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Research Article

Role and significance of serum Apelin in coronary artery diseases

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Abstract

Background: Worldwide, cardiovascular diseases (CVD) account for many deaths. Atherosclerotic coronary artery disease (CAD) accounts for approximately 45% of all cases. Atherosclerotic plaque builds up in the vascular lumen, leading to CAD. Consequently, the myocardium insufficiently receives oxygenated blood. Although several markers are available for diagnosing CAD, it is important to explore better diagnostic markers for better clinical treatment. Apelin is released by cells including adipocytes, endothelial cells and vascular smooth muscle cells. In the heart, it is a powerful inotrope, raises conduction velocity and has anti-arrhythmic effects. **Aim:** To evaluate serum level of Apelin in patients diagnosed with coronary atherosclerosis and to investigate the relation between Apelin level and severity of coronary atherosclerosis. **Methods:** The study was conducted on 71 subjects divided into 50 patients diagnosed with CAD by angiography and 21 subjects collected from patients presented with chest pain with normal coronary angiogram as control group, CAD severity was calculated by Gensini score. Serum Apelin level was assessed by enzyme-linked immunosorbent assay (ELISA). **Results:** Results revealed that patients with coronary artery atherosclerosis showed statistically significant decrease in serum Apelin when compared to control group ($P < 0.001$). There was significant positive correlation between Apelin and platelet count ($r = 0.319$, $p = 0.024$) and significant negative correlation between Apelin and uric acid ($r = -0.364$, $p = 0.009$). **Conclusion:** Serum Apelin level was lower among patients with myocardial infarction which highlights its value in CAD progression. Also, it could be an early predictor for atherosclerosis and ischemic events.

Key words: Apelin, Coronary artery disease, Risk factors.

Introduction

The majority of fatalities on a global scale are caused by cardiovascular disorders. Among cardiovascular diseases, atherosclerotic coronary heart disease accounts for nearly half of all occurrences and is the top killer in this group [(1)].

One hallmark of the pathogenesis of coronary artery disease is the development of atherosclerotic plaque, which accumulates within the arterial lumen and ultimately causes the disease. This leads to insufficient oxygen-nated blood reaching the myocardium [(2)].

A multitude of variables have the potential to influence the evolution of coronary artery disease (CAD). Numerous factors contribute to this, such as gender, smoking status, age, blood pressure, diabetes, and HDL cholesterol [(3)].

Several ischemia syndromes can be clinical manifestations of CAD. This class includes unstable angina, acute coronary syndromes,

stable angina, and non-ST-elevation myocardial infarction [4].

Activation of the apelin receptor (ApelinR, APLNR) allows the endogenous peptide hormone apelin to carry out its many biological tasks [5].
Adipokine production is attributed to cells such cardiomyocytes, vascular smooth muscle cells, endothelial cells, and adipocytes [6].

In the process of synthesizing apelin, the 77-amino acid pre-propeptide form is generated. White adipose tissue is the source of this ligand, which interacts with G proteins. Its expression has been reported to have increased in a variety of cardiovascular tissues, including cardiomyocytes. [7]

Atherosclerosis, heart failure, arrhythmias, myocardial infarction, and dysregulation of the apelin system are among the several cardiovascular disorders [6].

Aim of the work

The aim of this study was to evaluate serum level of Apelin in patients diagnosed with coronary atherosclerosis and to investigate the relation between Apelin level and severity of coronary atherosclerosis.

Subjects and methods

The study included a total of 71 participants; 51 were patients with coronary artery disease (CAD) as determined by angiography (STEMI, NSTEMI, and unstable angina), with CAD severity measured using the Gensini score. The remaining 21 participants were selected as a control group subjects who presented with chest pain but had normal coronary angiograms. The participants were chosen from the cardiology clinic at Minia University hospital - Faculty of Medicine between April and October of 2023. The hospital's ethics committee approved the study, and each participants provided a written consent. The date of approval is May 15, 2023, and the approval number is 746:5/2023. Patients with history of cerebrovascular stroke, chronic parenchymal lung disease, chronic renal failure, liver illness, or cancer were excluded from the study. About 10 ml of venous blood was withdrawn from each subject using sterile syringe with preservation of aseptic conditions. This sample was divided as follow: 2 ml in ethylene diamine tetra acetic acid (EDTA) containing tube for determination of CBC ,1.6 ml of blood was evacuated in a tube with 0.4 ml of sodium citrate for measurement of ESR (Dilution 4:1),1.8 ml of blood on a tube containing 0.2 ml sodium citrate for detection of prothrombin concentration and APTT (Dilution 9:1), 4.5 ml were let to be clotted in a plain tube in the incubator at 37 ºC then centrifuged for fifteen minutes at about 3000 rpm. Resulted serum was used for determination of kidney function tests, Uric acid, CRP and lipid profile. The remaining part was stored at -20°C for determination of Apelin later by ELISA.

Comprehensive medical history taking, physical examination, radiographic imaging (including coronary angiography) and laboratory testing including CBC determined by **(CelltacES, Nihon Kohden Corporation Automated Hematology Analyser, Japan)**, ESR determined by **(conventional Westergren Method**), renal function test, uric acid and lipid profile determined by **(auto-analyzer SELECTRA PRO XL, ELITech Group, clinical chemistry automation systems, Netherland**), CRP determined by (**GENRUI, BIOTECH INC, Kinetic Assay, China**), prothrombin concentration ,activated partial thromboplastin time and INR (PC, INR, APTT) determined by (**Stago, sta compact max, France**) were all performed on patients and controls. An enzyme-linked immunosorbent assay (ELISA) was used to measure the level of Apelin. The Bioassay Technology Laboratory in China (catalog no. E2014Hu) provided the kit. Statistical package of the social sciences (SPSS) version 27 was used for statistical analysis. We used the Kolmogorov-Smirnov test to make sure the data was normal. When it came to non-parametric quantitative data, the median (IQR) was used, whereas number and percentage were used for qualitative data. Two groups were compared using One-way ANOVA (Analysis of Variance) for parametric data. The Mann-Whitney U test was employed to compare two groups for non-parametric data. For data that was not parametric, Spearman's rank correlation was used. When the p-value was

less than 0.001, it was deemed very significant, and when it was less than 0.05, it was deemed significant.

Results

The age range in group I was from 23 to 80 years with mean ± SD of 54.4 ± 12.3 years. In group II, age was from 20-61 years with mean ± SD equals 40.1 ± 11.9, years. There was statistically significant difference between patients & control group regarding age (Fig.1 and table I). But there was no statistically significant difference between the two groups regarding sex. Moreover, there was high statistically significant increase regarding diabetes mellitus, hypertension and smoking in patients' group when compared to control (P value <0.001) (Table I). Regarding Gensini score, there was high statistically significant difference between patients' group and control group (P value <0.001). (Fig.2 and table I).

Table I: Comparison between the studied groups regarding demographic data.

Variables	Group I *(patients' group)* N=50	Group II *(control group)* N=21	P- value
Age (years)			
Range	(23-80)	(20-61)	***<0.001****
Mean ± SD	54.4±12.3	40.1±11.9	
Sex n (%)			
Male	38(76%)	13(62 %)	0.234
Female	12(24%)	8(38%)	
Diabetes mellitus n (%)			
No	33(66%)	21(100%)	***<0.001****
Yes	17(34%)	0(0%)	
Hypertension n (%)			
No	25(50%)	18(85.7%)	***<0.001****
Yes	25(50%)	3(14.3%)	
Smoking n (%)			
No	31(62%)	21(100%)	***<0.001****
Yes	19(38%)	0(0%)	
Gensini score			
Median	54.25	3	***<0.001****
IQR	(39-83.5)	(2-4)	

: *Significant level at p value< 0.05.

There was high statistically significant increase regarding serum cholesterol, serum triglycerides, serum LDL, and serum urea in patients' group when compared to control group **(P value <0.001)**. **(Fig 3.4 .5.6 respectively).** Also, there was no statistically significant difference regarding serum HDL, serum creatinine and serum uric acid when comparing patient's group and control group **(P value= 0.142, p=0.187, p=0.093),** respectively. **(Table II)**

Table II: Comparison between the studied groups regarding routine biochemical tests.

Variables	Group I *(patients' group)* N=50	Group II *(control group)* N=21	P- value
Cholesterol (mg/dl)			
Median	222.5	185	***<0.001****
IQR	(189.5-265)	(141-193.5)	
Triglycerides (mg/dl)			
Median	144.5	90	***<0.001****
IQR	(119-179)	(79-107.5)	
HDL (mg/dl)			
Median	31.5	40	0.142
IQR	(27-38)	(34-47)	
Mean ± SD	35.5±15.9	41±7.8	
LDL (mg/dl)			
Median	151	107	***<0.001****
IQR	(114-188.5)	(83-132)	
UREA (mg/dl)			
Median	33	24	***<0.001****
IQR	(30-42.3)	(20-29.5)	
CRAET (mg/dl)			
Median	1.1	1.05	0.187
IQR	(1.0-1.3)	(0.9-1.2)	
URIC ACID (mg/dl)			
Median	3.85	4.5	0.093
IQR	(3.2-4.6)	(4-4.9)	

: *Significant level at p value< 0.05

The results in **table (III)** reveal that the total leukocytic count (TLC) significantly increased in the patients' group compared to the control group (p value<0.001) (**Fig 7)**. In addition, the absolute neutrophil count in the patients' group was significantly higher than in the control group (p value<0.001) (**Fig 8).** The neutrophil-to-lymphocyte ratio (N/L ratio) significantly increased in the patients' group compared to the control group (p value <0.001) **(Fig 9).**When comparing the patient and control groups, no statistical significance was found for hemoglobin, platelets, absolute lymphocytes count, absolute monocytes count, absolute eosinophils count, or absolute basophils count (p=0.88, p=0.362, p=0.210, p=0.215, p=0.059, p=0.454, respectively).

Table III: Comparison between the studied groups regarding blood count parameters

Variables	Group I *(patients' group)* N=50	Group II *(control group)* N=21	P- value
Hb(g/dl) *Range* *Mean ± SD*	 (10.1-18.8) 14.4±1.9	 (11.1-17) 13.6±1.5	0.88
TLC (x10^3 /µl) *Median* *IQR*	 11400 (8575 - 13700)	 6400 (4900- 8650)	***<0.001****
PLT (x10^3 /µl) *Median* *IQR*	 263.5 (199- 314.3)	 250 (4900- 8650)	0.362
Absolute Neutrophiles count (cells/µL) *Median* *IQR*	 8770 6150-10631	 3315 2243-4943	***<0.001****
Absolute lymphocytes count (cells/µL) *Median* *IQR*	 1902 1218-3018	 2548 2100-2945	0.210
Absolute Monocytes count (cells/µL) *Median* *IQR*	 418 (246 -525)	 300 (230 -429)	0.215
Absolute Eosinophil count (cells/µL) *Median* *IQR*	 137 (101 -295)	 98 (62 -198)	0.059
Absolute Basophil count (cells/µL) *Median* *IQR*	 0 (0 -110)	 52 (43 -86)	0.454
N/L ratio *Median* *Range*	 4.2 2.52-6.55	 1.5 0.95-1.97	***<0.001****

: *Significant level at p value< 0.05.

The results in table (IV) show that, there was high statistically significant decrease in serum Apelin of patients' group when compared to control group (P value <0.001). **(Fig.10 and table IV)**

Table IV: Comparison between the studied groups regarding serum Apelin.

Variables	Group I *(patients' group)* N=50	Group II *(control group)* N=21	P- value
Apelin (ng/mL) *Median* *IQR*	 0.073 (0.064-0.091)	 0.31 (0.27-0.38)	***<0.001****

: *Significant level at p value< 0.05.

There was significant fair positive correlation between serum Apelin levels and platelet count in patients' group (r = **0.319,** p value = **0.024)** and there was significant fair negative correlation between serum Apelin levels and uric acid in patients' group (r = **-0.364*,** p value = **0.009*).(Table V).**

Table V: Correlations between Apelin and other parameters in patient group.

Variables	Apelin (ng/mL)	
	R	P
Platelets (x10^3 cell /cmm)	0.319*	**0.024**
Uric acid (mg/dL)	-0.364**	**0.009**

There was significant positive correlation between cholesterol and triglycerides, LDL and CRP among patients' group (r = **0.312*,** p value = **0.027),** (r = **0.869*,** p value <**0.001),** (r = **0.308,** p value = **0.03)** respectively. **(Table VI).**

Table VI: Correlations between Cholesterol and other parameters in patient group.

Variables	Cholesterol (mg/dl)	
	R	P
Triglycerides (mg/dl)	0.312*	**0.027**
LDL (mg/dl)	0.869**	**<0.001***
CRP (mg/dl)	0.308*	**0.03**

There was high significant positive correlation between LDL and CRP among patients' group (r = **0.869,** p value **<0.001),** (r = 0**.377,** p value = **0.007)** respectively. There was also significant negative correlation between LDL and HDL among patients' group (r = **-0.383,** p value = **0.006) (Table VII).**

Table VII: Correlations between LDL and other parameters in patient group.

Variables	LDL (mg/dl)	
	R	P
Cholesterol (mg/dl)	0.869**	**<0.001***
HDL (mg/dl)	-0.383**	**0.006**
CRP (mg/dl)	0.377**	**0.007**

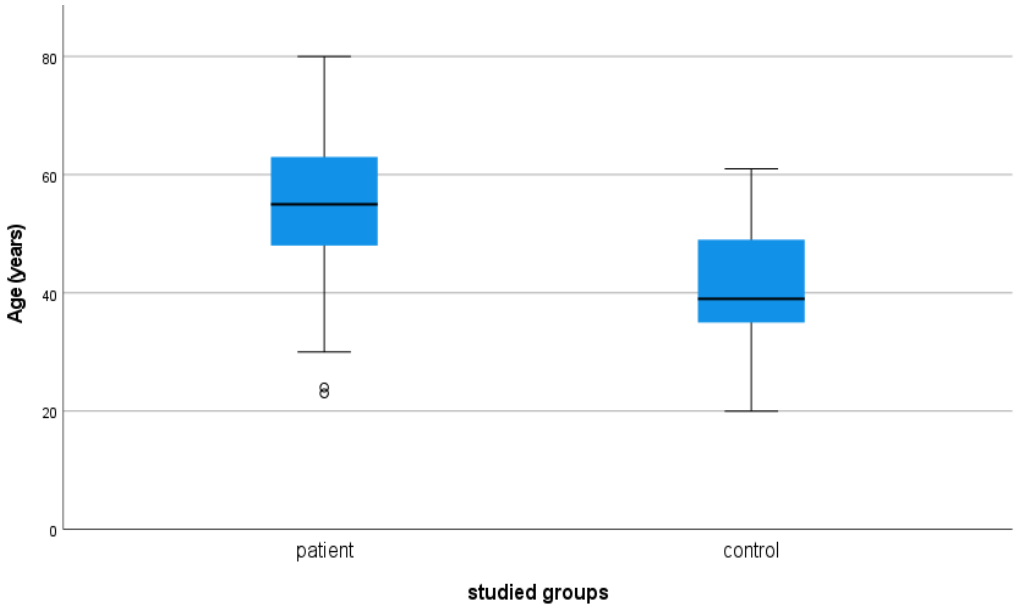

Figure (1): Comparison between the studied groups regarding age.

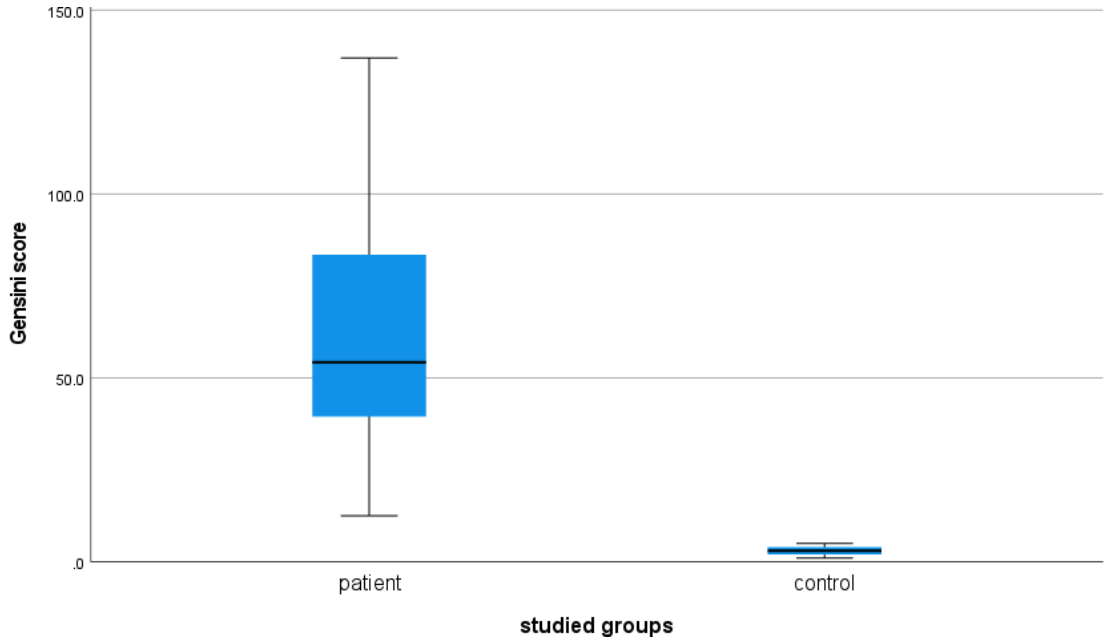

Figure (2): Comparison between the studied groups regarding Gensini score.

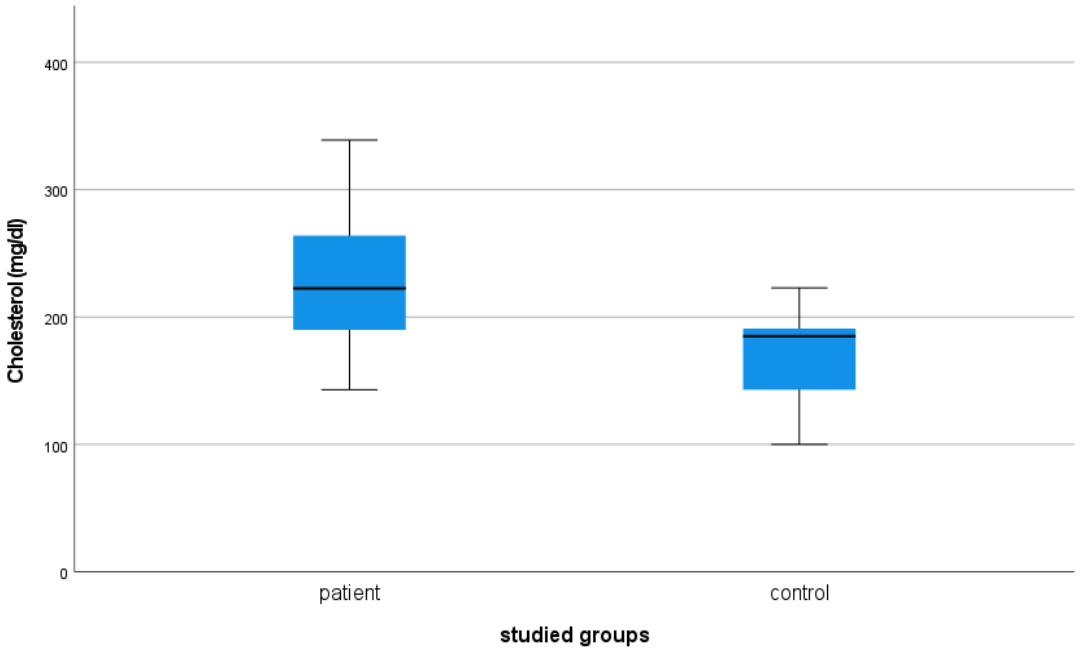

Figure (3): Comparison between the studied groups regarding serum cholesterol.

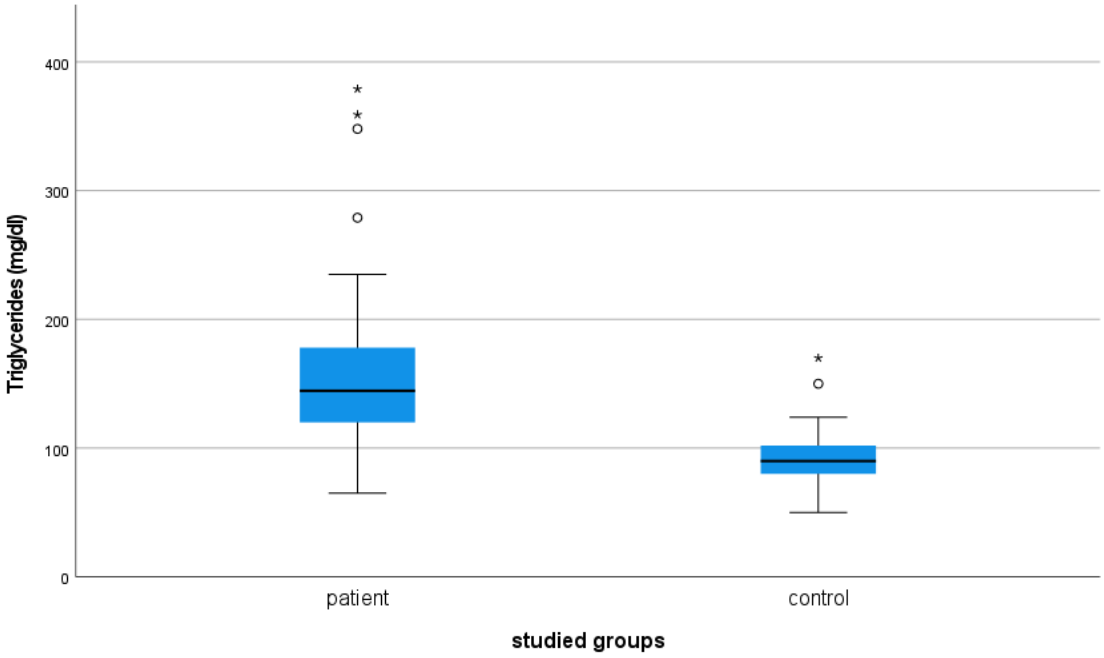

Figure (4): Comparison between the studied groups regarding serum triglyceride

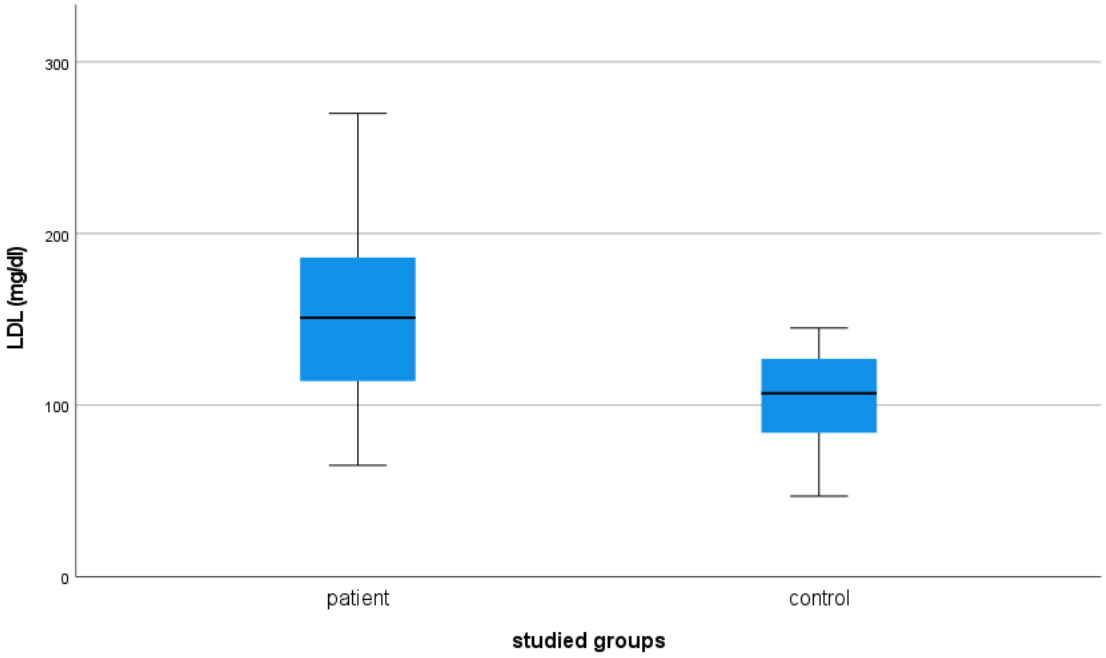

Figure (5): Comparison between the studied groups regarding serum LDL.

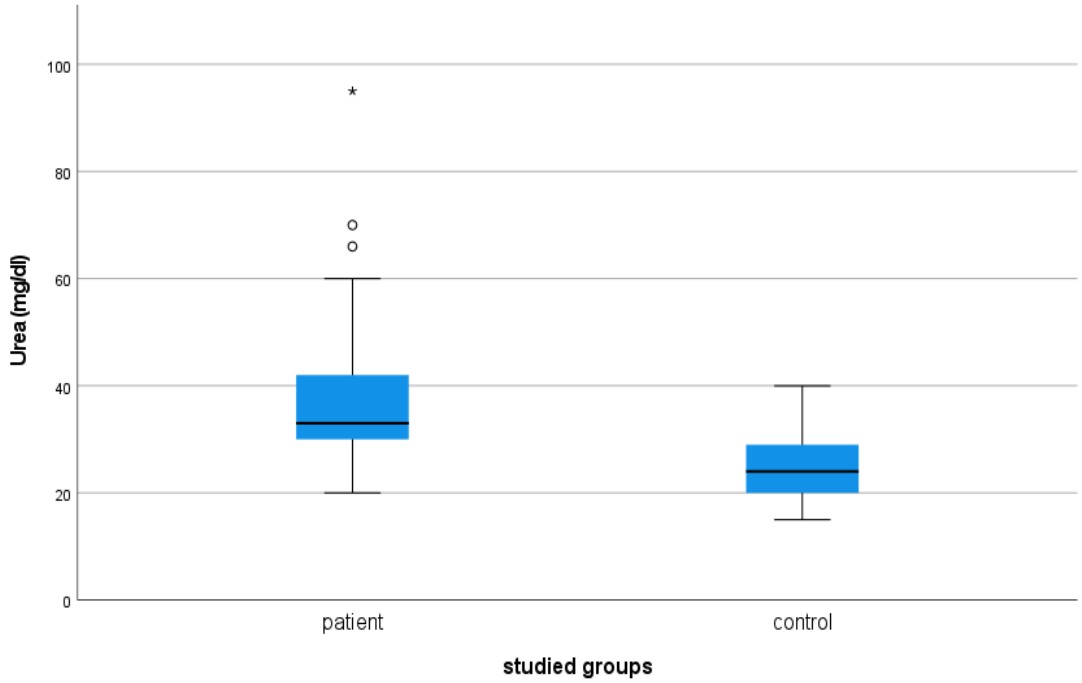

Figure (6): Comparison between the studied groups regarding serum urea.

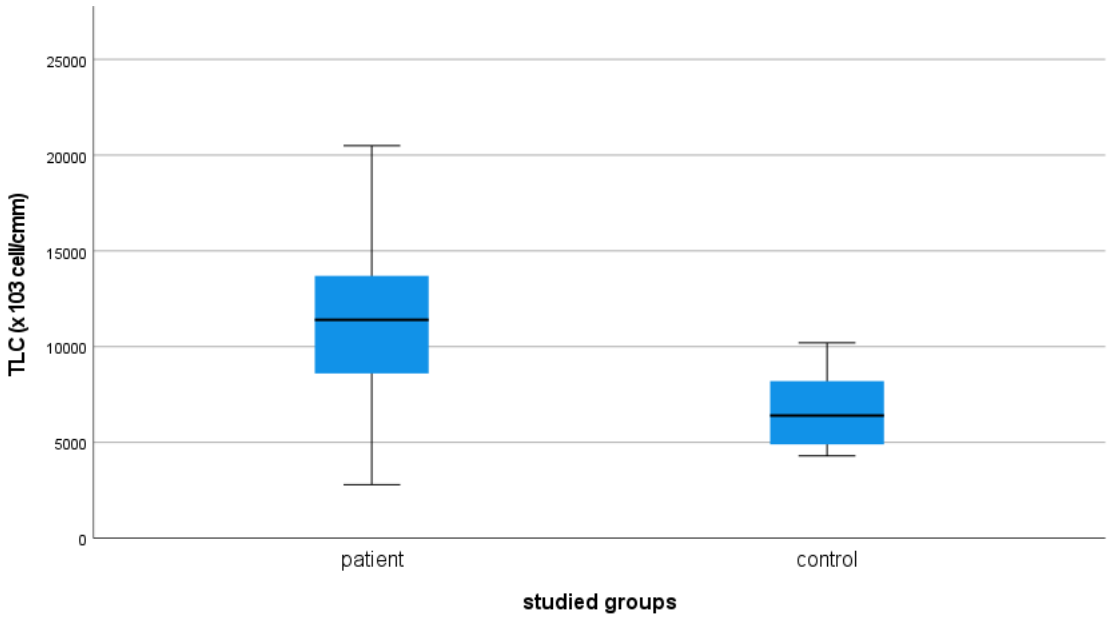

Figure (7): Comparison between the studied groups regarding TLC.

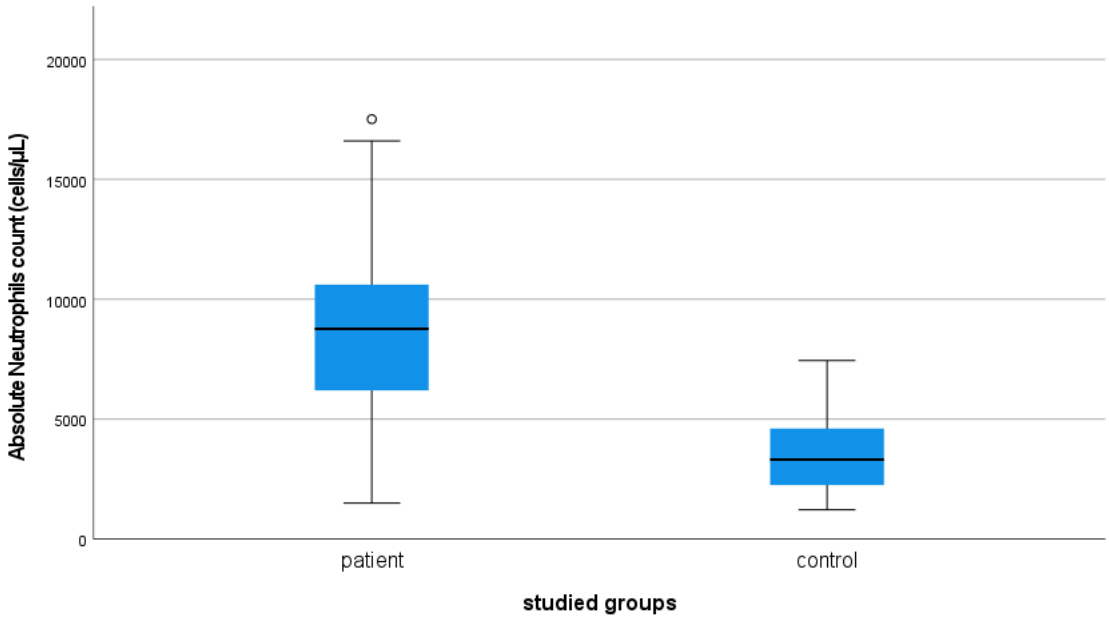

Figure (8): Comparison between the studied groups regarding absolute neutrophiles count.

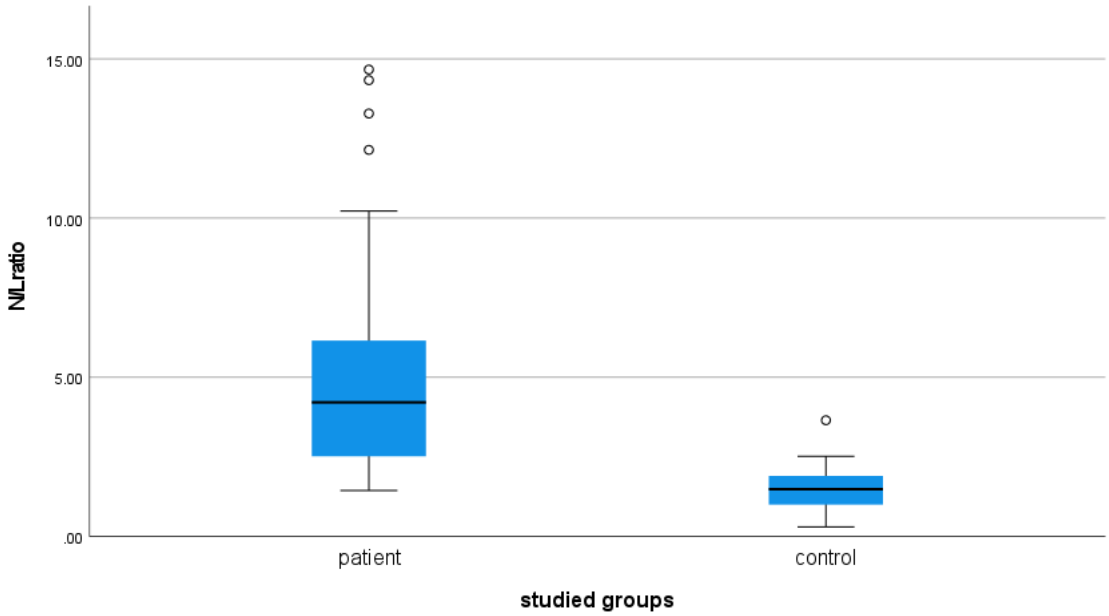

Figure (9): Comparison between the studied groups regarding N/L ratio.

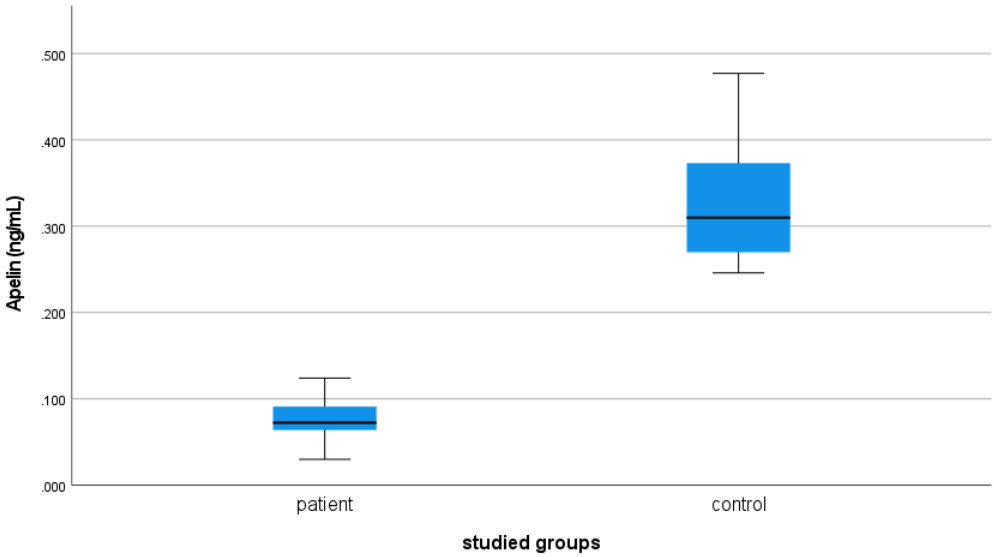

Figure (10): Comparison between the studied groups regarding serum Apelin.

Discussion

When the coronary arteries narrow and less blood reaches the myocardium, a condition known as coronary heart disease develops. To put it simply, atherosclerosis happens when cholesterol builds up inside the lining of the coronary arteries and forms plaque[(9)]. The formation of atherosclerosis is influenced by multiple mechanisms, such as lipid buildup, macrophage activation, vascular endothelial cell dysfunction, vascular smooth muscle cell migration and proliferation, and so on [(1)]. Even if there are approaches to diagnose coronary artery disease, better diagnostic markers are necessary to guide clinical treatment and improve clinical prognosis [(1)].

In the process of synthesizing apelin, the 77-amino acid pre-propeptide form is generated. White adipose tissue is the source of this ligand, which interacts with G proteins. Its expression has been observed to have increased in many CV tissues, including cardiomyocytes [(7)].

Adipokinins are a class of naturally occurring peptides that include this novel ligand for the Apelin receptor 1 (APJ). There are APJ receptors in the endothelium, kidneys, adipose tissue, heart, and lungs [(13)].

The current research shown that Apelin levels were significantly lower in the control group compared to individuals with coronary artery disease (P value <0.001). Consistent with our results, **Akbari and colleagues** [(11)] demonstrated that Apelin levels in the blood were substantially lower in patients with coronary artery disease compared to controls. As well, **Strohbach and colleagues** [(12)] found that circulating apelin peptides were considerably lower in MI patients compared to the control group. **Namazi and colleagues** [(10)] demonstrated that there was a negative correlation between the severity of coronary stenosis and serum apelin levels in individuals with coronary artery disease (CAD) ($p<0.05$). This finding suggests that this peptide may have a role in the development and instability of coronary plaques. However, **Diakowska and colleagues** [(13)] found that blood apelinergic system peptide levels were significantly higher in patients with acute coronary syndrome compared to healthy controls and those with chronic coronary syndrome, indicating compensatory up-regulation mechanisms. This is due to the potential role of the apelinergic system peptides in pathogenic processes of acute coronary syndrome, which suggests that higher levels of Apelin have a protective effect against CAD progression and vascular damage.

Also, the current study shows that Apelin serum levels and platelet count were positively correlated (r = 0.319, p value = 0.024) within the patient group which agrees with the data of **Huang and colleagues**[14]. Moreover, **Strohbach et al.** [12] found that, in comparison to controls of the same age, patients with AMI had substantially lower levels of platelet apelin receptor expression.

In our study, Apelin and uric acid showed a fair significant negative connection in the patients' group as well (r = -0.364, p value = 0.009). **Zhang and colleagues** [15] found similar results regarding apelin-13, suggesting that apelin-13 inhibits adipose RAS (renin-angiotensin system) expression and hence lowers uric acid-induced oxidative stress in adipose tissue. This went against the findings of **Maloberti and colleagues** [16], who demonstrated that uric acid has no correlation with coronary involvement or its severity because in the advanced stages of CAD, other factors (previous myocardial infarction and previous myocardial revascularization) may overshadow uric acid effects.

Our study's participants included 50% with hypertension, and 34% with diabetes mellitus. Accordingly, Hypertension and diabetes mellitus seem to have a more substantial impact on the risk of cardiovascular disease, as supported by findings from **Yen and colleagues**[17] and **Qi and colleagues** [18]**.**

When determining the extent of coronary artery disease, the Gensini score (GS) was used. This score was calculated by adding up the positional scores of all lesions and then multiplying the result by the obstruction severity score, which indicates how bad the disease is. [19]. When comparing
the patients' group with the control group, we found a statistically significant difference (P <0.001) in the Gensini score. Gensini score outperforms other total atherosclerotic load measures in distinguishing between CAD patients with varied degrees of severity and the extent to which their atherosclerosis burden is diffuse, in line with the results of **Aksu and Ahmed** [20].

When compared to the control group, patients with atherosclerosis demonstrated a highly significant rise in blood cholesterol, serum triglycerides, and serum LDL (P <0.001) in this study. This agrees with what **Aguilar-Ballester and colleagues** [21] have said, namely that atherosclerosis develops when modified lipoproteins accumulate in the subendothelial space, which in turn causes major alterations in the differentiation and function of immune cells. Another study by **Raposeiras-Roubin and colleagues** [22]**,** which looked at people at risk for cardiovascular disease, found that hypertriglyceridemia was linked to subclinical atherosclerosis and vascular inflammation, even in those whose LDL-C levels were normal. A similar study by **Mortensen and colleagues** [23], which looked at people with evidence of coronary atherosclerosis, found that LDL-C levels were strongly associated with atherosclerotic cardiovascular disease events. Consistent with previous research by **Helgadottir and his colleagues** [24] showing that an increase in HDL-cholesterol levels had no effect on the incidence of CAD, the current study also demonstrated no statistical significance between serum HDL and disease severity (P-value= 0.142). Atherosclerosis extension was greater in individuals with high TG/HDL levels compared to those with low TG/HDL levels, according to research by **Scicali and colleagues** [25].

Koziarska-Rościszewska and colleagues [26] found a similar relationship between serum CRP level and lipid profile variables including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides, and their results showed a significant positive correlation between cholesterol and CRP in the patients' group as well (r = 0.308, p value = 0.03). A correlation between CRP levels and dyslipidemia was also shown to be statistically significant in this study

This relates to low-density lipoprotein, Consistent with **Ahmed and colleagues** [27] who found lower HDL-C levels and greater serum TC, TG, and LDL-C, we found a strong negative association between LDL and HDL in the patients' group (r = -0.383, p value = 0.006). Among the patients surveyed, a favorable connection between LDL and CRP was also found (r = 0.377, p value = 0.007) The findings were comparable to those of **Koziarska-Rościszewska and colleagues** [26], who found a correlation between the lipid profile (total

cholesterol, LDL cholesterol, and triglycerides) and the serum level of CRP.

Patients with atherosclerosis had significantly higher serum urea levels compared to the control group in this study ($p < 0.001$). Participants with greater renal function tests had a dramatically elevated risk of mortality in coronary artery diseases, according to **Lin and colleagues' [28]**, prospective community-based cohort study on CVD patients.

This study's finding that patient groups had higher white blood cell counts than the control group ($p<0.001$) is in line with what **Kawabe and colleagues [29]** found in their study, which indicated that leukocytosis was common among CAD patients, particularly in severe cases. There were no statistically significant changes between the groups, according to **Matei and colleagues [30]**, who reported WBC count analysis. No reflow, in-hospital MACEs (Major adverse cardiac events), and a higher risk of long-term mortality in patients with STEMI are all connected with the neutrophile/ lymphocyte ratio (N/L) as an inflammatory marker, which is a simple indication of systemic inflammation [31]. In our study, we discovered that the patients' group had a higher absolute neutrophilic count and NLR (neutrophile/lymphocyte ratio) than the control group ($p<0.001$ for both). This finding agrees with **Matei and colleagues'** findings [30] which conclude that the absolute neutrophilia increases with the progression of disease and that there are statistically significant differences between the groups in terms of lymphocyte proportion.

Conclusions

Serum Apelin level was lower among patients with myocardial infarction which highlights its value in coronary artery disease progression, also it could be an early predictor of atherosclerosis and ischemic events which needs further investigations.

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