INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2024.28159
Int J Med Biochem 2024;7(3):150–155

Research Article

Decreased Elabela level in the first 24 hours of ST Elevation Myocardial Infarction patients

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Abstract

Objectives: Cardiovascular diseases are among the leading causes of death worldwide. ST Elevation Myocardial Infarction (STEMI) is one of the most important causes of cardiovascular mortality and morbidity. It has been determined that Elabela (ELA), a member of the apelinergic system, increases myocardial contractility and coronary vasodilation, and decreases blood pressure. The aim of this study was to evaluate the relationship between circulating ELA levels and various clinical, biochemical, and angiographic parameters in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods: Seventy-four patients hospitalized with the diagnosis of STEMI who underwent coronary angiography and primary PCI, and seventy-four patients with chest pain but no pathology detected in coronary angiography, were included in the study as the control group. Coronary lesion severity was measured using the SYNTAX score tool. Routine laboratory tests and ELA levels were measured.

Results: Plasma levels of ELA were significantly lower in patients with STEMI (0.68±0.68 ng/mL) than in controls (1.34±0.88 ng/mL, $p<0.001$). Glucose, cholesterol, LDL, CRP, troponin I, and SYNTAX score levels were statistically higher in the STEMI group, while ELA and HDL levels were lower. There was a high level of negative correlation between ELA and troponin I, SYNTAX score, cholesterol, LDL, and CRP.

Conclusion: In this study, it was determined that the level of ELA decreased in the first 24 hours of STEMI patients. In addition, a highly negative correlation was found between ELA and troponin I and SYNTAX scores.

Keywords: Coronary heart disease, Elabela (ELA), myocardial infarction, primary Percutaneous Coronary Intervention (PCI); ST Elevation Myocardial Infarction (STEMI)

How to cite this article: Canpolat Erkan RE, Adiyaman MS. Decreased Elabela level in the first 24 hours of ST Elevation Myocardial Infarction patients. Int J Med Biochem 2024;7(3):150–155.

ST Elevation Myocardial Infarction (STEMI), which is included in Coronary Heart Disease (CHD), is one of the most important causes of cardiovascular mortality and morbidity, especially in developed countries. Although interventional procedures such as Percutaneous Coronary Interventions (PCI) and Coronary Artery Bypass Grafting contribute significantly to the reduction of clinical symptoms and mortality, acute heart failure, cardiogenic shock, and various complications are observed after the procedure. The clinic, comorbidity, echocardiographic findings, and biochemical results of the patients may affect the prognosis of STEMI. New biomarkers are needed for the diagnosis of STEMI patients with high mortality and morbidity risk [1, 2].

Approximately 200 hormones and neuropeptides show their activities via cardiac G protein-coupled receptors (GPCRs), such as endothelin-1 receptor (ET1R), A1 adenosine receptors (A1R), and beta adrenergic receptor kinase 1 (βARK1) [3]. In DNA sequencing studies, receptors that encode GPCR-like sequences but whose ligands are unknown, so-called "orphan GPCRs," have been identified [4]. After the

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Submitted: May 08, 2024 **Revised:** June 14, 2024 **Accepted:** June 20, 2024 **Available Online:** August 13, 2024

discovery of Apelin, which can bind to Angiotensin Type 1 Receptor-Associated Proteins (APJ), defined as orphan GPCRs in 1998, a new endogenous peptide, Elabela (ELA, Toddler, and Apela) was found in the 2000s, which shares the same receptor [5]. APJ, Apelin, and ELA constitute the peptide family called the apelinergic system, and this family has been shown to have antihypertensive, cardiorenal protective, positive inotropic effects and regulate fluid homeostasis, vasodilation, angiogenesis, cellular differentiation, apoptosis, and oxidative stress [5, 6].

ELA has been shown mainly in human stem cells, kidneys, prostate, vascular endothelium, and plasma [7]. ELA has an antagonistic effect on the Renin-Angiotensin-Aldosterone system and lowers blood pressure. It has been determined that the effects of ELA to increase myocardial contractility and coronary vasodilation are stronger than Apelin [6, 8]. In addition, it has been found that the plasma level of ELA decreases in hypertensive patients and that this low level correlates with the risk of having hypertension [7]. Due to the positive inotropic effect of the apelinergic system and its upregulation of the remodeling phase after MI, the apelinergic system has begun to be emphasized in the treatment of cardiovascular diseases, and alternative treatment protocols are being developed over Apelin-Elabela Analogs and APJ agonists [6].

In this study, it was aimed to examine the circulating ELA levels in STEMI patients who underwent primary PCI. Therefore, the relationship between ELA levels and various clinical-biochemical and angiographic parameters in STEMI patients will be evaluated.

Materials and Methods

Study population

Patients who applied to the Cardiology Clinic and Emergency Department with the complaint of sudden onset chest pain, had no history of the disease, and had Acute Coronary Syndrome (ACS) findings in ECG changes and underwent coronary angiography were included in the study. The study was conducted in accordance with the Declaration of Helsinki. All patients were informed, and an informed consent form was signed. The study was conducted prospectively between the years 2021–2022. Ethics Committee approval was obtained for the study (No: 15/01/2021-616).

Patients with any chronic disease such as heart failure, cardiac arrhythmia, moderately advanced heart valve disease, chronic kidney disease, rheumatic or inflammatory disease were excluded.

According to the fourth universal definition of MI, patients with symptoms suggestive of ischemia and ST-segment elevation (at least two contiguous leads with ST-segment elevation ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2–V3 and/or ≥1 mm in the other leads) in at least two adjacent leads on the ECG were considered to have STEMI [9]. As a patient group, 74 patients who applied to the Cardiology Clinic and the Emergency Department with the complaint of chest pain, were diagnosed with Acute STEMI with ≥2 mm ST-segment elevation in any of the two adjacent leads in the first ECG and caused 100% narrowing in one or more coronary arteries in the coronary angiography and who underwent primary PCI due to thrombus were included. The SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score of the included patients was evaluated [10]. Seventy-four patients who were hospitalized with a prediagnosis of ACS but whose biochemical parameters (Troponin I) were negative, coronary angiography was normal and the diagnosis of ACS was excluded because of no specific findings on ECG were included as the control group.

Biochemical measurements

A second blood sample was taken for the ELA test and delivered to the laboratory during routine blood collection from patients who applied to the emergency clinic and had changes in their ECG and were referred for coronary angiography. These procedures were carried out within the first 6 hours. Clinical Chemistry Tests and CRP Spectrophotometric in ARCHITECT c16000 (Abbott Laboratories, USA) autoanalyzer, Hemogram measurements on Mindray BC 6800 (Mindray Building, High-Tech Industrial Park, Nanshan, Shenzhen China) device, HbA1c measurements in HA-8180 (ARKRAY, Inc. JAPAN) device by HPLC (High-Performance Liquid Chromatography) method, Serum Thyroid Stimulating Hormone (TSH), free T3, free T4, Folate, Vitamin B12, D Vitamin, Troponin I and Procalcitonin levels were studied with the electrochemiluminescence method in the Cobas e601 (Roche Diagnostics, Germany) device. For the ELA test, the blood was taken into standard clinical chemistry test tubes, centrifuged at 1500 g for 20 minutes, and the serum was separated and stored at -40°C. ELA test was performed with enzyme-linked immunosorbent assay (Human Elabela ELISA kit) method. Serum ELA levels were studied in accordance with the kit package insert (Sunred Biological Technology, Shanghai, China), and measurements were made in the Grifols Triturus Automated ELISA Analyzer device (Grifols Triturus, Grifols, S.A., Barcelona, Spain).

Statistical analysis

For the statistical analysis of the data obtained in the study, SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) for Windows package program running on Windows was used. Data are presented as percentage (%), mean ± standard deviation (SD), median, interquartile range (IQR), correlation coefficient (r).

The conformity of the variables to the normal distribution was examined with the Kolmogorov-Smirnov test. Mean and standard deviation were used for normally distributed variables. The student t-test was used to compare the variables in normal distribution between the two groups, and the Mann-Whitney U-test was used for variables that did not fit the normal distribution. The Chi-square test was used to compare categorical variables, and the relationship between numerical variables was evaluated using Spearman's Correlation Analysis. $P<0.05$ was considered statistically significant.

Table 1. Comparison of the baseline clinical and laboratory parameters

	STEMI n=74	Controls n=74	p
Age (years), median (IQR)	54 (13)	44 (9)	0.001***
Gender (n, %)			
Male	59 (67.8)	28 (32.2)	0.001***
Female	15 (24.6)	46 (75.4)	
Hypertension (n, %)	10 (13.51)	0 (0)	0.001***
Diabetes mellitus (n, %)	9 (12.16)	0 (0)	0.003**
Glucose (mg/dL) median (IQR)	96 (12)	91 (18)	0.003**
Urea (mg/dL) median (IQR)	30 (12)	24 (6)	0.001***
Creatinine (mg/dL) median (IQR)	0.846 (0.28)	0.72 (017)	0.001***
eGFR (mL/dk/1.73m^2) median (IQR)	90 (2.75)	90	0.001***
Albumin (g/L) median (IQR)	42 (5.45)	46 (4)	0.001***
Total cholesterol (mg/dL) median (IQR)	180 (53)	151 (37.25)	0.001***
LDL-C (mg/dL) median (IQR)	118 (42.25)	89.5 (26)	0.001***
HDL-C (mg/dL)	39.72±8.50	42.9±8.60	0.023*
TG (mg/dL), median (IQR)	94 (85)	82 (67.5)	0.093
Ca (mg/dL)	9.05±0.41	9.68±0.39	0.001***
Na (mmol/L) median (IQR)	137 (3)	139 (2)	0.001***
K (mmol/L)	4.13±0.36	4.38±0.36	0.001***
AST (U/L) median (IQR)	52.5 (80)	16.5 (6)	0.001***
ALT (U/L) median (IQR)	26.5 (27)	14 (11)	0.001***
LDH (U/L) median (IQR)	351 (378)	191 (54)	0.001***
WBC (10^3/uL) median (IQR)	14.01 (5.16)	7.33 (1.75)	0.001***
Hemoglobin (g/dL)	14.67±1.80	14.13±1.69	0.062
HCT (%)	45.22±4.46	43.87±3.97	0.054
PLT (10^3/uL)	256±64	273±54	0.077
TSH (mU/L) median (IQR)	1.18 (1.26)	1.67 (1.07)	0.01**
T3 (pg/mL)	3.17±0.65	3.64±0.43	0.001***
T4 (ng/dL) median (IQR)	1.29 (0.31)	1.23 (0.24)	0.142
B 12 (ng/L) median (IQR)	303 (134)	308 (177)	0.043*
Folat (ng/mL) median (IQR)	5.7 (3.15)	7.2 (3.95)	0.001***
D Vitamine (ng/mL) median (IQR)	11.4 (5.35)	10.3 (5.28)	0.135
HbA1c (%) median (IQR)	5.6 (0.45)	5.3 (0.2)	0.001***
CRP (mg/L) median (IQR)	4.5 (4.33)	2	0.001***
PCT (ng/mL)	0.24±0.06	0.28±0.05	0.001***
Troponin I (ng/mL) median (IQR)	12.92 (21.34)	0.1	0.001***
ELA (ng/mL) median (IQR)	0.45 (0.4)	0.88 (1.88)	0.001***
SYNTAX median (IQR)	20.5 (7.75)	0	0.001***

Data are presented as mean±SD or n (%), median. IQR. *: p<0.05 versus controls; **: p<0.01 versus controls; ***: p<0.001. IQR: Interquartile range; eGFR: Estimated glomerular filtration rate; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; Ca: Calcium; Na: Sodium; K: Potassium; AST: Aspartate aminotransferase; ALT: Alanine aminotransfease; LDH: Lactate dehydrogenase; WBC: White blood cell; HCT: Hematocrit; PLT: Platelet; TSH: Thyroid Stimulating Hormone; HbA1c: Hemoglobin A1c; CRP: C-Reactive protein; PCT: Procalcitonin; ELA: Elabela; SYNTAX: SYNergy between PCI with TAXUS and cardiac surgery.

Results

Our study consists of 74 STEMI patient groups and 74 control groups. In demographic comparison, the mean age of the group with STEMI was higher (54.42±9.99), and the ratio of men 59 (67.8%) was higher than women 15 (24.5%). The frequency of DM (diabetes mellitus) and HT (hypertension) was higher in the STEMI group than in the control group. WBC (white blood cell), glucose, urea, creatinine, TC (total cholesterol), LDL-C (low-density lipoprotein cholesterol), CRP (C-reactive protein), Troponin I, HbA1c, and SYNTAX score levels were statistically higher in the STEMI group (p<0.001); ELA, TSH, B12, folate, fT3, PCT (Procalcitonin), Ca, K, HDL-C (high-density lipoprotein cholesterol) levels were significantly lower (Table 1). There was a negative correlation between ELA and age, gender, creatinine, TC, LDL-C, WBC, HbA1c, CRP, Troponin I, SYNTAX score, and a positive

Table 2. Correlation between ELA and study variables in all subjects

	r	p
Age (years)	-0.183	0.026
Gender	-0.167	0.042
Diabetes mellitus	0.185	0.025
Creatinine (mg/dL)	-0.166	0.044
eGFR (mL/dk/1.73m^2)	0.019	0.019
Total cholesterol (mg/dL)	-0.215	0.009
LDL-C (mg/dL)	-0.254	0.002
Ca (mg/dL)	0.217	0.008
K (mmol/L)	0.199	0.015
WBC (10^3/uL)	-0.341	<0.001
TSH (mU/L)	0.181	0.027
fT3 (pg/mL)	0.177	0.031
Folat (ng/mL)	0.195	0.017
HbA1c (%)	-0.327	<0.001
CRP (mg/L)	-0.341	<0.001
Troponin I (ng/mL)	-0.412	<0.001
SYNTAX	-0.417	<0.001

ELA: Elabela; eGFR: Estimated glomerular filtration rate; LDL-C: Low density lipoprotein cholesterol; Ca: Calcium; K: Potassium; WBC: White blood cell count; TSH: Thyroid stimulating hormone; CRP: C-reactive protein; SYNTAX: SYNergy between PCI with TAXUS and cardiac surgery.

correlation between DM, eGFR (estimated glomerular filtration rate- calculated with CKD-EPI formula), Ca, K, TSH, fT3, and folate correlation was detected (Table 2).

ELA levels were significantly lower in patients with STEMI (0.68±0.68 ng/mL/0.45 (0.4) median (IQR)) than controls (1.34±0.88 ng/mL/0.88 (1.88) median (IQR), p<0.001) (Table 1, Fig. 1).

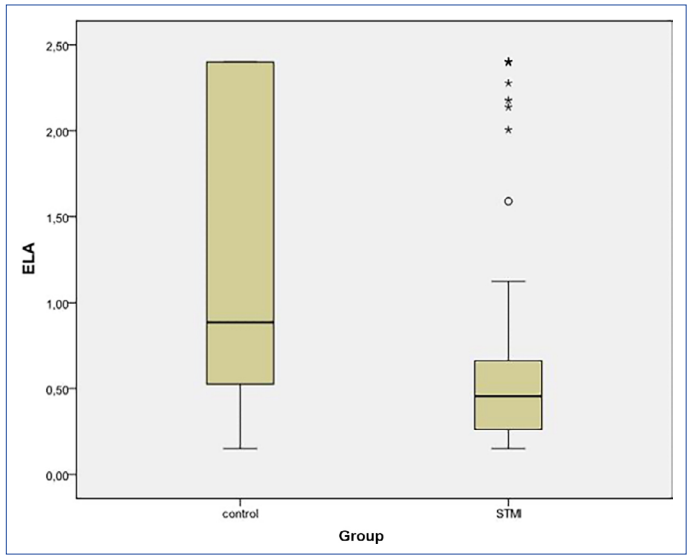

Figure 1. ELA levels on control and STMI groups.
ELA: Elabela; STMI: ST Elevation myocardial infarction.

Discussion

The main finding of our study is that it is the first study showing a statistically significant decrease in ELA levels in the first 24 hours in patients with STEMI. In addition, a negative correlation was found between ELA and Troponin I and SYNTAX scores in the study (p<0.001).

Cardiovascular Diseases (CVD) account for 31% of deaths worldwide, and these diseases need to be diagnosed quickly, and treatment should be started [11]. The research that started with the discovery of APJ has revealed the importance of the regulatory role of Apelin and ELA on the cardiovascular system and fluid electrolyte homeostasis. ELA works like a hormone due to its expression in pluripotent stem cells and especially in kidneys and its homeostatic and cardioprotective effects on blood pressure-fluid-electrolyte balance [12]. Many studies have been done on cardiovascular, endocrine, and tumor-related diseases on ELA, as well as comparative studies with Apelin [13]. It has been observed that ELA plays an important role in ischemic cardiovascular diseases by activating APJ earlier than Apelin and stimulating angiogenesis [12, 13].

ELA affects intracellular signaling through APJ activation, resulting in a decrease in cAMP levels, stimulation of ERK, and an increase in intracellular calcium mobilization. Wang et al. [12] have shown that ELA induces a relaxation independent of the endothelium by determining that while ELA caused 73.7% relaxation in vessels with an intact endothelium, the relaxation in vessels with stripped endothelium was only 20% less in their study where they used mouse aortic vessels with intact endothelium and stripped endothelium. It was also examined whether this relaxation is NO dependent or not, and it was determined that ELA does not need NO mediation for relaxation. In the study, the effect of Apelin on vessels was also examined in parallel, and they determined that while Apelin caused 79% relaxation in vessels with intact endothelium, the relaxation in vessels with stripped endothelium was 48% to 31% less, and they determined that Apelin was more endothelial-dependent than ELA for vascular relaxation. Therefore, although they act through the APJ, there is a difference between ELA and Apelin in terms of vasodilation mechanisms.

Years of studies have shown that the apelinergic system is a good homeostasis regulator through the cardiovascular system and water-electrolyte balance. Detection of ELA, especially in the kidney, showed that it has an important function in maintaining fluid homeostasis and blood pressure together with the heart in RT-PCR analyzes [12]. In our study, in parallel with this information, a negative correlation was found between ELA and creatinine and a positive correlation with eGFR (p<0.05). It is predicted that ELA, which acts as a paracrine or endocrine hormone, can be used as a good diuretic agent. In addition, over the APJ axis; while Apelin activates the ACE2 promoter activity, ELA decreases the ACE promoter activity in a dose-dependent manner, thus neutralizing the negative effects of RAS and showing a cardioprotective effect [5].

Dönmez et al. [8] found that ELA levels increased, but this was not statistically significant in their study on STEMI patients, and found a moderately positive correlation between ELA and Troponin I, NT-ProBNP, but no correlation between Hs-CRP. They also found a moderate negative correlation between ELA and left ventricular ejection fraction (LVEF). Aydın et al. [14] found an increase in ELA and Apelin levels in the blood after MI in their study. It is thought that blood levels increase due to the release of ELA and Apelin into the circulation by damaged cardiomyocytes after ischemia. They also suggested that ELA and Apelin could be new indicators for clinically determining the severity of MI and for the diagnosis of MI. Yavuz et al. [15] on the other hand, found that the ELA levels of patients with Chronic Complete Occlusion in their coronary arteries were lower than the control group. They also stated that ELA levels of patients with good collateral development were higher than patients with low collateral development, and this was due to the positive effects of ELA on angiogenesis and arteriogenesis. Similar to the study of Yavuz et al. [15], in our study, ELA levels (0.68±0.68 ng/mL/0.45 (0.4)) in patients with STEMI were found to be lower than the control (1.34±0.88 ng/mL/0.88 (1.88), p<0.001) group. While ELA is detected in fibroblasts and intact endothelial cells in the heart, ELA production decreases in impaired endothelial function. This may be attributed to the decrease in ELA production due to impaired vascular endothelium in the acute phase of MI in STEMI patients who already show signs of endothelial dysfunction (HT, DM, high lipid profile, CRP, glucose, and low HDL-C). In addition, in our study, contrary to the findings of Dönmez et al. [8] a high level of negative correlation was found between ELA and CRP and Troponin I levels in the STEMI group (p<0.001).

Du et al. [16] found that ELA levels in patients with the ACS were significantly higher than in the control group (95.04±18.66 vs 71.90±8.93, p<0.01). Although they did not report a difference between the ELA level and the number of narrowed coronary arteries, they reported that the SYNTAX I score increased with the increase in ELA levels between 63.75 ng/mL and 85.49 ng/mL. In the study conducted by Tian et al. [17] with CHD, they divided into 3 groups as stable angina (SA), unstable angina (UAP), and acute myocardial infarction (AMI), ELA levels in patients with CHD were found to be 10.71% higher (p<0.05) compared to controls, and it was higher in the patients in the UAP and AMI subgroups than in the controls and SA subgroup (p<0.05). However, they could not detect a correlation between ELA concentration and SYNTAX score, LVEF, and other biochemical parameters in coronary heart patients. In our study, however, a high level of negative correlation was found between the SYNTAX score and ELA (p<0.001).

Myocardial cell necrosis can induce an increased inflammatory response and elevated CRP levels, and experimental studies suggest that inhibiting CRP in AMI may reduce myocardial damage [18]. In an experimental study by Rakhshan et al. [19] ELA peptide was administered intraperitoneally to rats with MI, and the development of infarction and myocardial necrosis after reperfusion were examined. They showed that the ELA peptide significantly reduced markers of myocardial damage, such as CK-MB and Troponin I, in the treatment groups. They also found an increase in LVIDd (Left Ventricular Internal Dimension At End-diastole) and LVIDs (Left Ventricular Internal Dimension At End-systole), and EF (Ejection Fraction) and FS (Fractional Shortening) decreased myocardial cell damage and improved cardiac function. In their study, Xi et al. [20] developed Fc-ELA-21 (longer half-life ELA analogue); found that this ELA peptide, which they infused continuously sc daily, significantly improved cardiac dysfunction by increasing angiogenesis and cardiomyocyte proliferation, reducing myocardial fibrosis and apoptosis in MI-induced rats. In our study, Troponin I and CRP levels, which are the ideal indicators of myocardial damage and inflammation, were found to be statistically higher and ELA levels lower in the STEMI group, and a high level of negative correlation was found between them and ELA (p<0.001). In addition, we found a positive correlation (p<0.001) between CRP and TC, LDL-C, and Troponin I, and a negative correlation (p<0.001) with ELA, which supports the view that inhibiting CRP can reduce myocardial damage. As a result of clinical studies to be conducted by administering ELA analogue to AMI patients in the future, the status of myocardial damage, inflammation markers (CRP, CK-MB, Troponin I, etc.) and necrosis area size can be determined.

Known risk factors for the development of AMI include high LDL-C and TG levels. It is known that LDL-C causes inflammation and formation of atherosclerotic plaques in the endothelium [21]. In addition, CRP is also stated to be a mechanical mediator of myocardial damage after STEMI, in addition to its involvement in cardiovascular risk factors [18]. In our study, TC, LDL-C, and CRP levels were found to be higher and HDL-C levels to be lower in patients with STEMI (p<0.001). Our negative correlation (p<0.01) between TC, LDL-C, CRP and ELA, which are risk factors for AMI, supports the prediction that ELA deficiency may be a risk factor for CVD.

Study limitations

The main limitation of our study is that it is single-centered, and the sample size is relatively small. In addition, ELA levels were measured only in STEMI patients and in the first 6 hours of the study. We believe that it would be more meaningful to perform both STEMI and non-STEMI MI type and sequential measurements in larger patient groups to determine the course of ELA.

Conclusion

In this study, it was determined that the level of ELA decreased in the first 6 hours of STEMI patients (compared to the control group). In addition, a highly negative correlation was found between ELA and Troponin I and SYNTAX scores.

ELA is expected to be a new biomarker for CVD and an effective drug in treatment. Therefore, it is important to comprehensively investigate how ELA affects CVD and its contribution to treatment.

Ethics Committee Approval: The study was approved by The University of Health Sciences Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee (No: 616, Date: 15/01/2021).

Authorship Contributions: Concept – R.E.C.E., M.S.A.; Design – R.E.C.E., M.S.A.; Supervision – R.E.C.E., M.S.A.; Funding – R.E.C.E., M.S.A.; Materials – R.E.C.E., M.S.A.; Data collection &/or processing – R.E.C.E., M.S.A.; Analysis and/or interpretation – R.E.C.E., M.S.A.; Literature search – R.E.C.E.; Writing – R.E.C.E., M.S.A.; Critical review – R.E.C.E., M.S.A.

Conflict of Interest: The authors declare that there is no conflict of interest.

Use of AI for Writing Assistance: No AI was used for writing assistance.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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