Acute Myocardial Infarction: Melatonin, Apelin, and Visfatin as Predictors of Disease

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Abstract

Background: Acute myocardial infarction continues to be a major health concern. It contributes to morbidity and may end fatally.
Objective: To evaluate Visfatin, apelin melatonin, and interleukin-6 levels in patients with acute myocardial.
Patients and Methods: The study included 30 AMI patients (group :I)and 30 as healthy control group(group: II). Visfatin, apelin melatonin, interleukin-6 levels were assessed.
Results: Significantly higher levels of serum apelin, IL-6, cholesterol, and triglyceride, while significantly lower levels of serum melatonin, visfatin , and HDL were observed in the cases than in the controls. Receiver operator characteristic curve investigation shown the levels of melatonin and apelin are the best biomarkers differentiating subjects with AMI.(AUC=0.997; 95% CI: 0.933 to 1.000, cutoff value ≤ pg/ml)], (AUC =0.952; 95% CI: 0.863 to 0.990, cutoff value >3.21 pg/ml respectively)].
Conclusion: This study shows a significantly increase in apelin, IL-6 while a significantly decrease melatonin, visfatin in the circulation of G:I as compared with G:II. The results obtained in the present study indicate that serum melatonin; apelin might play an important pathogenic role not only in the occurrence but also in the severity of AMI. The circulating level of melatonin provides highly specific biomarker for AMI more than apelin.
Key words: Acute myocardial infarction, Visfatin, Apelin, Melatonin, Interleukin-6.
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Introduction

Myocardial infarction commonly known as heart attack leads to changes in size, shape, and functions of the heart. These changes are referred to as cardiac remodeling and encompass a vast array of pathophysiological alterations, including electrophysiological changes, ventricular dilatation, myocyte hypertrophy, and interstitial fibrosis[1].Visfatin, an adipokine that is highly enriched in the visceral fat, It is a pleiotropic adipocytokine, which acts as a cytokine, a growth factor and an enzyme. Visfatin plays an essential role in a variety of metabolic and stress responses as well as in the cellular energy metabolism[2].

Apelin is a novel adipocytokine produced by white adipose tissue, known as the endogenous ligand of the G-protein coupled receptor with high affinity, involved in the regulation of cardiovascular and fluid homeostasis, angiogenesis and inhibition of apoptosis[3].In the cardiovascular system, it has been detected in endothelial cells of

large channel arteries, coronary vessels, and the endocardium of the right atrium [4].

Melatonin hormone is an endocrine product of the pineal gland; it is released following a circadian rhythm that regulates several physiological and neuroendocrine functions [5]. Melatonin by its antioxidant and anti-inflammatory properties acts a protective factor in atherosclerosis[6].

The aim of the present study was to analyze the circulating levels of visfatin, apelin melatonin, interleukin-6 in patients with acute myocardial.

Patients and Methods

The study was conducted on randomly selected 30 patients with ST-segment elevation acute myocardial infarction (STEMI) (aged 40-60 yrs) who admitted to Tikrit Teaching Hospital / Tikrit / Iraq during the period February 2015 - January 2016, and a group of 30 apparently control subjects(G: II) were included as a healthy group.

Blood samples were taken from all patients after having thoroughly examined after exclusion of subjects with a history a AMI or diabetes mellitus or any chronic diseases, in the morning between 8-9 a.m , then centrifuged at 3500 rpm for 10 minutes, and stored at freeze until assayed. Serum apelin, visfatin, melatonin, and IL-6 were measured by using the commercial enzyme-linked immunosorbent assay,(Ref:54021. IBL International GMBH, Floghafenstrasse 52a. D-22335 Hamburg , Germany) .

Serum Cholesterol, TG and HDL-C concentrations were measured by enzymatic methods using spectrophotometer techniques (Model JENWAY 6105 UV / VIS).

Statistical Analysis

All results are presented as mean ± SD. Student's t-test was used for the analysis of data. Values were considered to be significant at $P < 0.05$. Receiver operator characteristic curve (ROC) analysis was done using MedCalc software for evolution of sensitivity and specificity of the different biomarkers.

Results

The biochemical parameters of the patients, group versus the control group are presented in Table 1, in the form of mean ± SD. The results showed highly significant decrease in the levels of visfatin, melatonin in G:1versus G:2 (0.60±0.03 vs 1.60±0.04 ng/ml;)(Fig.3), (5.4020±0.19422 vs 10.4857±0.24614 pg/ml;) respectively, also, there was highly significant (34.20±1.45 vs6.79±0.20)increase in the levels of interleukine-6 of G:1 when compared to G:2 , as shown in Figure (4).

Cholesterol, triglyceride and glucose levels were higher in the patients compared to the controls (5.7483±0.14793 vs 4.0483± 0.12095 mmol/l; $P < 0.0001$), (2.3172±.11091 vs1.4150 ±.07196 mmol/l ;$P < 0.0001$) ,(5.7225±0.15404 vs4.7452±0.10583 mmol/l; $P< 0.0001$) respectively. High-density lipoprotein, and creatinine levels were significantly lower in the cases than the controls (1.0853±0.02270 vs 1.6133±0.03577 mmol/l ; $p < 0.0001$), (1.0432±.09976 vs0.8737±.01821 mg/dl; $P < 0.0001$) respectively.

The ability of log melatonin and apelin to detect patients with AMI was explored using a ROC curve. The area under the ROC curve of melatonin was 0.997(95% CI: 0.933 to 1.000) (sensitivity 96.67and specificity 100.00) Figure (1), and the cut of point ≤7. The corresponding values of apelin were 0.952 (95% CI: 0.863 to 0.990) (sensitivity 76.67 and specificity 100.00) and cut of point >3.21 respectively Figure (2).

Table (1): Baseline biochemical parameters of MI and control groups.

Parameter	Mean± SD	
	Control group	MI group
melatonin (pg/ml)	10.4857±0.24614	5.4020±0.19422
Visfatin (ng/ml)	1.60±0.04	0.60±0.03*
IL-6 (pg/ml)	6.79±0.20	34.20±1.45*
Total cholesterol(mmol/l)	4.0483± 0.12095	5.7483±0.14793**
TG (mmol/l)	1.4150 ±.07196	2.3172±.11091**
HDL-C(mmol/l)	1.6133±0.03577	1.0853±0.02270**
Glucose(mmol/l)	4.7452±0.10583	5.7225±0.15404**
Creatinine (mg/dl)	0.8737±.01821	1.0432±.09976**

* P<0.01, ** P< 0.0001

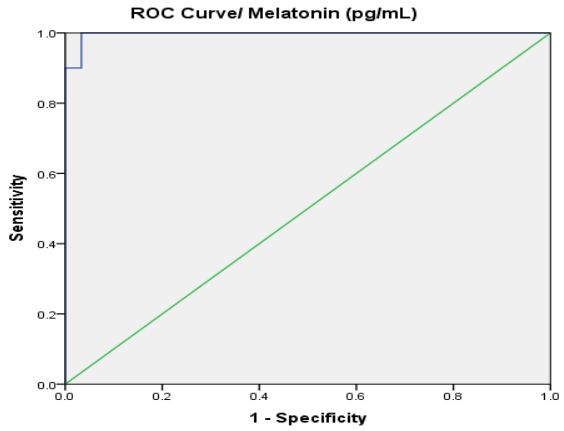

Figure (1):ROC curve for melatonin.

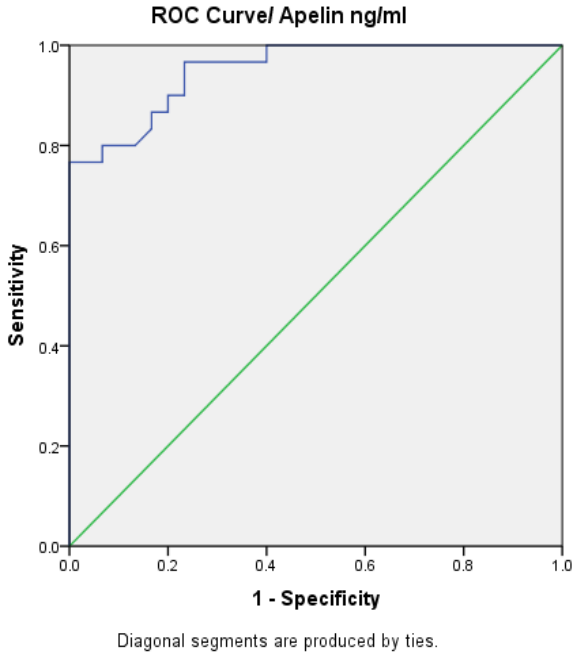

Figure (2):ROC curve for apelin.

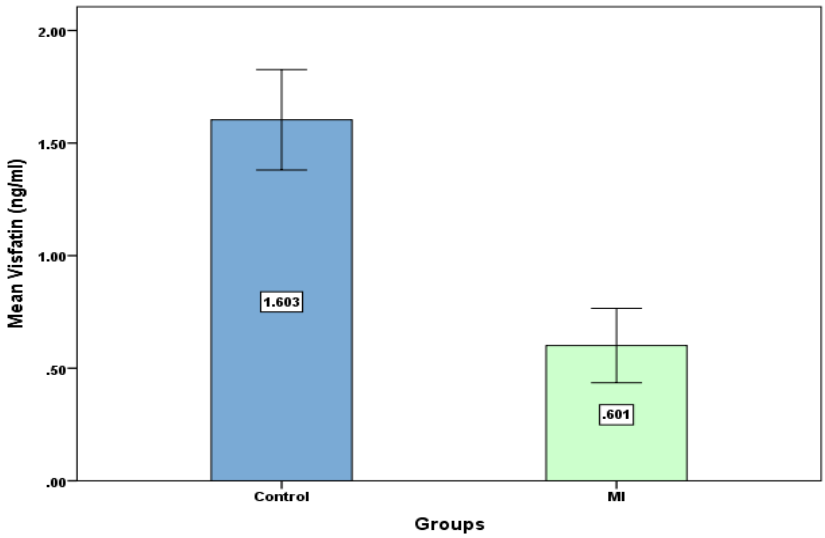

Figure (3): Serum visfatin in patients with AMI and the controls.

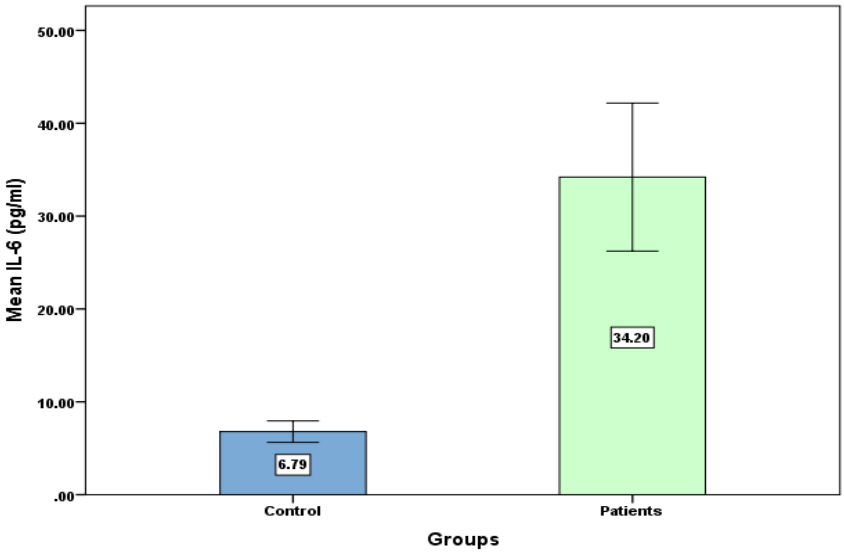

Figure (4): Serum IL-6 in patients with AMI and the controls.

Discussion

Our results showed that apelin level was markedly increased in the G:1 compared to G:2 .Apelin, which is synthesized by endothelial cells, exerts its functions through the autocrine and paracrine pathways by binding to endogenous ligand of the G-protein coupled receptor be expressed absolute presence in most types of cells in the heart, including myocytes, and smooth muscle cells and fibroblasts. After myocardial infarction, necrotic or apoptotic myocytes are substituted with collagen produced by replacement fibroblast cells that are converted to contractile myofibroblasts. This interesting phenomenon in particular is known about the effect of these fibroblasts has on other types of local cells and talk through what's going on, which led to the

proliferation and migration of fibroblasts and myofibroblasts during remodeling the least amount. The inotropic effect apelin has on cardiomyocytes and the vasopressor effect it has on smooth muscle cells are well authenticated, and are reflected important compensatory rejoinders displayed by apelin in MI [1].However little is known about its effect on fibroblast cells, although fibroblasts express the receptor APJ which is the main organizers during remodeling [7].

Apelin has been recognized to play a cardioprotective role in the renovation process that leads to many diseases. Its initial up-regulation at the start of cardiac stress, a tendency revealed in patients [8] is thought to be compensatory. However, its ultimate decay/normalization could donate to the contrary cardiac remodeling[9].

Visfatin is associated with pro-inflammatory state that can contribute in several pathologic changes such as atherosclerosis. In the current work , serum level of visfatin was found to be significantly decreased in patients with AMI .Dahl *et al.*, [10]stated that visfatin would be stared as an inflammatory mediator that is localized to foam cell macrophages within unsettled table atherosclerotic lesions that Likely to be play a role in plaque destabilization. Grounded on this conclusion Adya *et al.* [11] have displayed that visfatin, as a strong catalyst MMP 09/02 may lead to instability of atherosclerotic plaque through the activation of NF- KB. In addition, it was well recognized that visfatin involved in endothelial cells, which causes atherosclerosis, and thus plays an important role in various forms of cardiovascular disease [11].

The present study showed that the decrease in serum levels of melatonin in AMI vs control group. Myocardial ischemia-reperfusion injury is always accompanied by myocardial infarction. Reduce the size of infarction is of great importance in myocardial recovery after injury. Lee *et al.*, [12]stated That melatonin caused a significant decrease in the size of infarction. Bent on cardioprotective action of melatonin may be due to its antioxidant activity, due to its ability to inhibitor of neutrophils in myocardial tissue. Dominguez-Rodriguez *et al.*, [13]advises that melatonin plays a key role in the incidence of coronary heart disease; this is reliable with explanations that melatonin reduces infarct size after heart attack Sahna *et a*l., [14]. Vazan *et a*l., [15] reported that melatonin significantly shorten the overall duration of arrhythmia arising from ischemia-reperfusion.

Dominguez-Rodriguez , Abreu-Gonzalez and Reiter [16] confirmed that melatonin has cardioprotective effect as it acts direct free radical scavenger and indirect antioxidant , it reacts with various with various reactive oxygen species and reactive nitrogen species, it also upregulates antioxidant enzymes and down regulates pro-oxidant enzymes. This decrease in melatonin levels may be due to the depletion of melatonin because it functioned in protection against ischemic - myocardial reperfusion damage, despite the fact that there is a difference in the mechanism by which this compound exerts of the protective effects of the heart .

Interleukin-6 (IL-6) is a multifunctional inflammatory cytokine that plays an important role in the response to environmental stress and has been implicated in the pathogenesis of many chronic diseases including vascular disease [17]. The level of IL-6 is higher in patients with AMI than control group. Our findings are in the line with Leal et al. 2012, and Dah *et al*.2007 [18, 19]. Shpektor [20] assume that the Beside ischemic heart infarction, ischemia whole body, extreme vasopressor treatment, and noncardiac device failure are factors that contributed the release of IL-6.

Conclusion: The present study showed that AMI was associated with low serum

melatonin, and visfatin levels. In contrast, AMI was associated with high levels of both serum apelin, and IL-6, melatonin, and visfatin. The results obtained in the present study indicate that serum melatonin, and apelin might play an important pathogenic role not only in the occurrence but also in the severity of AMI.

The limitation to the present study is the relatively small patients' number included in the study. The future plan will be directed towards melatonin receptor gene polymorphisms and their effects on the circulating levels of melatonin and the signaling capacity of melatonin.

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