (5) among patients admitted to the intensive care unit with a diagnosis of ARDS, a higher thrombosis rate was found in patients with COVID-19-associated ARDS compared with those with non-COVID-19-associated ARDS. Predisposition to thrombosis that can be detected in many coronavirus patients has been termed coronavirus-associated coagulopathy. Coronavirus-associated coagulopathy may manifest itself as increased D-Dimer levels, increased prothrombin time, and decreased platelet counts (6).

A Thrombospondin Type-1 Motif, Member 13 (ADAMTS13) is a zinc-containing metalloproteinase enzyme that degrades von Willebrand factor (vWF). ADAMTS13 is not stored in cells but is secreted directly out of cells from the Golgi apparatus after synthesis. The release is constant and regular (7). If there is a decrease in the amount or activity of ADAMTS13, the breakdown of vWF into small fragments cannot occur. Large vWF multimers adhere to the endothelium and form chains. In microcirculation, in which circulation is slower, platelet aggregates are formed by the binding platelets to vWF multimers (8,9).

During acute inflammation and/or infection, ADAMTS13 synthesis may decrease due to the secretion of inflammatory cytokines. Indeed, Cao et al. (10) showed that interferon-gamma, interleukin (IL)-4 and tumor necrosis factor-alpha (TNF-α) inhibited ADAMTS13 synthesis without affecting vWF secretion. As a result, in the presence of inflammation, the degradation of vWF multimers is impaired, predisposing them to thrombosis (11).

The aim of this study was to determine ADAMTS13 levels in patients with SARS-CoV-2 infection with lung involvement who received steroid treatment and in patients without lung involvement who did not receive corticosteroid treatment.

MATERIALS AND METHODS

Approval for the study was obtained from the Fırat University Non-interventional Research Ethics Committee (approval number: 2021-3769, dated: 22.09.2021). The study groups consisted of 30 patients with pulmonary involvement who received pulse steroid therapy and 30 patients without pulmonary involvement diagnosed with COVID-19 according to the Republic of Turkey Ministry of Health COVID-19 diagnosis and treatment guidelines and 30 controls (12,13). Disintegrin and metalloproteinase with ADAMTS13 levels in serum samples from COVID-19 patients and healthy controls were assessed by Enzyme-Linked Immunosorbent Assay (ELISA) using the Human ADAMTS13 ELISA Kit obtained from Bioassay Technology Laboratory (Shanghai, China) in accordance with the study procedures specified in the manufacturer's catalog (catalog number: E3484Hu). The assay range of the kit was 0.05-15 ng/mL-15 ng/mL and the minimum measurable level (sensitivity) was 0.025 ng/mL. In addition, the Intra-Assay: CV value of the kit was <8%, whereas the Inter-Assay: CV value was <10%.

Demographic, clinical, and laboratory data of the patients were recorded. Patients were examined for thrombotic thrombocytopenic purpura (TTP) and Hemolytic Uremic Syndrome, and these diseases were excluded. Written informed consent was obtained from the patients or their legal representatives.

Statistical Analysis

The Statistical Package for Social Sciences version 22.0 package program was used to analyze the data obtained. The conformity of the data to the normal distribution was analyzed by Kolmogorov-Smirnov test. Continuous variables with normal distribution were analyzed using the independent samples t-test, and continuous variables without normal distribution were analyzed using the Mann-Whitney U test. Data are presented as mean ± standard deviation. p-values below 0.05 were considered statistically significant.

RESULTS

The mean ages of the patients included in the study was 57.12±14.96 years in the COVID-19 group without lung involvement and 66.93±10.46 years in the COVID-19 group with lung involvement. Gender distribution was similar between

the groups. When patients diagnosed with COVID-19 were compared with the control group, ADAMTS13 was found to be lower in patients diagnosed with COVID-19 than in the control group (p=0.006) (Table 1). When the groups were compared, the ADAMTS13 level was lower in the COVID-19 group without lung involvement than in the control (p=0.037) (Table 2). In the COVID-19 group with lung involvement, ADAMTS13 levels were lower than those in the control group (p=0.016). ADAMTS13 levels were lower in the COVID-19 group with lung involvement than in the outpatient COVID-19 group, but there was no statistical significance (p=0.797) (Table 1). When the ADAMTS13 levels were compared, they were lower in the non-survivors than in the survivors, but no significant difference was found (p=0.110) (Table 3).

Lymphocyte counts were lower in the COVID group with lung involvement (p=0.003). However, leukocyte counts were higher with neutrophil dominance in the covid group with lung involvement (p<0.001). D-Dimer levels were higher in the covid group with lung involvement (p=0.011), fibrinogen levels were higher in the covid group with lung involvement (p=0.865) and international normalized ratio was higher in the covid group with lung involvement (p=0.362). Among the infectious parameters, C-reactive protein was higher in the COVID group with lung involvement (p<0.001) and procalcitonin was higher in the COVID group with lung involvement (p=0.560) (Table 4).

Clinical and laboratory data for patients with COVID-19 with lung involvement according to the presence of chronic disease are presented in Table 5.

There were no clinical thrombosis findings or data detected in the COVID-19 group with or without lung involvement. When the groups were analyzed in terms of the presence of chronic diseases, 13.3% of the group without lung involvement had hypertension and 13.3% had hypertension and diabetes. In the lung involvement group, 20%, 16.6%, 16.6%, and 3.3% had hypertension, 16.6% had hypertension and ischemic heart disease, 6.6% had hypertension and chronic obstructive pulmonary disease, and 3.3% had hypertension and chronic renal failure. In patients with COVID-19 with lung involvement, the ADAMTS13 level was higher in patients with chronic disease, but the difference was not statistically significant difference (p=0.573) (Table 5).

In patients with COVID-19 without lung involvement, ADAMTS13 levels and laboratory parameters were evaluated in terms of chronic disease, and no statistically significant difference was observed (Table 6).

DISCUSSION

In this study, we investigated the ADAMTS13 levels in patients with SARS-CoV-2 infection without pulmonary involvement and those with pulmonary involvement who were followed up in

Table 1. Age, sex, and ADAMTS13 data of all COVID patients versus controls

	Control (n=30)	COVID-19 (n=60)	p-value
Age (years)	45.89	61.53	<0.001
Gender (Male/Female)	15/15	30/30	0.035
ADAMTS13, ng/mL	1.26±0.72	0.89±0.53	0.006

ADAMTS13: A Thrombospondin Type-1 Motif, Member 13, COVID-19: Coronavirus disease of 2019

Table 2. Age, sex, and ADAMTS13 level in the control and COVID groups

	Control (n=30)	COVID-19 without lung involvement (n=30)	COVID-19 with lung involvement (n=30)	P1	P2	P3
Age (years)	45.89±17.199	57.12±14.96	66.93±10.46	0.009	0.001	0.006
Gender (Male/Female)	15/15	15/15	15/15	0.177	0.185	0.897
ADAMTS13, ng/mL	1.26±0.72	0.91±0.58	0.87±0.49	0.037	0.016	0.797

P1: Control and COVID group without lung involvement, P2: Control and COVID group with lung involvement, P3: COVID group without lung involvement and covid group with lung involvement, ADAMTS13: A Thrombospondin Type-1 Motif, Member 13, COVID-19: Coronavirus disease of 2019

Table 3. ADAMTS13 levels between non-survivors and survivors in the COVID-19 group

	Non-survivors (n=24)	Survivors (n=36)	p-value
ADAMTS13, ng/mL	0.77±0.44	0.98±0.59	0.110

ADAMTS13: A Thrombospondin Type-1 Motif, Member 13, COVID-19: Coronavirus disease of 2019

Table 4. Laboratory data in the COVID-19 group without and with lung involvement

	COVID-19 without lung involvement (n=30)	COVID-19 with lung involvement (n=30)	p-value
HGB, gr/dL	13.69±1.81	12.97±2.27	0.195
Lym, 10^3/µL	1.14±0.56	0.75±0.33	0.003
Neu, 10^3/µL	3.54±2.28	8.25±4.21	0.000
PLT, 10^3/µL	186.17±54.31	209.85±93.06	0.246
WBC, 10^3/µL	5.13±2.39	9.67±4.35	0.000
ALT, µ/L	28.12±15.16	72.22±130.94	0.082
AST, µ/L	32.26±14.24	113.63±248.77	0.090
CRP, mg/dL	29.70±30.22	162.55±125.10	0.000
DD, ng/mL	0.80±0.52	2.57±3.29	0.011
Ferritin, mL/ng	215.00±162.96	598.93±431.57	0.005
Fibrinogen, mg/dL	4.69±0.97	4.82±2.33	0.865
INR	1.01±0.06	1.05±0.15	0.362
Cre, mg/dL	0.97±0.20	1.38±1.44	0.148
Procalcitonin, ng/mL	0.061±0.028	3.72±12.22	0.560
Urea, mg/dL	35.15±14.36	68.10±41.72	0.000

HGB: Hemoglobin, Lym: Lymphocyte, Neu: Neutrophil, PLT: Trombocyte, WBC: White blood cell count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, DD: D-Dimer, INR: International normalized ratio, Cre: Creatinine, LDH: Lactate dehydrogenase

Table 5. Variation of parameters among patients with covid-19 and lung involvement receiving pulse steroid depending on the presence or absence of chronic disease.

	Chronic disease is absent (n=8)	Chronic disease is present (n=22)	p-value
ADAMTS13, ng/mL	0.81±0.55	0.91±0.45	0.573
Age (years)	63.38±12.23	68.42±9.59	0.261
Clinical hospitalization days	7.13±14.55	1.74±3.66	0.136
Symptom duration	31.00±14.94	20.53±9.64	0.039
HGB, gr/dL	13.17±0.69	12.88±2.70	0.773
Lym, 10^3/µL	0.66±0.18	0.79±0.37	0.366
PLT, 10^3/µL	239.63±111.84	197.32±84.17	0.289
WBC, 10^3/µL	8.56±3.80	10.14±4.58	0.399
AST, µ/L	75.75±47.63	129.57±295.98	0.617
ALT, µ/L	55.87±18.89	79.10±156.40	0.682
CRP, mg/dL	192.83±129.12	149.80±124.68	0.425
DD, ng/mL	3.00±3.53	2.39±3.27	0.667
Ferritin, mL/ng	569.25±354.21	611.42±468.71	0.822
Fibrinogen, mg/dL	5.77±2.23	4.48±2.33	0.257
INR	1.00±0.08	1.07±0.17	0.292
Procalcitonin, ng/mL	1.62±3.76	4.49±14.15	0.605

ADAMTS13: A Thrombospondin Type-1 Motif, Member 13, HGB: Hemoglobin, Lym: Lymphocyte, Neu: Neutrophil, PLT: Trombocyte, WBC: White blood cell count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, DD: D-Dimer, INR: International normalized ratio

Table 6. Variation in parameters among COVID patients without lung involvement depending on the presence or absence of chronic disease

	Chronic disease is absent (n=17)	Chronic disease is present (n=13)	p-value
ADAMTS13, ng/mL	0.84±0.62	1.01±0.52	0.400
Age	53.55±14.55	62.62±14.42	0.089
Clinical hospitalization days	4.50±4.38	3.15±3.28	0.367
Symptom duration	7.25±2.95	6.23±2.16	0.309
HGB, gr/dL	14.16±1.44	13.10±2.09	0.119
Lym, 10^3/µL	1.21±0.53	1.05±0.60	0.444
PLT, 10^3/µL	189.63±35.40	181.92±72.66	0.711
WBC, 10^3/µL	5.38±2.86	4.831.72	0.544
AST, µ/L	32.73±12.84	31.63±16.49	0.844
ALT, µ/L	32.00±16.88	22.96±11.18	0.121
CRP, mg/dL	27.55±24.91	32.57±37.15	0.672
DD, ng/mL	0.76±0.36	0.84±0.64	0.824
Ferritin, mL/ng	275.00±204.16	172.14±125.53	0.303
Fibrinogen, mg/dL	4.56±1.33	4.80±0.66	0.710
INR	1.06±0.08	0.99±0.05	0.204

ADAMTS13: A Thrombospondin Type-1 Motif, Member 13, HGB: Hemoglobin, Lym: Lymphocyte, PLT: Trombocyte, WBC: White blood cell count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, DD: D-Dimer, INR: International normalized ratio

intensive care and received pulse steroid therapy according to the Ministry of Health regulations.

In various studies, high rates of venous thrombotic events have been observed in patients with SARS-CoV-2. In China, venous thrombosis was reported at a rate of 25% in a group of 81 patients who were not treated with routine thromboprophylaxis (14). In a study by Middeldorp et al. (15), venous thrombosis was detected in 35 of 75 intensive care unit patients who received thrombosis prophylaxis. In addition, coagulopathy and abnormal coagulation parameters can lead to increased mortality (16). For all these reasons, it is important to recognize the etiology of thrombosis in patients with SARS-CoV-2 to reduce mortality.

SARS-Cov-2 infects the pulmonary excess alveolar epithelium and subsequently the endothelium via the angiotensin-converting enzyme 2 (ACE-2) receptor. vWF multimers are released from damaged endothelium, leading to excessive cytokine release develops. Because the virus enters the cell via ACE-2, ACE-2 deficiency develops and angiotensin 1-7 is reduced (anti-thrombotic, anti-inflammatory, anti-fibrotic, vadodilator and reactive oxygen species neutralizer). Hyperinflammation predominates in the proinflammatory and prothrombotic phases, resulting in the release of vWF, decreases in angiotensin 1-7, and hyperinflammation leading to the development of thrombosis (17-19).

Excessive vWF release from damaged endothelium may decrease the amount of ADAMTS13 due to depletion. Neutrophil extracellular traps (NETs) are active in the COVID-19 prothrombotic phase. Various stimuli such as bacteria, fungi, viruses, parasites, activated platelets, and certain chemicals can induce NET formation, which is known as NETosis. NETs are composed of DNA, histones, and proteins, as well as neutrophil elastase (NE), myeloperoxidase, cathepsin G, proteinase 3, metalloproteinase 9, and human neutrophil peptide 1. In NETosis, ADAMTS13 is inactivated by NE and other proteases and its levels are decreased (20-22).

In addition, IL-8, TNF-α, and IL-6 stimulate the release of ultra-large vWF multimers, leading to the formation of platelet arrays under flow conditions, and IL-6 prevents ADAMTS13 from cleaving vWF. It is known that IL-6 levels are elevated in patients diagnosed with COVID-19. In our study, the significantly lower ADAMTS13 level in the outpatient COVID-19 group compared to the control group may be due to an increase in the amount of vWF due to IL-6 release and a decrease in ADAMTS13 as a result of consumption (22-24). Similar to our study, another study showed that ADAMTS13 activity decreased in COVID-19 patients (25).

In addition, another study reported a relative decrease in ADAMTS13 levels (26). Martinelli et al. (27) found an increase in D-Dimer levels in patients with SARS-CoV-2, an inverse correlation between D-Dimer levels and ADAMTS13 levels, and a relative decrease in ADAMTS13 levels, although not statistically significant.

In our study, the ADAMTS13 level was lower in the COVID-19 group without lung involvement than in the control group. The decreased expression of ADAMTS13 may be explained by disease-specific mechanisms and mechanisms observed in other infections and inflammations.

In Disseminated Intravascular Coagulopathy (DIC), tissue factor expression increases and microthrombus formation is observed as a result of excessive cytokine release, supporting the hypothesis that cytokine increase decreases ADAMTS13 levels. Proteases such as thrombin and plasmin degrade ADAMTS13 in DIC and decrease its amount. Mancini et al. (28) showed that ADAMTS13 levels decreased with increasing lung involvement. Similarly, in our study, ADAMTS13 levels were lower in the group with lung involvement than in the control and non-lung involvement.

One study showed that α1-antitrypsin treatment was effective in preventing the appearance of unusually large vWF multimers in the circulation, but not in preventing TTP recurrence. This suggests that granulocyte elastase cleaves ADAMTS13, thereby reducing its activity and quantity. In other words, in sepsis, proteases may degrade ADAMTS13 and reduce its activity and quantity (29).

Antibodies against ADAMTS13 are known. This condition is defined as the cause of acquired TTP in patients with TTP. Binding of autoantibodies to ADAMTS13 either inhibits ADAMTS13 activity or induces clearance of the resulting immunocomplexes. As a result, the number of ADAMTS13 decreases, vWF multimers increase in the circulation, and ADAMTS13 immunocomplexes with reduced activity appear. As a result, there is a predisposition to thrombosis (30,31).

Study Limitations

In our study, the limitation of the study was that the ADAMTS13 level was not measured before pulse steroid treatment in patients with COVID-19 and lung involvement. The change in ADAMTS13 level according to the level of lung involvement was not studied, and the ADAMTS13 activity was not assessed. In addition, the statistically significant difference in age between the control and patient groups was a limitation of our study

CONCLUSION

In our study, the significant decrease in ADAMTS13 levels in the COVID-19 group without lung involvement indicates that there may be a predisposition to thrombosis even in the initial stage of COVID-19 and in mild cases without lung involvement. This picture calls into question the necessity of anti-thrombotic therapy even in mild cases of COVID-19. In patients with lung involvement, ADAMTS13 levels were lower than those without lung involvement, indicating that lung involvement in COVID-19 patients may increase susceptibility to thrombosis. In addition, the lower ADAMTS13 levels in patients who died, although not significant, suggests that the decrease in ADAMTS13 levels indicates that the prognosis will worsen.There are many examples of the mechanism of thrombosis development in patients with COVID-19. The use of steroids may reduce the development of thrombosis by suppressing the inflammatory and immunologic pathways. The use of vWF antibodies, IL-1, and IL-6 antibodies, or recombinant ADAMTS13 as novel treatment strategies may reduce thrombosis, and new studies are needed in this respect.

Footnote

Ethics Committee Approval: Ethical approval for the study was obtained from the Fırat University Non-interventional Research Ethics Committee (approval number: 2021-3769, dated: 22.09.2021).

Informed Consent: Written informed consent was obtained from the patients or their legal representatives.

Authorship Contributions

Surgical and Medical Practices: U.A., B.Ö., A.K., Concept: U.A., D.D., F.A., R.F.A., B.Ö., A.K., Design: U.A., D.D., F.A., R.F.A., B.Ö., A.K., Data Collection or Processing: U.A., F.A., R.F.A., B.Ö., A.K., Analysis or Interpretation: U.A., F.A., R.F.A., B.Ö., A.K., Literature Search: U.A., F.A., R.F.A., B.Ö., A.K., Writing: U.A., D.D., F.A., R.F.A., B.Ö., A.K.

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