

The Use of Plasma Apelin Alteration in Diagnosis of Atherosclerosis

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Abstract

Apelin is a bioactive peptide. Apelin and its receptor APJ are widely distributed in different cell tissues, and involved in a wide range of functions in the cardiovascular system. In this study we investigated whether plasma apelin and some other parameters of coronary artery diseases (lipid profile, creatinine kinase "CK-MB", lactate dehydrogenase "LDH", Troponin T "Tn-T", and High Sensitivity C-reactive protein "hs-CRP") levels were altered in plasma of normal and atherosclerotic subjects. We also assessed the association between plasma apelin and other body parameters in these subjects. Methods: The study included 60 patients with coronary artery disease. Patients compared with 24 healthy subjects as control group. The apelin and Tn-T were estimated by competitive ELISA test using commercially available kit. Lipid profile, CK-MB, LDH, and hs-CRP were estimated by colorimetric method. Lipid profiles were determined by using available commercial kits. Results: Plasma levels of apelin in patients were significantly lower ($p < 0.05$) than controls. While, CK-MB, LDH, Tn-T and hs-CRP show significant elevation ($P < 0.05$) in patients compared to control group. Plasma levels of total Cholesterol (TC), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and Triglyceride (TG) were significantly higher ($p < 0.05$) in patients as compared to control group. However, high density lipoprotein (HDL) in patients shows significant decreasing ($P < 0.05$) in comparison to control. Apelin shows no significant correlation with other body parameters in these patients. Conclusion: In this study obtained apelin levels were found to be significantly lower in patients as compared to control group, but not correlated with other studied parameters in patients. Decreasing apelin may be one of the causes for development of vascular disease, or decreasing apelin may be another factor increasing atherosclerotic process, and can be used for diagnosing Atherosclerosis.

Keywords: Apelin, Lipid profile, CK-MB, LDH, Atherosclerosis.

Introduction

In homology cloning, the apelin receptor (APJ) has been designated as an 'orphan', because the function of this receptor was unknown at the time (O'Dowd et al., 1993). In 1998, the endogenous ligand of this receptor was discovered and identified as apelin (Tatemoto et al., 1998). Since this pairing, a number of roles for the apelin/APJ system have been emerged

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including regulation of the cardiovascular system (Kleinz et al., 2005; Masri et al., 2005; Lee et al., 2006; Carpéné et al., 2007; Japp et al., 2008; Ladeiras-Lopes et al., 2008; Pitkin et al., 2010). Apelin is a bioactive peptide. Apelin and its receptor APJ are widely distributed in different cell tissues, and involved in a wide range of physiological and pathological functions in the cardiovascular system. Researches indicated that apelin is a critical factor in the development of atherosclerosis (Lv D et al., 2013). Apelin via a nitric oxide-dependent mechanism lowers blood pressure (Kiyoshige et al., 2001). The signal of Apelin-APJ reduces the risk of cardiovascular diseases (Gunter et al., 2017). In the human cardiovascular system, apelin in the cardiomyocytes behaves as one of the most potent stimulators of cardiac contractility, also apelin has been shown to cause vasodilatation when infused into the human forearm to modulate cardiac contractility. Apelin acts as a mediator of blood pressure and blood flow (Szokodi et al., 2002; Ashley et al., 2005; Japp et al., 2008; Japp et al. 2010). There have been a number of reports of changes in plasma apelin levels in patients with heart failure, with somewhat disparate results. Overall plasma apelin appears to rise in early heart failure but normalize or decrease in later stages. The source of plasma apelin is unclear, and it is not known how this relates to tissue levels (Chen et al., 2003; Chong et al., 2006; Miettinen et al., 2007; Simpkin et al., 2007).

In animal models, Apelin appears to be protecting against ischemia-reperfusion injury and improving cardiac function when administered. There is evidence for the role of the apelin/APJ system in atherosclerosis in mice. Apelin signaling opposed angiotensin II-induced atherosclerosis in mice (Simpkin et al., 2007; Zeng et al., 2009; Ashley et al., 2005).

Implicates of the apelin/APJ system in the pathogenesis of atherosclerosis in man has been investigated (Pitkin et al., 2010).

Materials and Methods

The present study is conducted on 84 subjects, of which 60 subjects were with coronary artery disease patients that visited Cardio Care Unit (CCU) of Baqubah Teaching hospital in a period from October 2017 to February 2018. Patients consisted of 32 males and 28 females. The patients were compared with 24 healthy subjects (20 males and 4 females) chosen as control

group in the study, whom age and body mass index (BMI) matched with patients.

All blood samples were collected in the morning after overnight (8-12 hours) fasting. 8 ml of vein blood was drawn by venipuncture using a 10 ml disposable syringes from each subject. Each blood sample transferred into a separator tube and left for 15 min to clot at room temperature then centrifuged at 4000 rpm for 5min.

The serum TC, HDL-C, and TG were evaluated. Serum LDL-C and VLDL-C were calculated by using Friedewald 's formula. Estimation of plasma apelin was done by competitive Elisa test using commercially available kit.

Statistical analyses were done for tabulated results of all undertaken parameters by the Pearson correlation and t-test, from which p-value were obtained.

Results

Table1 represents the Mean ± standard division (M±SD) values for Age and BMI in patients and control group. The patients and healthy control group were matched in age and BMI.

Table 1- The comparison of M±SD for Age and BMI of patients with healthy control group.

Parameter	M±SD of control (n=24)	M±SD of patients(n=60)	P-value
Age (years)	55.38±10.35	57.78±9.85	0.34
BMI(Kg/m ²)	23.82±1.52	26.56±5.89	0.42

Levels of TC, TG, LDL-C, and VLDL-C were significantly higher (p<0.05) in atherosclerotic patients than in controls, whereas level of HDL-C was significantly lower in patients in comparison to controls as shown in Table 2.

Table 2- The comparison of M±SD for lipid profile of patients with healthy control group.

Parameter	M±SD of control (n=24)	M±SD of patients(n=60)	P-value
TC (mg/dl)	144.95± 75	207.62 ± 19.25	0.001
TG (mg/dl)	98.80± 17.40	168.16 ±26.55	0.001
LDL-C (mg/dl)	75.45 ± 15.40	101.67 ± 23.07	0.049
VLDL-C (mg/dl)	14.16 ± 1.42	33.95 ± 5.36	0.036
HDL-C (mg/dl)	55.44 ± 6.36	31.63 ± 5.33	0.048

Table 3 represents the M±SD values obtained for CK-MB, LDH, Tn-T, hs-CRP, and apelin in patients in comparison with control group. Statistically, patients of atherosclerosis had significantly higher levels of CK-MB, LDH, Tn-T, and hs-CRP than control group (p<0.05), while apelin was significantly lower in patients than control group.

Table 3- M±SD for CK-MB, LDH, Tn-T, hs-CRP, and Apelin in patients in comparison with control group.

Parameter	M± SD of control (n=24)	Mean ± SD of group1(n=60)	P-value
CK-MB (IU/L)	15.14±7.53	78.47±45.78	0.046
LDH (IU/L)	209.13±65.03	410.28 ±393.02	0.043
Tn-T (pg/ml)	4.95 ± 1.86	103.39 ±39.50	0.001
hs-CRP (mg/L)	1.22± 1.07	32.11 ± 24.53	0.001
Apelin (pg/ml)	393.75 ± 153.60	202.15 ± 104.39	0.001

Generally, all levels of studied parameters showed statistically significant differences in patients in comparison to control group as shown in tables 2 and 3.

Correlations

Apelin showed no significant correlation (p>0.05) with other studied body parameters in patients as shown in table 4.

Table 4- Shows the correlation of apelin with other studied parameters in patients

Parameter	r	Apelin (pg/ml) Patients (n=60)
Age (years)	r	-0.064
	p	0.627
BMI(Kg/m ²)	r	0.065
	p	0.620
TC (mg/dl)	r	-0.138
	p	0.292
TG (mg/dl)	r	0.048
	p	0.718
LDL-C (mg/dl)	r	0.161
	p	0.221
VLDL-C (mg/dl)	r	0.048
	p	0.718
HDL-C (mg/dl)	r	-0.004
	p	0.974
CK-MB (IU/L)	r	0.005
	p	0.968
LDH (IU/L)	r	0.045
	p	0.735
Tn-T (pg/ml)	r	0.068
	p	0.607
hs-CRP (mg/L)	r	-0.053
	p	0.687

Discussion

The results of the present study indicated that there is a significant difference in the levels of Apelin between the patients and healthy subjects (low level of Apelin in patients; Table 3).

Atherosclerosis is a chronic lipid metabolism disorder linked with lipid accumulation within the arterial wall, and subsequent formation of foam cells and vascular disease (Moore and Tabas, 2011; Zhang et al., 2014). The level of apelin is decreased in human atherosclerotic coronary arteries (Wang et al. 2013).

Recently, it has become apparent that adipose tissue is an active endocrine and paracrine organ that releases several bioactive mediators (Wilson et al., 2008). The discovery of the apelin-APJ axis is an exciting development in cardiovascular research. Apelin is thought to play roles in cardiovascular functions and volume regulation like vasodilation and decreased blood pressure, vasoconstriction in the presence of dysfunctional endothelium, positive inotropic effects, dilation of afferent and efferent arterioles, and vasoconstrictive effects on smooth muscle cells (Taheri et al., 2002). Increased apelin expression has been found in cardiovascular tissues, cardiomyocytes, vascular smooth muscle cells, and endothelial cells. Notably, apelin recently has been implicated in cardiovascular system physiology in regard to endothelium-dependent vasodilation, cardiac contractility, and the reduction of vascular wall inflammation (Farkasfalvi et al., 2007). Apelin peptides involves widely in the enzymatic reactions or cascades of renin

angiotensin aldosterone system (RAAS) and it also acts as antagonist or counter regulatory towards the action of angiotensin-2, supports the possible role of apelin in vascular reactivity maintenance in diabetes, also cardiovascular diseases and blood pressure maintenance. Any dysfunction or abnormalities in apelin-apelin receptor (APJ) signaling pathway contribute the decreased vasodilation and increased vasoconstriction responses, and also is related to insulin resistance-related disorders (Jiu-Chang et al., 2007). The wide distribution of apelin and APJ throughout the body and its predominant localization in vascular endothelium mirror the distribution of angiotensin-II receptor type I (AT1). The physiological effects of apelin (positive inotropism, vasodilation, decreased blood pressure and diuresis through effect on central nervous system) are opposite to the actions of angiotensin-II. Therefore, apelin acting through APJ receptor may modulate the detrimental effects of AT1 activation and help to prevent progressive left ventricular systolic dysfunction and the onset of heart failure (Chandrasekeran et al., 2008).

The results of the present study are consistent with the study performed by Arnaout and colleagues (Arnaout et al., 2017), which showed that the concentration of Apelin was lower in patients with acute coronary syndrome compared to the healthy group. The results of the study also agreed with the study conducted by Abd Elmouttaleb et al. (2016), which showed that the concentration of aspirin in serum was reduced in patients with acute myocardial infarction.

The results of this study indicated that there were correlations but insignificant values between the apelin and the other biochemical indicators in the study group (Table 4).

The results of the present study are consistent with the study performed by El Dayem et al. (2017), which showed no significant correlation between the reduction of apelin and age, BMI and fat content. However, it contrasted with the study conducted by Abd Elmouttaleb et al. (2016), which showed a significant correlation between apelin with T-cardiopulmonary T, and high-sensitivity C protein.

Conclusion

Apelin levels were found to be significantly lower in patients in comparison to control group, but the decreasing in apelin did not correlated with changing of other studied parameters in patients. Decreasing apelin may be one of the causes of development of vascular disease, or another factor for increase of atherosclerotic process, and can be used for diagnosis of Atherosclerosis. Manufactured or natural apelin can be used for treatment of atherosclerosis.

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