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Original Research

Asymmetric Dimethylarginine in COPD Exacerbation

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Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) is a disease with progressive airway limitation. The asymmetric dimethylarginine (ADMA) molecule is known to be effective in airway inflammation and remodeling. We investigated the relationship between ADMA and COPD, and its role in the course of the disease in cases with exacerbation.

Methods: This single-center study performed in our patient clinic included 56 patients (57.1% of males) with median age 67 (41–88) presented with COPD exacerbation and 26 sex-matched healthy controls. ADMA, white blood cell count, eosinophil, neutrophil, lymphocyte, C-reactive protein, fibrinogen, oxygen saturation%, and pulmonary function test values were compared.

Results: ADMA values were significantly higher (516.93 vs. 320.05 median, $p<0.05$) in the COPD group compared to the control group. No significant difference was demonstrated in ADMA concentrations according to Global Initiative for Chronic Obstructive Lung Disease Stages ($p>0.05$). In the receiver operating characteristic analysis to estimate the predictive power of COPD, the cutoff ADMA concentration >301 ng/ml was found to be able to distinguish COPD patients in all cases.

Conclusion: ADMA levels increase with complex mechanisms in COPD. It can be a significant indicator of the disease. However, more extensive research is needed for its use as a biomarker in severity and progression of COPD.

Keywords: Asymmetric dimethylarginine, Chronic obstructive pulmonary disease, Exacerbation

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease but is one of the top three causes of death in the developing countries.[1] In these patients, it is known that systemic inflammatory markers increase with airway limitation, which is associated with impaired lung function.[2] Chronic inflammation can lead to oxidative stress, resulting in permanent structural changes such as emphysema or the development of fibrosis in small airways.[1] Examples of oxidative stress are infections, hypoxia, inflammation, smoking, and toxic gases.[3] Asymmetric dimethylarginine (ADMA) is a natural analog of L-arginine. It is a competitive inhibitor of all three isoforms of nitric oxide synthetase (NOS) and plays a reducing function on the formation of nitric oxide (NO).[4] NOS is expressed in the lungs, contributes to the production of intracellular oxidants, and enables NO production from the L-arginine substrate. NO is important for airway tone and its functions and has a strong vasodilator effect. In hypoxic cases, NO-dependent vasodilatation is impaired. NO reduction results in airway obstruction and exacerbation.[5-6] Lungs are the major source for ADMA formation, and therefore, impairment of ADMA regulation in the lungs and

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its increase in systemic circulation may result in conditions such as pulmonary arterial hypertension, idiopathic pulmonary fibrosis, asthma, and COPD.[7]

Airway obstruction was formed by the increasing collagen formation; this suggests that ADMA may play a role in airway diseases.[8] L-Arginine metabolism is crucial for collagen production in the lung and L-arginine pathway molecules have been suggested as prognostic markers for exacerbation of COPD episode.[9] Airway inflammation and oxidative stress increase during COPD exacerbations triggered by viral or bacterial respiratory infections, which negatively affect morbidity and mortality. Studies show that 80% of COPD exacerbations can be treated by adding bronchodilators, corticosteroids, and antibiotics on an outpatient basis.[10] In our study, we measured C-reactive protein (CRP), fibrinogen, white blood cell count, neutrophil, eosinophil, lymphocyte, and ADMA values to evaluate the inflammatory and oxidative process in patients who were admitted to our outpatient clinic with COPD exacerbation symptoms. Furthermore, we compared them with pulmonary function test (PFT) parameters and oxygen saturation% (SO_2%) values and examined the relationship between them. Our aim was to investigate the possible new treatment modalities that can be developed through the arginine metabolism in chronic pulmonary diseases alternative to inhalation therapies.

Methods

Fifty-six consecutive COPD patients (32 males and 24 females) with exacerbation symptoms who were admitted to Chest Diseases Outpatient Clinic between April 2019 and May 2019 were enrolled in this study. Twenty-six individuals (14 females and 12 males) over the age of 40, healthy, non-smoking, were included as a control group. They had previous diagnosis of COPD, and all were under treatment. The diagnosis of COPD was based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria; with post-bronchodilator FEV1 <80% (forced expiratory volume 1 s) and %FEV1/FVC ratio <70% (forced expiratory volume 1 s/forced vital capacity). These were considered as an airflow obstruction in PFT and clinical evaluation.[1] Dyspnea, coughing, and increase in sputum purulence were determined as exacerbation criteria in COPD patients.[11]

Our patients had diagnosis of only mild-to-moderate exacerbation, and their follow-up was decided to be done in the outpatient clinic. The patient and control groups were selected from non-smokers, and non-smoking was determined as a criterion for those who quit smoking for at least 6 months. Patients with bronchiectasis, pulmonary embolism, pulmonary tuberculosis, interstitial pulmonary disease, pneumonia, congestive heart failure, coronary artery disease, uncontrollable hypertension, diabetes mellitus, chronic renal failure, chronic liver disease, and rheumatological diseases and malignancies were excluded from the study.

PFTs were performed at least 3 times by the same experienced technician with MIR-SPIROLAB III system, COLOUR LCD Rome, Italy. The predicted normal reference values were obtained, the best of the PFT results were evaluated according to the American Thoracic Society criteria.[8] Forced vital capacity (FVC% predicted) as a percent of predicted value, forced expiratory volume in the first second (FEV1% predicted), and ratio of FEV1 to FVC (FEV1/FVC %) were measured. Patients were staged according to GOLD 2021 guideline as:

FEV1 ≥80% GOLD Stage 1, 50% <FEV1 <80% GOLD Stage 2, 30% <FEV1 <50% GOLD Stage 3, and FEV1 ≤30% GOLD Stage 4.

The patients' blood was taken in the morning after 12 h of fasting. SO2% values were measured by pulse oximeter at the fingertips of the patient and the control group. For ADMA, venous blood samples were taken into containing vacuum tubes (BD, Plymouth, England). After the samples were kept at room temperature for 2 h, they were centrifuged at + 4°C at 1000 × g for 15 min. Separated serums were kept at −80°C until the analysis. Serum ADMA levels were analyzed by enzyme-linked immunosorbent assay (ELISA) method using ADMA ELISA kit (Elabscience Pharmaceuticals, Houston, Texas, USA). The measurable range was 15.63–1000 ng/mL, sensitivity <9.38 ng/mL, and coefficient of variation was <10%. The patients and control groups were informed about the study and their written consent was obtained. The study was carried out by obtaining the approval of the Ethics Committee of the hospital (1212 No-16/04/2019) and complying with the Helsinki Declaration.

Statistical Analysis

Statistical analysis of the data was performed in IBM SPSS Statistics version 22 program. (IBM, New York, USA) Pearson Chi-square, Fisher's exact test, and Chi-square trend tests were used for comparing categorical data between groups. Independent sample t-test was applied for comparing continuous variables with parametric properties between groups. Kolmogorov–Smirnov and Shapiro–Wilk were used for the comparison of non-parametrically continuous variables, Mann–Whitney U-test was used for the comparison of non-parametrically continuous variables between two groups and Kruskal–Wallis H (Mann–Whitney U-test with post hoc Bonferroni correction) was used for the comparison of non-parametrically continuous variables more than

2 groups. The relationship between ADMA values and other variables was evaluated with Spearman's rho analysis. Linear regression was used for the effect of variables on ADMA values. The predictive power of variables for the diagnosis of COPD was evaluated by receiver operating characteristics (ROC) analysis, and p<0.05 was considered as statistically significant.

Results

Thirty-two male (57.1%) out of 56 total patients who were admitted to the outpatient clinic met the inclusion criteria of the study. The mean±standard deviation age for COPD patients was 64.91±10.32 and 60.42±5.38 for healthy group. COPD patients are grouped according to GOLD 2021 criteria based on FEV1 % (pred.) values in spirometry: 24 patients (42%) were GOLD Stage 2, 25 patients (41%) were GOLD Stage 3, and 7 patients (16%) were defined as GOLD Stage 4.

In Table 1, The characteristics of the cases are given.

There was no statistically significant difference between the groups in terms of the gender (p>0.05), but the control group cases were younger than the COPD group cases (p=0.022).

According to GOLD, adding only short-acting bronchodilators to treatment are appropriate for mild exacerbation, while antibiotics and/or oral corticosteroids may be added in moderate exacerbations.[1] Nine patients (16%) used long-acting antimuscarinic (LAMA), 10 (17%) used long-acting beta-agonist (LABA), 12 (21%) used LAMA-LABA combination, and 25 (44%) used LAMA-LABA and inhaled corticosteroid combination. Three patients (5%) received long-term oxygen therapy at home (data not shown).

The laboratory findings and PFT values were outlined according to the groups and SO_2%, ADMA, neutrophil, and lymphocyte levels were found to be significantly higher in COPD group than the control group (p<0.05), as shown in Table 2. The median serum ADMA level in COPD patients (516.93 [146.24–4819.99]) was higher than the control group (320.05 [107.23–649.07]) (p=0.000).

In Table 3, the COPD patients were classified according to

Table 1. The characteristics of the cases by groups

	COPD group		Control group		X^2	p
	n	%	n	%		
Gender						
Male	32	57.1	12	46.2	0.862	0.353
Woman	24	42.9	14	53.8		
	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)	Z	p
Age	64.91±10.32	67 (41–88)	60.42±5.38	60.5 (50–68)	–2. 284	0.022

Independent sample t-test was used for age, Pearson Chi-square was used for gender, data are presented as n, mean (standard deviation, SD), or n (%).

Table 2. The laboratory findings and PFT values of cases by groups

	COPD group Median (Min.-Max.)	Control group Median (Min.-Max.)	Z	p
SO2%	95 (93–98)	98 (96–99)	–6.689	0.000
ADMA	516.93 (146. 24–4819. 99)	320.05 (107.23–649.07)	–3.563	0.000
CRP	4.85 (0.4–139. 7)	3.2 (0.8–50.4)	–1.505	0.132
White blood cell count	8,25 (0. 37–13. 09)	7.11 (4.6–13.23)	–1.639	0.101
Eosinophil	0.3 (0. 01–6. 64)	0.05 (0.01–1.7)	–1.219	0.223
Neutrophil	4.3 (0.1–11.5)	1.5 (0.02–9.1)	–2.230	0.026
Lymphocytes	2.5 (1.2–3.9)	1.55 (1.1–2.9)	–3.213	0.001
Fibrinogen	3.3 (2.1–4.5)	3 (2.1–4.35)	–1927	0.054
FVC%	74 (35–102)	92.5 (61–114)	–3.643	0.000
FEV1/FVC%	68.5 (39–70)	99 (78–116)	–7.242	0.000
FEV1%	46.5 (21–70)	84 (70–110)	–7.303	0.000

Mann–Whitney U-test analysis.

Table 3. Distribution of laboratory findings by GOLD stages in patients with COPD

	COPD/GOLD stage			X^2	p
	Stage 2, n=24 Median (Min.-Max.)	Stage 3, n=25 Median (Min.-Max.)	Stage 4, n=7 Median (Min.-Max.)		
SO2%	95 (93–98)	95 (93–97)	95 (93–97)	0.591	0.744
ADMA	516.93 (151.43–2682.08)	443.04 (146.24–4819.99)	556.03 (336.4–833.13)	0.117	0.943
CRP	7.64 (1.5–139.7)	4.9 (0.8–112)	1.4 (0.4–53.1)	5.511	0.064
White blood cell count	8.62 (4.28–13.09)	8.14 (5.12–12.79)	6.86 (0.37–11.38)	0.615	0.735
Eosinophil	0.18 (0.03–6.64)	0.4 (0.01–0.7)	0.3 (0.04–0.9)	1.854	0.396
Neutrophil	1.5 (0.1–8.98)	5.2 (0.5–11.5)	6 (0.7–7.08)	2.075	0.354
Lymphocytes	2.5 (1.2–3.9)	2.3 (1.2–3.8)	2.6 (1.23–2.8)	1.656	0.437
Fibrinogen	3.3 (2.1–4.5)	3.2 (2.1–4.2)	3.3 (3–4.4)	1.246	0.536

Kruskal–Wallis H analysis (data are presented as n, patients were staged according to GOLD guideline).

GOLD stages and the laboratory findings were analyzed; it was noted that ADMA levels and other inflammatory parameters did not differ according to COPD/GOLD stages (p>0.05). The median ADMA levels for Stage 2, Stage 3, and Stage 4 were 516.93, 443.04, and 556.03 (p=0.943), respectively.

When ADMA levels, with laboratory findings and PFT values of all cases, were examined by the Spearman's rho correlation, inverse and statistically significant correlation were found between ADMA levels and FEV1% (r=–0.289, p=0.009) and FEV1/FVC% (r=–0.411, p=0.000) values (Table 4).

In the univariate linear regression analysis made for variables was considered to be effective on ADMA levels, only the effect of FEV1% (Beta = –0.260, p=0.018) and FEV1/FVC% (Beta = –0.262, P = 0.018) variables on ADMA levels was found to be statistically significant and negatively associated (Table 5).

Discussion

Secondary to hypoxia in COPD causing both the increase of NOS, one of the oxidative stress enzymes, and ADMA, a uremic toxin, and the decrease of NO in the lungs was shown.[12] In compliance with the literature, the key point of our study was that ADMA levels were found to be higher in outpatients who were admitted to hospital with mild-to-moderate COPD exacerbation compared to healthy group (516,93 vs. 320.05 [p<0.05]). In Spearman's rho correlation between ADMA and the laboratory findings, FEV1% and FEV1/FVC% values were inversely correlated with ADMA concentrations in our study (p=0.009 and p=0.000 respectively). Furthermore, it was noted that ADMA did not differ significantly in the group with COPD according to GOLD stages (p=0.943). In our study, the SO2% values of the COPD patients, which were measured by pulse oximetry in the outpatient clinic were not found to correlate with ADMA levels. As the lungs serve as the major source for ADMA,

Table 4. Correlation of ADMA levels and laboratory findings and PFT values of the cases

	All cases		COPD group		Control group	
	p	r	p	r	p	r
SO2%	–0.207	0.062	0.147	0.279	0.090	0.662
CRP	0.180	0.105	0.146	0.283	0.055	0.789
WBC	0.129	0.249	0.048	0.725	0.169	0.410
Eosinophil	0.136	0.223	0.029	0.830	0.099	0.632
Neutrophil	0.174	0.118	0.220	0.103	–0.247	0.225
Lymphocytes	0.147	0.188	0.061	0.653	–0.163	0.426
Fibrinogen	0.152	0.172	0.096	0.479	–0.005	0.979
FVC%	–0.074	0.510	0.046	0.737	0.245	0.228
FEV1%	–0.289	0.009	0.019	0.889	0.334	0.095
FEV1/FVC%	–0.411	0.000	–0.155	0.253	–0.075	0.715

Spearman's rho correlation.

Table 5. Univariate linear regression analysis results made for variables considered to be effective in ADMA levels in the COPD and control group

	B	Beta	p	95.0% CI	
Age	–0.158	–0.002	0.984	–15.914	15.598
SO2%	–51.476	–0.138	0.215	–133.439	30.488
CRP	6.111	0.196	0.078	–0.699	12.921
WBC	19.302	0.066	0.553	–45.224	83.828
Eosinophil	–8.637	–0.011	0.924	–189.058	171.784
Neutrophil	45.066	0.204	0.066	–3.093	93.226
Lymphocytes	33.768	0.041	0.712	–147.808	215.344
Fibrinogen	233.737	0.190	0.087	–35.144	502.618
FVC%	–4.968	–0.148	0.185	–12.357	2.420
FEV1%	–7.752	–0.260	0.018	–14.160	–1.344
FEV1/FVC%	–10.730	–0.262	0.018	–19.536	–1.924

B: Regression constant. Beta: Square root of correlation. CI: Confidence interval.

even the small elevation in systemic ADMA concentrations may reflect eloquent changes in pulmonary compartment. The accumulation of ADMA in the airways of the COPD patients has important functional consequences, leading to airway obstruction in these patients by tissue remodeling. Our results were partially correlated with the previous studies. According to Vogeli et al.,[13] no relationship was noted between ADMA levels and the severity of COPD on the long-term clinical results of COPD acute exacerbation. They also showed the effect of ADMA only on the long-term mortality of COPD exacerbation patients who were followed up in the hospital. Zinellu et al.[14] in their study reported that ADMA levels did not differ between Stage 1 and Stage 2 COPD patients and the control group. Arginine metabolism affects airway tone and functions with its impact on NOS pathway and NO formation. These studies emphasize that it is ADMA/arginine ratio rather than the increased ADMA levels, related to the severity of COPD is of consideration. Aydin et al.[15] found a strong relationship between ADMA and COPD/GOLD stages, which were determined by post-bronchodilator FEV1% in COPD patients. They dedicated this to the role of ADMA and NO on remodeling in COPD airway limitation. Both increases in ADMA levels and expression of arginase activity were reported previously in COPD cases.[16] Furthermore, a strong negative correlation between arginase and FEV1% was demonstrated and proposed that arginase inhibition prevented airway inflammation and remodeling in animal models with COPD.[17] In a study of Telo et al.,[18] while healthy control group and COPD patients without pulmonary hypertension had no higher but similar concentrations of ADMA, higher concentrations of ADMA were found only in the group of COPD patients with pulmonary hypertension. Additionally, they observed no significant difference in ADMA concentrations between the COPD groups who were staged according to GOLD Guidelines.

It is known that neutrophil count increases as COPD worsens.[19] In our study, SO_2%, ADMA, neutrophil, and lymphocyte levels were found to be significantly higher in the COPD group than the control group (p=0.000, p=0.000, p=0.026, and p=0.001, respectively). However, no correlation was shown between ADMA and other inflammatory markers. CRP as a biomarker is not enough to explain infectious or non-infectious causes of exacerbation in COPD patients, but follow-up values may be a guide in the management of exacerbation. In the ROC analysis of the COPD estimation power of variables in all cases (healthy and patient group), ADMA was found to be a good indicator in distinguishing COPD patients (p=0.03) (Fig. 1) from the healthy control group in our study. Differently, Csoma et al.[20] previously found correlation between ADMA, blood neutrophil percentage and age, in both stable COPD patients and COPD exacerbation group. This supports the impaired eNOS function in COPD, whereas they did not detect correlation with lung function, blood gas parameters, and CRP in their study. Tajti et al.[16] in their study group of COPD showed strong correlation between ADMA; Raw the airway resistance indicator, and the FEF25–75% showing small airway functions, and CRP the systemic inflammation marker. Costanzo et al.[21] reported no difference for ADMA or CRP levels between COPD and the control group in their study which is consistent with ours. Exacerbations of COPD are heterogeneous events with complex etiopathology which some parts of it still remain unknown. For the definition of COPD exacerbations, Barnes et al.[22] proposed that elevated levels of blood neutrophil and CRP counts even without any clinical evidence of pneumonia or heart failure should be taken as objective parameters. As COPD patients frequently have comorbidities, in clinical practice, it should

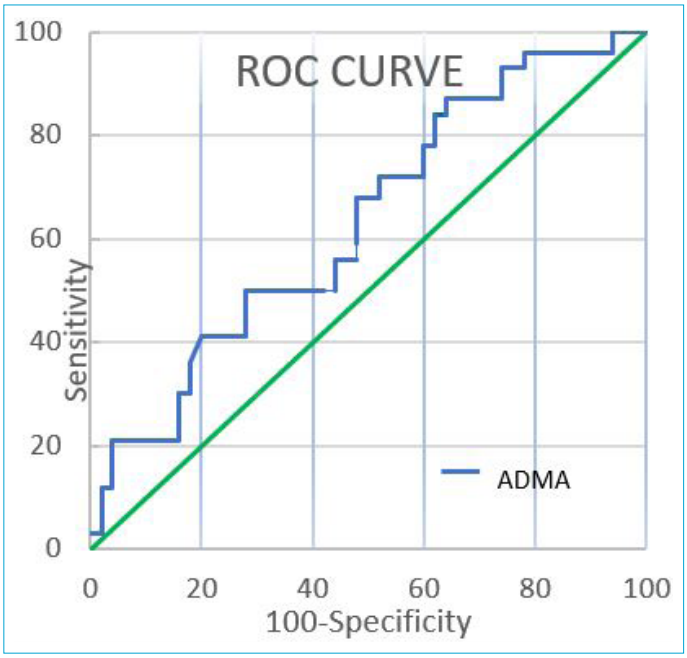

Figure 1. The receiver operating characteristic (ROC) curve analysis made for the ability to estimate COPD disease in all cases; the area under curve (AUC) value was detected as 95% confidence interval (CI), 0.636 (0.522–0.739), p=0.03, for ADMA. The optimal cutoff value specified for ADMA was 301.4 ng/ml (with 87.5% sensitivity and 36% specificity, respectively) and was found to be statistically significant.

be taken into consideration that exacerbations are not only worsening the respiratory symptoms but also may be the cause of deterioration of the chronic disease or both. These comorbidities contribute to poor clinical outcome, the major focus in the management of exacerbations should comprise this point. Urban et al.[23,24] demonstrated no significant difference in ADMA concentrations between the COPD patients and control groups; but interestingly found positive correlation between the brachial artery intima-media thickness in COPD patients, which is known to predict cardiovascular risk and ADMA concentrations. It can be hypothesized that cardiovascular diseases are as the most common diseases in COPD patients and lowering the ADMA levels may be useful in the acute management and prevention of COPD exacerbations. In all these studies, the patients were under treatment with some drugs prescribed for COPD. This point should be taken into consideration when evaluating the inconsistent reports of the studies investigating the association between COPD and ADMA.

Smoking alters serum ADMA levels; controversial results have been found in studies related to this.[16] Therefore, we selected the patient and control group from non-smoking individuals. The potential limitation of our study was that the age of the control group we chose was younger than the COPD patients and our study group had a small number of cases to be studied. However, in the results of univariate linear regression analysis performed for variables considered to be effective on ADMA levels, the effect of laboratory findings on ADMA in the COPD and control group was found to be statistically insignificant ($p>0.05$). Meanwhile, the values of FEV1% and FEV1/FVC% were found to have a significant effect on ADMA ($p<0.05$). We concluded that this finding shows that ADMA is effective in airway obstruction as an independent variable in COPD. We propose ADMA could be involved during disease worsening. Lowering ADMA levels and the reduced arginine concentrations in COPD may be a new target for therapeutic options.

Conclusion

We have observed that serum ADMA levels are increased during the exacerbation period of COPD patients but noted no association according to stages classified by GOLD guidelines. Furthermore, ADMA was found to differentiate the COPD patients from healthy group. As the exacerbation episodes have huge burden for health-care systems, new strategies to improve health outcomes of COPD are required. Further studies should investigate the characteristics of ADMA if it is a risk-related marker for COPD and delineate the importance of new treatment modalities which should also cover the factors contributing to the mortality of the disease.

Disclosures

Ethics Committee Approval: The study was carried out by obtaining the approval of the Ethics Committee of the hospital (1212 No-16/04/2019) and complying with the Helsinki Declaration.

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