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Original Article

Opium Addiction is Associated With Increased Damage to Cardiomyocytes: Protective Roles Played by Apelins

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ABSTRACT

Background: It has been reported that opium can deteriorate the complications of acute myocardial infarction (AMI). Apelins are molecules whose protective roles against cardiomyocytes have been documented previously. The aim of this study was to evaluate the effects of opium on the serum apelin levels in patients with AMI.

Methods: This study was performed on 60 patients with AMI (30 addicted and 30 nonaddicted). The serum levels of apelins, low-density lipoprotein, high-density lipoprotein, triglyceride, cholesterol, total creatine phosphokinase (CPK), and CPK-MB were evaluated using commercial kits.

Results: The results showed that although the serum level of apelins was not different between the addicted and nonaddicted patients, it was significantly associated with heart rate and CPK levels in the addicted patients.

Conclusions: Considering our results, opium addiction may be associated with increased damage to cardiomyocytes. Additionally, the positive association between apelins and CPK may indicate the protective roles played by these molecules during AMI. ***(Iranian Heart Journal 2020; 21(3): 6-14)***

KEYWORDS: Opium, Acute myocardial infarction, Apelin

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Coronary artery disease (CAD) is the most widespread noninfectious disease. [1] This disorder is a major cause of morbidities and mortalities among the Iranian population. [2] Several physiological and pathological pathways, including hormones and cytokines, play key roles in the pathophysiology of CAD. [2] Recently, the roles played by apelin in the functions of the cardiovascular system have been documented. [3] Apelins are important series of endogenous molecules that participate in the regulation of several pathways such as metabolic homeostasis, hypothalamic-pituitary-adrenal axis, cardiovascular functions, and water balance. [4] Apelins are produced as 55-amino acid peptides entitled “preproapelins” and are then cleaved to produce several isomers,

including apelin-36, 19, 17, 13, 12, 11, and 10. [5, 6] Although all forms are biologically active, apelin-36 and apelin-13 are the most important molecules that participate in the induction of the physiological functions of the cardiovascular system. [5, 6] Thus, the environmental factors that affect the expression of apelin-36 may alter the functions of the cardiovascular-related cells and tissues and, hence, may be considered risk factors for the induction of the related disorders, including CAD. Altered serum levels of apelins among patients suffering from cardiovascular diseases have been demonstrated previously. [7]

It has been reported that opium is a crucial risk factor for the development of cardiovascular diseases. [8, 9] Our previous investigation revealed that opium was the main cause of hyperhomocysteinemia in the Iranian population. [10] Therefore, it appears that opium induces cardiovascular diseases via the down- and upregulation of the molecules related to the physiological and pathological conditions of the disorders, respectively.

Due to the fact that apelins play key roles in the physiological functions of the cardiovascular system and opium is a risk factor for the progression of the related diseases, it has been hypothesized that opium may be associated with the diseases by the induction of the altered expression of apelins. [7] We, therefore, performed the present study on patients with AMI to explore the effects of opium addiction on the serum levels of apelins.

METHODS

Subjects

This cross-sectional study was performed on 60 patients with AMI, comprised of 30 opium-addicted and 30 non–opium-addicted patients. Patients with AMI were selected based on clinical symptoms such as chest pain for more than 20 minutes at rest, ST elevation in at least 2 leads more than 0.1 mV, and elevated serum levels of creatine phosphokinase (CPK), CPK-MB, and troponin. Patients who suffered from other disorders such as rheumatic fever, heart failure, cardiomyopathy, liver and kidney diseases, heart arrhythmias, acute infectious diseases, cancers, recent major surgery, autoimmune diseases, and hyperthyroidism were excluded from the study.

Opium addiction was diagnosed based on the criteria of the diagnostic and statistical manual of mental disorders, fourth edition, (DSM-IV). [11] Accordingly, patients were recruited if they had consumed opium at least 3 times a week regularly for a minimum of 3 years.

The ethnic information was collected using a standard questionnaire.

Apelin measurement

Apelin serum levels were evaluated using a commercial kit from Phoenix Pharmaceutical Company, USA, and according to the manufacturer's guidelines.

CPK and CPK-MB levels

Total CPK serum levels were evaluated at the time of the entrance of the patients to the hospital (CPK D1) and then 24 (CPK D2) and 48 (CPK D3) hours after hospitalization using a commercial kit from Pars Azmoon Company, Iran.

CPK-MB was also measured at the time of the entrance of the patients to the hospital (CPK-MB D1) and subsequently 24 (CPK-MB D2) and 48 (CPK-MB D3) hours after hospitalization using a commercial kit (Pars Azmoon Company, Iran.

Biochemical test analysis

The serum levels of triglyceride, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were evaluated using commercial kits (Pars Azmoon Company, Iran).

Statistical Analysis

The data analyses were conducted using the SPSS software, version 18. Due to the normal

distribution of the data in both groups of addicted and nonaddicted patients, the independent Student *t*-test was used to compare the data between the addicted and nonaddicted patients, male and female patients, patients with diabetes mellitus and those without it, patients with hypertension and those without it, patients with hyperlipidemia and those without it, smokers and nonsmokers, and patients with a family history of CAD and those without it. Repeated measure tests were applied to compare the CPK and CPK-MB levels between days 1, 2, and 3. Additionally, the Pearson correlation test was utilized to evaluate the correlations between the numerical data.

RESULTS

The results demonstrated that the serum level of apelins was 18.97 ± 0.99 pg/mL in the opium-addicted patients and 19.24 ± 2.58 pg/mL in the nonaddicted patients. The statistical analyses demonstrated that the difference between the addicted and nonaddicted patients regarding the serum level of apelins was not significant ($P = 0.921$) (Fig. 1). The results also demonstrated that the serum level of apelins in the male addicted patients was not altered when compared with the female addicted patients (19.24 ± 3.05 vs 17.23 ± 0.30; $P = 0.281$) and in the male nonaddicted patients in comparison with the female nonaddicted patients (20.03 ± 3.59 vs 17.26 ± 1.21; $P = 0.637$). In the addicted patients, the serum level of apelins was not also different between the patients with hypertension and those without it ($P = 0.556$), between the patients with type 2 diabetes and those without it ($P = 0.368$), between the patients with hyperlipidemia and those without it ($P = 0.755$), between the smokers and the nonsmokers ($P = 0.973$), and between the patients with a family history of CAD and those without it ($P = 0.460$). The values among the nonaddicted patients were also nonsignificant (Fig. 1).

The Pearson correlation test revealed significant positive correlations between the serum level of apelins and heart rate ($r = 0.392$, $P = 0.032$), CPK D1 ($r = 0.441$, $P = 0.015$), and CPK D2 ($r = 0.428$, $P = 0.018$) in the addicted patients (Table 1), while there was a significant positive correlation between the serum level of apelins and CPK D2 ($r = 0.650$, $P > 0.001$) in the nonaddicted patients (Table 2). Age also had a significant negative correlation with the serum level of apelins in the addicted patients ($r = -0.466$, $P = 0.009$), but not in the nonaddicted patients ($r = 0.298$, $P = 0.124$).

The results showed that the serum levels of triglyceride ($P = 0.021$) and HDL ($P = 0.001$) were lower in the addicted patients than in the nonaddicted patients. There were no significant differences regarding systolic blood pressure ($P = 0.141$), diastolic blood pressure ($P = 0.140$), cholesterol ($P = 0.123$), LDL ($P = 0.989$), CPK D1 ($P = 0.979$), CPK D2 ($P = 0.787$), and CPK D3 ($P = 0.170$) between the addicted and nonaddicted patients.

In the addicted patients, the serum level of CPK D1 was significantly higher in the men than in the women (531.40 ± 111.06 ng/mL vs 143.00 ± 71.85 ng/mL; $P = 0.008$), while the CPK D3 serum level was higher in the male nonaddicted patients than in the female nonaddicted patients (692.13 ± 120.89 ng/mL vs 356.66 ± 75.10 ng/mL; $P = 0.025$).

The serum levels of cholesterol ($P = 0.015$) and LDL ($P = 0.013$) were decreased in the addicted patients with hypertension when compared with those without hypertension. The addicted patients with hypertension also had lower levels of CPK D1 than the addicted patients without hypertension ($P = 0.003$).

However, smoking and familial history of CAD had no effects on the variables in both addicted and nonaddicted patients.

The correlations between the other variables according to the Pearson correlation test in the addicted and nonaddicted patients are presented in Table 1 and Table 2, respectively. The repeated measure tests showed that the levels of CPK-MB D1, D2, and D3 were 55.03 ± 9.12 ng/mL, 147.90 ± 13.20 ng/mL, and 72.61 ± 6.21 ng/mL in the addicted (P < 0.001) and 55.40 ± 5.54 ng/mL, 116.97 ± 8.42 ng/mL, and 64.06 ± 7.41 ng/mL in the nonaddicted patients (P < 0.001), respectively. In the addicted patients, the CPK D1 level was 481.29 ± 55.51 ng/mL, the CPK D2 level was 1448 ± 133.14 ng/mL, and the CPK D3 level was 828.93 ± 77.6 ng/mL (P < 0.001), while the values were 476.71 ± 76.98 ng/mL, 1365.75 ± 107.88 ng/mL, and 597.78 ± 52.45 ng/mL, respectively, in the nonaddicted patients (P < 0.001).

Table 1: Data analysis using the Pearson correlation test in the addicted patients with AMI

		Age	BMI	BPsys	BPdias	PR	TG	Chol	LDL	HDL	CPK D1	CPK D2	CPK D3	CPK-MB D1	CPK-MB D2	CPK-MB D3
Age	PCT	1	.038	.141	-.029	-.162	-.097	-.174	-.162	-.016	-.159	-.244	.128	.149	.037	.211
	P value		.841	.448	.876	.384	.604	.349	.384	.934	.394	.187	.491	.423	.845	.255
BMI	PCT	.038	1	.059	.155	.101	.253	.047	.023	-.188	-.301	.079	-.061	-.503	-.182	-.195
	P value	.841		.751	.405	.587	.169	.800	.901	.312	.100	.674	.745	.004	.328	.294
BPsys	PCT	.141	.059	1	.778	.133	-.297	.121	.160	.270	-.192	-.341	-.112	-.084	-.272	-.244
	P value	.448	.751		.000	.475	.104	.517	.391	.141	.301	.060	.548	.652	.139	.187
BPdias	PCT	-.029	.155	.778	1	.160	-.163	.190	.237	.053	-.335	-.382	-.254	-.323	-.307	-.353
	P value	.876	.405	.000		.390	.380	.306	.199	.775	.065	.034	.168	.076	.093	.052
PR	PCT	-.162	.101	.133	.160	1	.083	-.085	-.085	.014	.377	.292	.032	.302	.290	.101
	P value	.384	.587	.475	.390		.657	.648	.649	.941	.037	.111	.863	.099	.113	.591
TG	PCT	-.097	.253	-.297	-.163	.083	1	-.153	-.320	-.186	.183	.496	.481	.092	.287	.368
	P value	.604	.169	.104	.380	.657		.410	.079	.317	.325	.005	.006	.621	.117	.042
Chol	PCT	-.174	.047	.121	.190	-.085	-.153	1	.978	.421	.006	-.027	-.152	-.212	-.139	-.276
	P value	.349	.800	.517	.306	.648	.410		.000	.018	.974	.887	.413	.252	.454	.133
LDL	PCT	-.162	.023	.160	.237	-.085	-.320	.978	1	.336	-.038	-.138	-.265	-.244	-.205	-.347
	P value	.384	.901	.391	.199	.649	.079	.000		.065	.839	.459	.150	.185	.270	.056
HDL	PCT	-.016	-.188	.270	.053	.014	-.186	.421	.336	1	.039	.022	.029	.075	.020	-.109
	P value	.934	.312	.141	.775	.941	.317	.018	.065		.833	.908	.877	.688	.916	.559
CPK D1	PCT	-.159	-.301	-.192	-.335	.377	.183	.006	-.038	.039	1	.655	.419	.781	.394	.337
	P value	.394	.100	.301	.065	.037	.325	.974	.839	.833		.000	.019	.000	.028	.064
CPK D2	PCT	-.244	.079	-.341	-.382	.292	.496	-.027	-.138	.022	.655	1	.648	.395	.622	.440
	P value	.187	.674	.060	.034	.111	.005	.887	.459	.908	.000		.000	.028	.000	.013
CPK D3	PCT	.128	-.061	-.112	-.254	.032	.481	-.152	-.265	.029	.419	.648	1	.344	.586	.744
	P value	.491	.745	.548	.168	.863	.006	.413	.150	.877	.019	.000		.058	.001	.000
Apelin	PCT	-.466	.225	-.012	.041	.392	.025	.266	.249	.084	.441	.428	.162	.120	.109	.006
	P value	.009	.231	.951	.829	.032	.896	.155	.185	.658	.015	.018	.391	.527	.566	.974

The Pearson correlation test revealed significant positive correlations between the serum levels of apelins and the serum levels of PR, CPK D1, and CPK D2, while age had a significant negative correlation with the serum levels of apelins in the addicted patients. Additionally, there was a negative correlation between BPdias and CPK D2; positive correlations between the TG serum level and the serum levels of CPK D2, CPK D3, and CPK-MB D3; and a positive correlation between PR and CPK D2.

AMI, Acute myocardial infarction; BPsys, Systolic blood pressure; BPdias, Diastolic blood pressure; BMI, Body mass index; TG, Triglyceride; Chol, Cholesterol; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; CPK, Creatine phosphokinase

Table 2: Data analysis using the Pearson correlation test in the nonaddicted patients with AMI

		Age	BMI	BPsys	BPdias	PR	TG	Chol	LDL	HDL	CPK D1	CPK D2	CPK D3	CPK-MB D1	CPK-MB D2	CPK-MB D3
Age	PCT	1	.200	-.119	-.264	-.407	-.298	-.282	-.293	.326	-.191	.239	.098	-.190	.133	.245
	P value		.272	.515	.144	.021	.098	.118	.103	.069	.295	.188	.593	.298	.467	.177
BMI	PCT	.200	1	.201	.167	.098	.100	.186	.177	-.176	-.009	-.189	-.222	-.091	-.169	-.294
	P value	.272		.271	.360	.593	.586	.309	.333	.335	.962	.301	.222	.621	.356	.102
BPsys	PCT	-.119	.201	1	.806	.212	.125	.141	.198	-.280	-.198	-.033	-.099	-.250	-.028	-.074
	P value	.515	.271		.000	.243	.497	.441	.279	.121	.278	.857	.590	.167	.880	.687
BPdias	PCT	-.264	.167	.806	1	.368	.107	.076	.111	-.258	-.011	-.156	-.282	-.053	-.133	-.342
	P value	.144	.360	.000		.038	.559	.679	.546	.154	.951	.395	.117	.772	.469	.056
PR	PCT	-.407	.098	.212	.368	1	.224	.275	.293	-.130	.127	.079	-.086	.090	.092	-.207
	P value	.021	.593	.243	.038		.219	.127	.104	.477	.489	.668	.639	.624	.616	.256
TG	PCT	-.298	.100	.125	.107	.224	1	.703	.225	-.125	-.030	-.136	-.197	-.059	-.054	-.102
	P value	.098	.586	.497	.559	.219		.000	.215	.496	.868	.459	.281	.749	.768	.578
Chol	PCT	-.282	.186	.141	.076	.275	.703	1	.751	.139	-.118	-.185	.041	-.134	.004	-.061
	P value	.118	.309	.441	.679	.127	.000		.000	.447	.519	.312	.825	.466	.981	.740
LDL	PCT	-.293	.177	.198	.111	.293	.225	.751	1	-.052	-.140	-.134	.023	-.139	.010	-.043
	P value	.103	.333	.279	.546	.104	.215	.000		.779	.443	.463	.899	.446	.959	.816
HDL	PCT	.326	-.176	-.280	-.258	-.130	-.125	.139	-.052	1	-.002	.133	.376	.044	.202	.198
	P value	.069	.335	.121	.154	.477	.496	.447	.779		.993	.469	.034	.810	.268	.277
CPK D1	PCT	-.191	-.009	-.198	-.011	.127	-.030	-.118	-.140	-.002	1	.240	.010	.979	.273	-.110
	P value	.295	.962	.278	.951	.489	.868	.519	.443	.993		.186	.955	.000	.130	.551
CPK D2	PCT	.239	-.189	-.033	-.156	.079	-.136	-.185	-.134	.133	.240	1	.481	.279	.869	.658
	P value	.188	.301	.857	.395	.668	.459	.312	.463	.469	.186		.005	.122	.000	.000
CPK D3	PCT	.098	-.222	-.099	-.282	-.086	-.197	.041	.023	.376	.010	.481	1	.031	.593	.489
	P value	.593	.222	.590	.117	.639	.281	.825	.899	.034	.955	.005		.867	.000	.005
Apelin	PCT	.298	-.130	.006	-.215	-.215	-.097	-.148	-.113	-.014	-.104	.650	.099	-.045	-.233	-.302
	P value	.124	.510	.976	.271	.272	.622	.452	.566	.943	.599	.000	.617	.823	.242	.126

The Pearson correlation test revealed significant positive correlations between the serum level of apelins and the serum levels of CPK D2 and also between HDL and CPK D3, while age had a significant negative correlation with PR in the nonaddicted patients.

AMI, Acute myocardial infarction; BPsys, Systolic blood pressure; BPdias, Diastolic blood pressure; BMI, Body mass index; TG, Triglyceride; Chol, Cholesterol; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; CPK, Creatine phosphokinase

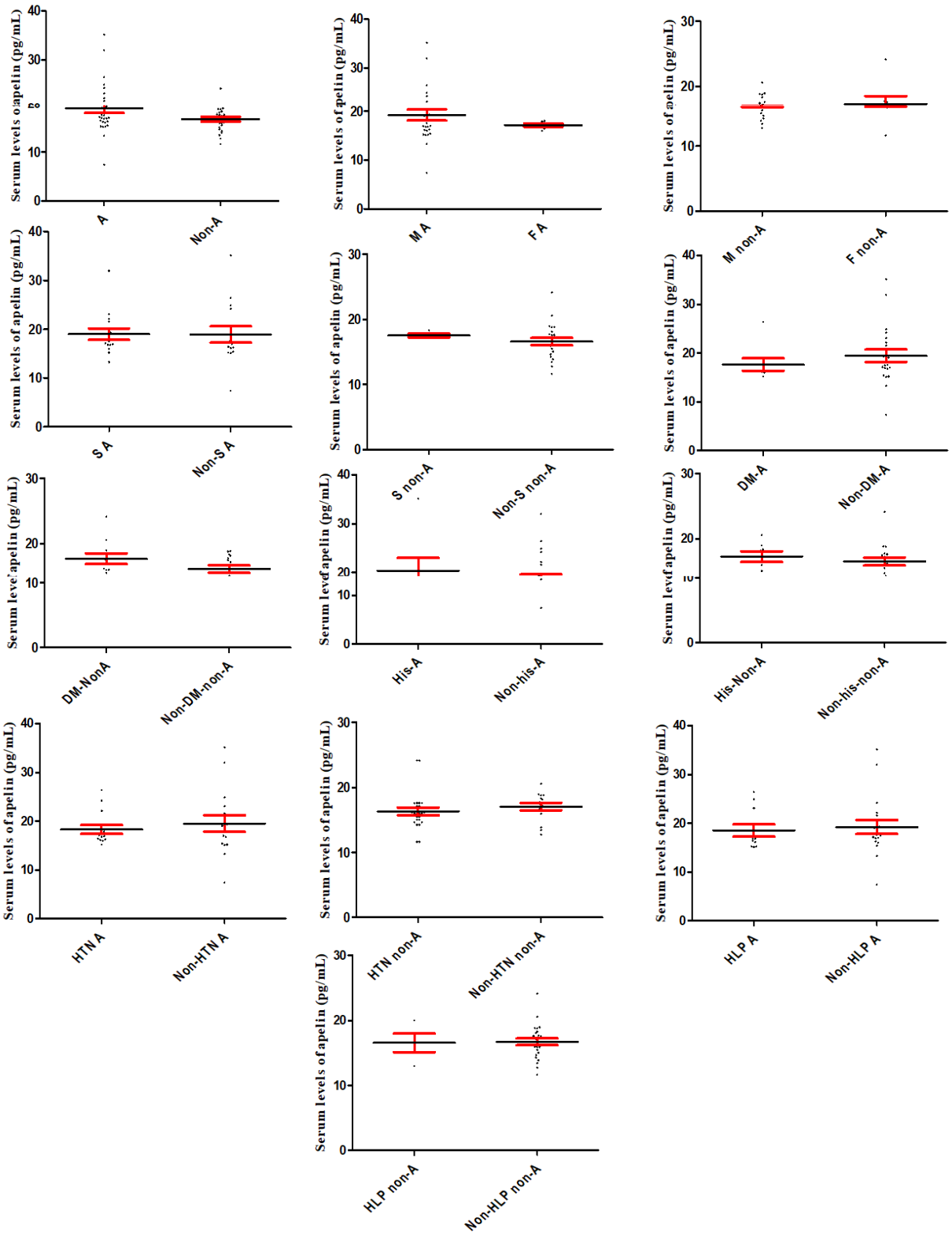

Figure 1: Serum levels of apelins in the addicted and nonaddicted patients with acute myocardial infarction and their related groups are illustrated herein. The serum levels of apelins were not significantly changed between the groups.

A, Opium addicted patients; M, Male; F, Female; S, Smoking; DM, Diabetes mellitus; His, Familial history of CAD; HTN, Hypertension; HLP, Hyperlipidemia

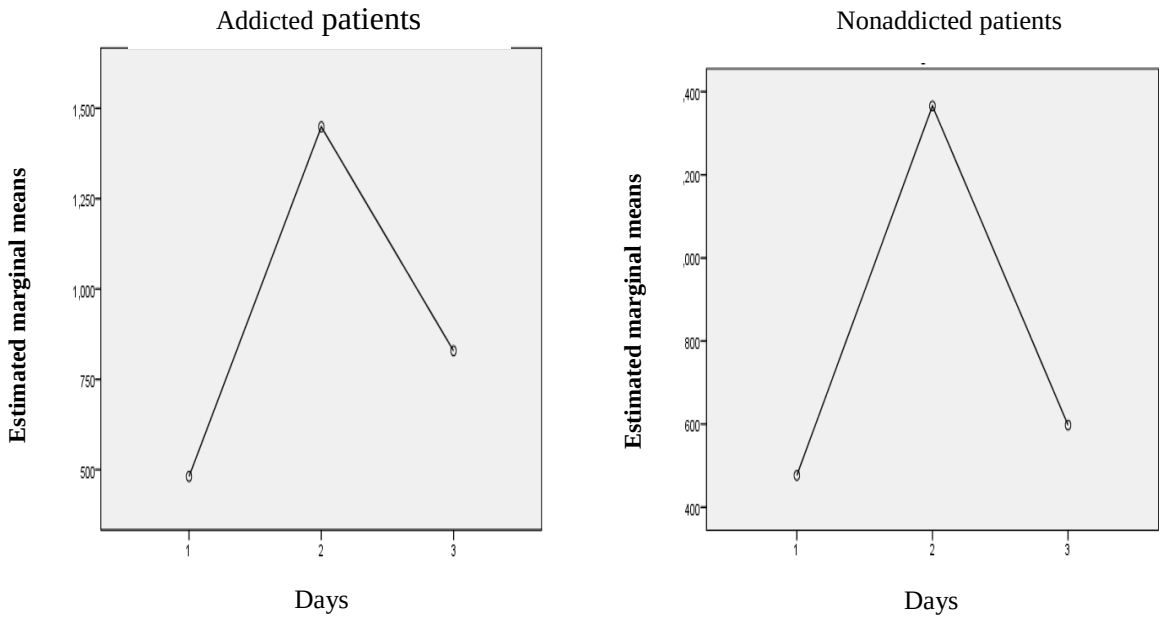

Figure 2: CPK levels on days 1, 2, and 3 in both addicted and nonaddicted patients are illustrated herein. Based on the figure, the serum levels of CPK were lower in the nonaddicted patients than in the addicted patients.
CPK, Creatine phosphokinase

DISCUSSION

Our results demonstrated no significant differences between our opium-addicted and nonaddicted patients regarding the serum level of apelins. Nonetheless, the Pearson correlation test showed significant positive correlations between the serum level of apelins and heart rate, CPK D1, and CPK D2. Further, age had a significant negative correlation with the serum level of apelins in the addicted patients. There was also a positive correlation between the serum level of apelins and CPK D2 in the nonaddicted patients. Based on the results, it appears that apelins were more associated with risk factors in the addicted patients than nonaddicted patients. Due to the fact that the CPK level was significantly higher in the addicted patients than in their nonaddicted counterparts and CPK D3 was decreased more in the nonaddicted patients than in the addicted patients, it appears that AMI complications were worse in the addicted patients. The association between the serum level of apelins and risk factors in our addicted patients may indicate a wider range of damage in opium-addicted patients with AMI. In other words, given that apelins are key molecules in the induction of cardiovascular recovery, their level may be increased to overcome the complications of AMI. Moreover, we found that the values of the risk factors were higher in our addicted patients. We can, therefore, conclude that the serum level of apelins had a positive correlation with the risk factors to overcome the side effects.

To the best of our knowledge, this is the first investigation of its kind to evaluate the relationship between opium addiction and the serum level of apelins; however, previous investigations have reported that opium is a risk factor for the development of AMI. [8, 9] The results of the current study demonstrated that addiction to opium was not associated with an increased expression of apelins; nevertheless,, opium addiction was associated with increased CPK serum

levels and heart rate, which can be associated with the increased expression of apelins. As was mentioned in the Introduction, apelins play crucial roles in the induction of appropriate cardiovascular functions[12, 13]; thus, our results may confirm the protective roles played by apelins against AMI and its complications. Additionally, it has been documented that apoptosis in cardiomyocytes is the most significant complication of AMI. [14, 15] Apelins are important molecules for the regulation of apoptosis. [16] Hence, it may be hypothesized that the serum level of apelins is increased in addicted patients in parallel with risk factors to regulate apoptosis in cardiomyocytes in AMI.

Although diabetes mellitus, smoking, hypertension, and hyperlipidemia are the main risk factors for the development of AMI, [17-19] the serum level of apelins in our study was not associated with the risk factors in both addicted and nonaddicted patients.

Overall, it appears that apelin expression may be associated with the extent of damage to cardiomyocytes, which could be a consequence of the protective roles of apelins against apoptosis in cells.

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