ORIGINAL ARTICLE

Negative association of apelin plasma levels with epicardial fat thickness in patients with stable angina and acute myocardial infarction: A case–control study

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Background: Apelin is one of the endogenous peptides that play a key role in the homeostasis of cardiovascular diseases. The purpose of the current study was to evaluate the correlation between apelin levels and epicardial fat thickness (EFT) in patients with stable angina and acute myocardial infarction (AMI). **Materials and Methods:** In a case–control study, 90 patients nominated for angiography were enrolled in the study and divided into three groups: healthy subjects without angiographic findings (Con), stable angina pectoris group (SAP), and acute AMI group. Data collected from all subjects included biochemical, echocardiographic, and angiographical parameters. The Gensini score analyzed the severity of coronary artery disease (CAD). **Results:** A decrease in adjusted apelin levels was evident in the AMI and SAP groups compared with healthy individuals (for both $P < 0.001$), especially in the AMI group. In addition, a detectable negative association was identified between apelin and Gensini score (r = −0.288, $P = 0.006$), Ck-MB (r = −0.300, $P = 0.004$), EFT (r = −0.300, $P = 0.004$), and troponin-T (r = −0.288, $P = 0.006$). **Conclusion:** Myocardial injury in patients with CAD appears to play a significant role in apelin concentration independent of the role of adipose tissue, which requires further studies.

Key words: Acute myocardial infarction, angiography, apelin, epicardial fat thickness

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INTRODUCTION

Recent data show the role of adipokines secreted from adipose tissue in the pathophysiology of various diseases, particularly chronic inflammatory diseases.[1,2] Apelin is an endogenous peptide highly expressed in various body tissues such as the adipose tissue, kidneys, vascular endothelium, lungs, cerebellum, cardiomyocytes, and pancreas.[3] Apelin has been suggested as a potent vasodilator and inotropic and has been shown in various studies as a key regulator of cardiovascular homeostasis.[4] Apelin is also a mitogen and angiogenic factor for endothelial and vascular smooth muscle cells.[5]

The role of apelin in cardiovascular diseases (CVDs) in animal and human studies has been reported with contradictory findings. High apelin levels were reported in the early stages of heart failure, while values decreased in chronic heart failure (CHF).[5] Animal studies have shown that apelin in the ischemic/reperfusion model has protective effects against ischemia and, when administered, has inotropic effects on heart failure.[6] Decreased expression of the apelin receptor in the heart tissue of ischemic heart disease probably suggests its role in the pathogenesis of the disease.[5] In mice, it has been shown that apelin inhibits the formation of aortic aneurysms, possibly by activating chemokines and inhibiting inflammatory cytokines.[7] New evidence suggests that apelin is a beneficial adipokine in

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various diseases such as kidney disease, cardiopulmonary disease, dyslipidemia, and type 2 diabetes.[8,9]

Under pathological conditions, epicardial fat thickness (EFT) has played a key role in various CVDs by releasing proinflammatory and proatherogenic factors through paracrine or vasocrine pathways.[10] Elevated levels of apelin are associated with metabolic syndrome and the severity of CVD.[11] Accordingly, the current research aimed to assess apelin levels in acute myocardial infarction (AMI) patients compared with noncoronary artery disease (non-CAD) and stable angina. The association between apelin levels and some echocardiographic parameters, such as EFT, has also been investigated.

MATERIALS AND METHODS

In a case–control study, 90 male patients nominated for angiography were included at Imam Khomeini Hospital in Ardabil, Iran. Based on angiographic results, patients were divided into three groups, including the AMI group, $n = 30$, stable angina pectoris group (SAP group, $n = 30$), and patients clinically with chest pain but no angiographic findings (Con group, $n = 30$).

Previously, the inclusion and exclusion criteria were fully addressed.[1] The exclusion criteria were individuals with a history of myocarditis, AMI, pericardial effusion, heart failure, valvular heart diseases, respiratory diseases, steroid therapy, infectious diseases, poor echocardiographic imaging, autoimmune diseases, and chronic renal failure. Diagnostic criteria in the AMI group were based on laboratory analyses (elevated troponin T and creatine kinase-MB [CK-MB] levels) or changes in electrocardiogram (ECG) (elevated ST segment). Patients with stable angina were also included in the study based on ECG findings during exercise testing.

Data collected in the current study included demographics (age, weight, and height), waist-to-hip ratio (WHR), body mass index (BMI), and laboratory parameters (hemoglobin [Hb], blood urea nitrogen [BUN], white blood cell [WBC], creatinine [Cr], low-density lipoprotein [LDL], high-sensitivity troponin T, total cholesterol [TC], fasting blood glucose (FBG), high-density lipoprotein [HDL], CK-MB, and triglyceride). Before angiography, three cc blood samples were taken from all patients. Stored plasma samples (at −70°C) were used to determine apelin plasma levels using commercial ELISA kits and standard methods.

Parameters measured for echocardiography in the current study included EFT, mitral valve septal annular systolic velocity (e′ Septal), tricuspid lateral annular systolic velocity (TV TDI), annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF), and mitral valve lateral annular systolic velocity (e′ Lateral). Echocardiography was performed by an echocardiologist and examined blindly by two cardiologists. The angiographic procedure was performed by standard Judkins technique as well as 5 or 6 Fr catheters by interventional cardiologists through radial or femoral arteries. Gensini score was used to evaluation of the disease severity.[12] Briefly, the Gensini score was calculated as follows: a severity score for each coronary stenosis was assigned depending on the degree of luminal narrowing and the location of the stenosis. Luminal stenosis of 25%, 50%, 75%, 90%, 99%, and complete occlusion were scored as 1, 2, 4, 8, 16, and 32, respectively. These scores were then multiplied by a factor according to the location: 5 for the left main coronary artery; 2.5 for the proximal segment of the left anterior descending coronary artery and proximal segment of the circumflex artery; 1.5 for mid-segment of the left anterior descending coronary artery; 1.0 for right coronary artery, the distal segment of the left anterior descending coronary artery, posterior descending artery, and obtuse marginal artery; and 0.5 for other segments.

Statistical analysis

The data are presented as mean ± standard deviation. Normal distribution was performed using Shapiro and Kolmogorov test. ANOVA test (with Tukey's *post hoc* test) was used for data analysis. Pearson's test was used to determine the correlation coefficient. Analysis of ANOVA was used to adjust the results for WHR, BMI, and age. The $P < 0.05$ in terms of the significance of the results. SPSS (version 21; IBM Corp.; USA) and GraphPad Prism 7.0 (GraphPad Software, LLC; USA) were used to analyze the results and draw graphs.

RESULTS

Clinical and demographic characteristics are summarized in Table 1. The significant parameters in the comparison between the groups were mean age ($P < 0.01$), CK-MB ($P < 0.001$), WHR ($P < 0.05$), troponin T ($P < 0.001$), TC ($P < 0.05$), HDL-C ($P < 0.01$), LDL-C ($P < 0.001$), Gensini score ($P < 0.001$), and WBC ($P < 0.001$).

AMI group had a significantly lower mean age compared to SAP and Con groups. W.H.R., WBC, LDL-C, and T.C. were significantly lower in the Con group compared to the AMI and SAP groups, while HDL-C was significantly higher. In addition, troponin T and CK-MB plasma levels were higher in the AMI group than SAP and Con groups ($P < 0.001$ for both). Concerning the Gensini score, there was a significant difference between the AMI group and the SAP and Con groups ($P < 0.001$ for both). No significant differences were observed about other parameters such as FBG, triglycerides, BMI, uric acid, BUN, platelets, Cr, and Hb between groups [Table 1].

Decreased levels of apelin were observed in the AMI group (302.80 ± 48.52) compared with SAP (363.80 ± 93.32,

Table 1: Demographic and laboratory findings in study groups

Variable	Control (*n*=30)	SAP (*n*=30)	AMI (*n*=30)	*P*
Age (year)	61.96±13.08	62.73±8.50	54.43±10.63*,+	0.007
Weight (kg)	74.50±12.85	77.90±13.90	81.16±11.04	0.131
Height (m)	1.68±0.07	1.70±0.05	1.71±0.06	0.180
BMI (kg/m^2)	26.00±3.03	26.74±4.10	27.46±3.31	0.278
Waist circumference (cm)	94.20±5.69	95.76±8.24	97.73±6.22	0.138
Hip circumference (cm)	100.76±4.89	99.56±8.00	102.03±8.38	0.425
WHR	0.93±0.04	0.96±0.02*	0.96±0.05*	0.027
TC (mg/dL)	154.30±20.58	168.46±31.35	172.50±27.12*	0.025
TG (mg/dL)	113.16±44.94	128.56±54.71	126.23±40.96	0.400
HDL-C (mg/dL)	44.76±7.90	40.16±5.50*	40.40±4.88*	0.007
LDL-C (mg/dL)	81.16±18.44	99.13±18.67**	106.46±19.26***	0.000
FBG (mg/dL)	98.36±9.49	102.43±9.44	100.43±8.45	0.233
BUN (mg/dL)	36.76±9.26	38.00±11.21	43.80±29.59	0.316
Creatinine (mg/dL)	1.21±0.21	1.24±0.29	1.27±0.40	0.808
Uric acid (mg/dL)	5.45±1.37	5.79±1.83	6.01±1.80	0.432
Hemoglobin (g/dL)	14.37±1.79	14.13±1.22	14.58±2.25	0.633
WBC (10^3/mm^3)	7.32±1.73	8.70±1.19**	9.28±1.77***	0.000
CK-MB (ng/mL)	2.62±0.79	3.67±1.57***	33.38±11.50***,+++	0.000
HsTnT (ng/L)	2.83±2.10	10.66±5.19***	34.58±11.38***,+++	0.000
Gensini score	Not done	31.46±14.63	45.70±17.38+++	0.000
Apelin (pg/mL)	380.82±100.84	363.80±93.32	302.80±48.52	0.001
Apelin (adjusted), (pg/mL)[a]	389.03±9.91	347.85±4.67	311.44±9.35	0.000

For statistical differences between the control group and other groups: *P<0.05, **P<0.01, ***P<0.001. For statistical differences between SAP with AMI: +P<0.05, +++P<0.001. Comparison between groups was done using ANOVA test. Data are expressed as mean±SD. SAP=Stable angina pectoris; AMI=Acute myocardial infarction; BMI=Body mass index; TC=Total cholesterol; TG=Triglyceride; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; FBG=Fasting blood glucose; BUN=Blood urea nitrogen; WBC=White blood cell; CK-MB=Creatine kinase-MB; HsTnT=High-sensitivity troponin T; SD=Standard deviation; WHR=Waist–hip ratio

$P < 0.05$) and Con groups (380.82 ± 100.84, $P < 0.01$), but no significant difference was identified between SAP and Con groups [Figure 1a]. Interestingly, after adjusting the plasma level of apelin with age, WHR, and BMI, plasma levels of apelin were significantly lower in AMI patients compared to SAP and Con groups ($P < 0.001$ for both) as well as SAP group compared to Con group ($P < 0.001$) [Figure 1b].

On the other hand, the EFT was significantly higher in the AMI (7.75 ± 1.19, $P < 0.001$) group compared to SAP (6.02 ± 0.96) and Con groups (4.28 ± 1.05, $P < 0.001$). EFT was also significantly higher in the SAP patients than in the Con subjects [$P < 0.001$, Figure 2a]. Furthermore, adjusting EFT results demonstrated that there was still a significant difference [Figure 2b]. LVEF (%) in the AMI group (36.56 ± 9.92) was less than SAP (43.50 ± 7.44, $P < 0.001$) and Con groups (53.33 ± 7.58, $P < 0.001$). LVEF (%) in SAP patients was significantly also lower than in Con individuals ($P < 0.001$). There was no significant difference concerning other echocardiographic parameters (e' Septal, e' Lateral, TAPSE, and TV TDI) [Table 2].

A significant negative correlation was evident between apelin and EFT [$r = -0.300$, $P = 0.004$; Figure 3e], CK-MP [$r = -0.300$, $P = 0.004$; Figure 3a], Gencini score ($r = -0.288$, $P = 0.006$; Figure 3c], troponin-T [$r = -0.288$, $P = 0.006$; Figure 3b], and a positive association with LVEF [$r = 0.237$, $P = 0.025$; Figure 3d].

DISCUSSION

The main findings of the current study were (1) decreased levels of apelin in patients with acute MI and stable angina and (2) negative association between apelin and EFT, CK-MB, Gensini score, and troponin-T.

Adipose tissue is a source of energy storage and an endocrine organ. Adipose tissue plays an endocrine role in releasing various adipokines such as visfatin, leptin, adiponectin, interleukin-6 (IL-6), fatty acid binding protein-4, tumor necrosis factor (TNF)-α, nesfatin, adipolin, and apelin.[13-16] Studies have shown that changes in adipokine secretory levels play a crucial role in the pathogenesis of diseases, especially chronic inflammatory diseases.[17-19] As an adipokine, apelin expression has been reported in various tissues such as the kidneys, adipose tissue, brain, heart, liver, lungs, and cardiovascular system.[3] Interestingly, the level of apelin gene expression in the tissues of the heart and kidneys was significantly higher than in adipose tissues.[20] In addition, increased apelin expression in the atria in cardiac tissue compared with the ventricles has been reported, suggesting that heart tissue is the main source of circulating apelin.[20] A variety of physiological functions have been demonstrated for apelin, such as fluid balance regulation, cardiac contractile function, carbohydrate use, vascular tone, angiogenesis, neuroprotection, cellular proliferation, and immunologic functions.[21]

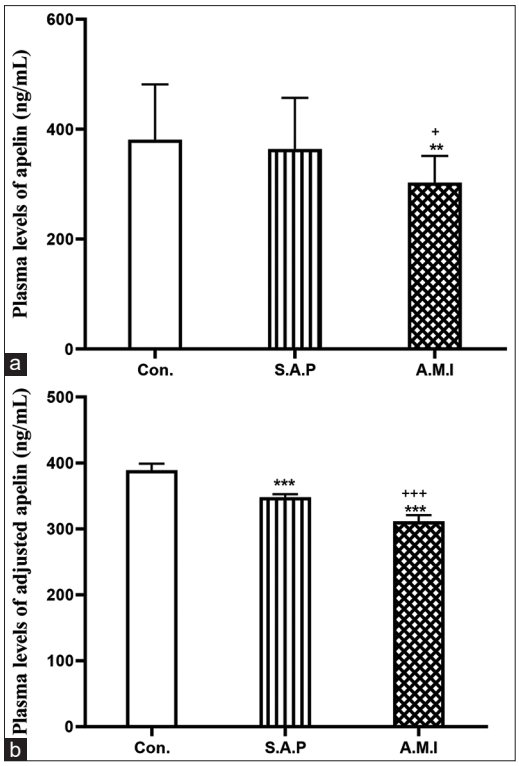

Figure 1: The mean ± standard deviation of plasma levels of (a) apelin, and (b) Adjusted apelin for the age, body mass index, waist–hip ratio, and group. Con = Control group, SAP = Stable angina pectoris group, AMI = Acute myocardial infarction. For statistical differences between the control (con) group and other groups: **: P <0.01, ***; P < 0.001. For statistical differences between SAP with AMI: +: P <0.05, +++; P < 0.001. Comparison between groups was done using ANOVA test

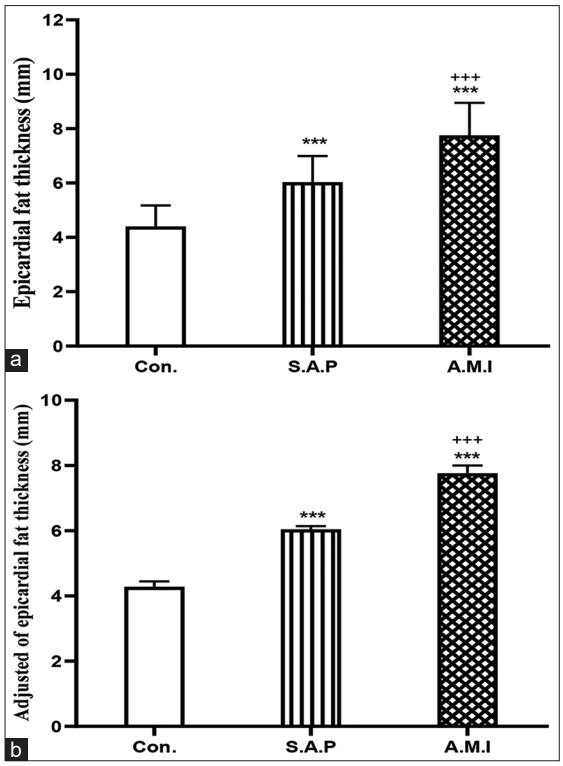

Figure 2: The mean ± standard deviation of the epicardial fat thickness of (a) baseline, and (b) adjusted for the age, body mass index, waist–hip ratio, and group. Con = Control group, SAP = Stable angina pectoris group, AMI = Acute myocardial infarction. For statistical differences between the control group and other groups: ***; P < 0.001. For statistical differences between SAP with AMI: +++; P < 0.001. Comparison between groups was done using ANOVA test

Table 2: Echocardiographic finding

Variable	Control	SAP	AMI	*P*
LVEF (%)	53.33±7.58	43.50±7.44	36.56±9.92	0.000
e' septal (cm/s)	6.80±1.35	6.24±1.69	6.79±1.97	0.354
e' lateral (cm/s)	9.66±2.24	9.59±2.41	9.27±2.51	0.803
TAPSE (mm)	19.41±3.43	17.69±3.08	17.68±3.08	0.059
TV TDI (cm/s)	11.63±1.61	12.27±1.89	11.29±2.08	0.131
EFT (mm)	4.28±1.05	6.02±0.96	7.75±1.19	0.000
EFT (adjusted) (mm)[a]	4.27±0.17	6.04±0.09	7.76±0.23	0.000

[a]Mean±SD by general linear model with adjustment for age, BMI, WHR, and group. Data are expressed as mean±SD. Comparison between groups was done using ANOVA test. SAP: Stable angina pectoris group, AMI=Acute myocardial infarction; SD=Standard deviation; LVEF=Left ventricular ejection fraction; TAPSE=Tricuspid annular plane systolic excursion; TV TDI=Tissue velocity tissue Doppler imaging; WHR=Waist–hip ratio; BMI=Body mass index; EFT=Epicardial fat thickness

The current study demonstrated that plasma levels of apelin were lower in patients with AMI and stable angina. Moreover, the decrease in apelin was also more significant in AMI patients than in stable angina patients. Compared to healthy individuals, decreased serum/plasma apelin levels were reported in ST-elevation AMI,[22] unstable angina,[23] stable angina,[24] AMI,[24] and patients with acute or CHF.[25] Some studies also compared healthy subjects; increased apelin levels in patients with CVD or lack of differences have been reported, in contrast to us.[26] In addition, the present study showed a clear negative association between apelin plasma concentrations and some cardiac markers (troponin-T and CK-MB). Although this association's exact mechanism is unclear, it may be linked to the depletion of myocardial cells or coronary endothelial lesions, which requires further study.[27] In AMI status, many myocardial cells develop infarction, leading to elevation in cardiac markers (CK-MB), and may be a factor in reducing the production of apelin.

In the present study, it was also shown for the first time that there was a significant association between some echocardiographic parameters and apelin, with a positive relationship with LVEF (%) and a negative relationship with EFT. Indeed, the results suggest that apelin plasma levels were independent of epicardial fat thickness (EFT). In previous studies, EFT was reported to be correlated with coronary severity in patients with AMI and stable angina based on the Gencini score.[1,15] Epicardial fat tissue affects coronary artery involvement in acute coronary syndrome patients by releasing paracrine/endocrine inflammatory mediators.[1,15] Based on the results of the present study, it was found that although apelin is mainly released from adipose tissue, myocardial cell damage in patients with AMI had a more significant effect on apelin levels than EFT.

Although the exact mechanism of apelin on its cardioprotective effects is unclear, several possible mechanisms can be

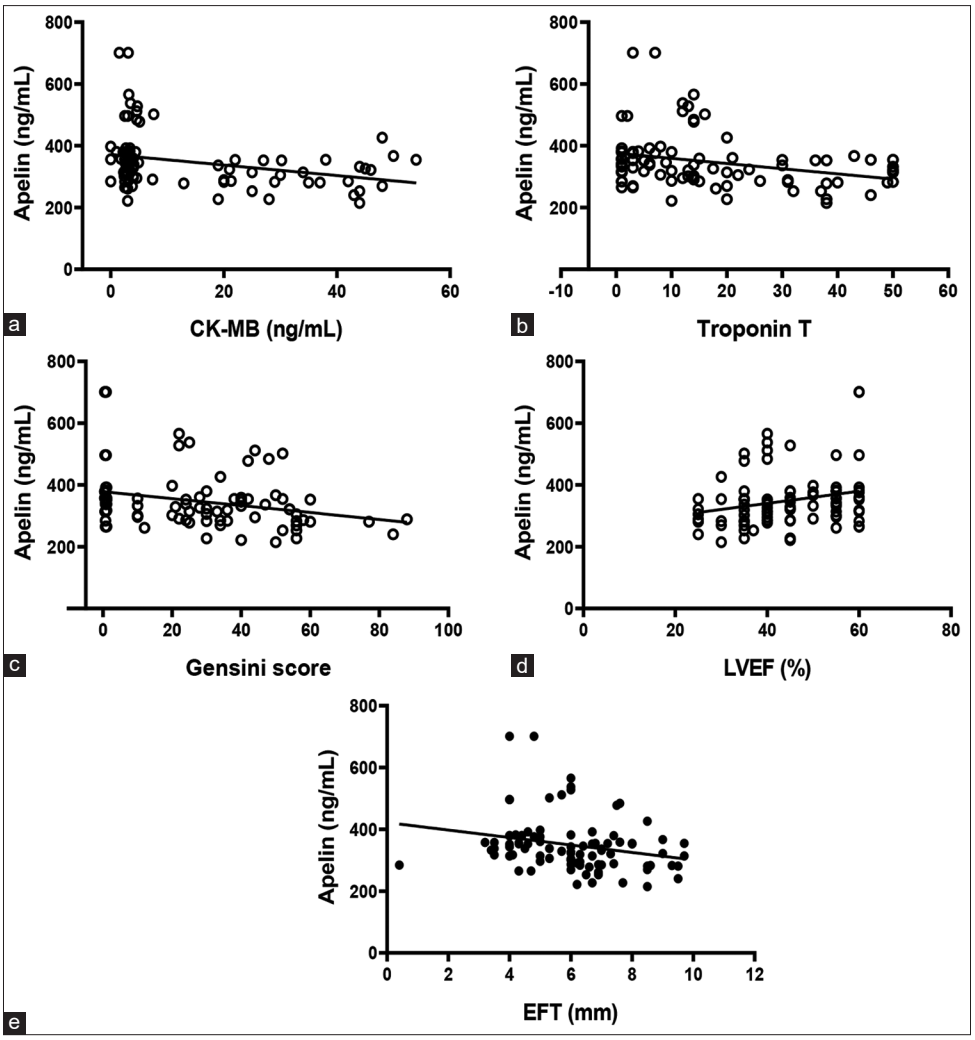

Figure 3: Pearson's correlation analysis of (a) apelin and creatine kinase-MB, (b) apelin and troponin-T, (c) apelin and Gensini score, (d) apelin and left ventricular ejection fraction (%), and (e) apelin and epicardial fat thickness. EFT = Epicardial fat thickness, CK-MB = Creatine kinase-MB, LVEF = Left ventricular ejection fraction

considered for apelin. The anti-atherogenic effects of apelin have been observed by reducing macrophage foam cell formation and promoting intracellular cholesterol efflux.[28] Increased apelin and apelin receptor expression levels in the arteriosclerotic coronary artery may indicate an increase in the anti-inflammatory activity of macrophages in the coronary plaque and thus limit its instability.[5] Apelin has also been shown to reduce the progression of atherosclerosis by inhibiting the effects of angiotensin II.[28] One of the factors influencing the onset and development of atherosclerotic disease is the presence of inflammation. Atherosclerosis is associated with inflammatory markers such as IL-1β, TNF-α, and IL-6.[1] Interestingly, animal studies have demonstrated apelin injection to reduce the expression of monocyte chemoattractant protein-1, macrophage inflammatory protein-1, TNF-α, and IL-6 reflecting its anti-inflammatory effects.[29] Apelin cardioprotective effects have also been observed under ischemia–reperfusion (I/R) conditions. Apelin administration in I/R injury has been shown to have protective effects on the heart, including reducing the size of the infarct, reducing the number of damaged cardiomyocytes, regulating myocardial regeneration, and recovering cardiac function after AMI.[26]

The limitations seen in the current study were the moderate sample size, which requires a large sample size to more accurately investigate the association of apelin in patients with CAD. Since serial apelin measurement was not available in AMI patients, the effects of treatment on changes in apelin concentration were known. Another limitation of the study was the inclusion of only the male sex, which should be considered sex differences in future studies.

CONCLUSION

In summary, the results revealed that apelin levels decreased in AMI and stable angina patients and a detectable negative association with EFT. In addition, the results of the current study showed that changes in apelin levels were more independently associated with cardiac tissue damage.

Despite the association between apelin and EFT levels, further studies are needed to understand its role in the pathophysiology of CADs.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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