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Serum Level of Interleukin-33, C-Reactive Protein, and Troponin in Iraqi Coronary Artery Disease Patients

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Abstract

Coronary artery disease (CAD) is a condition of an inadequate supply of oxygenated blood to a portion of the myocardium. It typically occurs when there is an imbalance between supply and demand of myocardial oxygen. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery or arteries which is sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. Fifty CAD subjects (23 females and 27 males) were enrolled in this study in addition to thirty healthy control subjects (13 female and 17 male). This study aimed to measure the serum levels of interleukin IL- 33, C- reactive protein and troponin in CAD and their association with lipid profile by using enzyme-linked immune sorbent assay (ELISA). T results showed that high-density lipoprotein (HDL) was statistically high while differences in cholesterol, triglyceride and low-density lipoprotein (LDL) were statistically non-significant between CAD patients and controls. Moreover, the serum level of IL-33 and CRP were statistically higher in patients than controls, while troponin levels were not significantly different. In addition, the present study demonstrates that IL-33, CRP, and Troponin were not associated with lipid profile. The relationship of IL-33 with CRP and troponin was non-significant.

Keywords: Coronary artery disease, Interleukin-33, C-reactive protein, Troponin, High-density lipoprotein, Low-density lipoprotein, Cholesterol, Triglyceride.

المستويات المصلية للبين ابيضاض – 33 والبروتين التفاعلي سي والتروبونين ، للعراقيين المصابين بمرض الشريان التاجي

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الخلاصة

مرض الشريان التاجي (CAD) هو الحالة التي لا تصل فيها إمدادات كافية من الدم والأكسجين إلى اجزاء من عضلة القلب ، ويحدث عادة عندما يكون هناك اختلال في التوازن بين تغذية وحاجة عضلة القلب للاوكسجين. وان السبب الأكثر شيوعا لنقص تروية عضلة القلب هو مرض تصلب الشرايين في شريان واحد او عدة شرايين تاجية نخابية كافية لتضييق منطقة جريان الدم في عضلة القلب وعدم كفاية التروية في عضلة القلب التي تجهز عن طريق الشريان التاجي. وقد اجريت هذه التجربة بالاستعانة بخمسين مريض ممن يعانون من مرض الشريان التاجي (23 اناث و27 ذكور). بالإضافة إلى ذلك تمت الاستعانة بثلاثين متطوع من

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الاصحاء (13 اناث و17 ذكور). صممت هذه الدراسة لقياس المستويات المصلية للانترلوكين–33 والبروتين التفاعلي–سي والتروبونين عند مرضى الشريان التاجي وارتباطها بمستوى الدهون باستخدام تقنيةالامتزاز المناعي المرتبط بالانظيم (ELISA).أظهرت النتائج ان للبروتين الدهني عالي الكثافة قيم عالية وذات دلالة احصائية بين مجموعتي المرضى والاصحاء ، بينما لم تظهر نتائج الكولسترول والدهون الثلاثية و البروتين الدهني منخفض الكثافة فروقات ذات دلاله احصائية بين الاشخاص المصابين بمرض الشريان التاجي والاصحاء ، وان مستوى الانترلوكين–33 والبروتين التفاعلي–سي سجلت ارتفاعا معنويا في المرضى دون الاصحاء. مع ذلك فان مستوى التروبونين لم يظهر فرقا ذا دلالة بين المجموعتين قيد الدراسة. وعلى ضوء نتائج هذه الدراسة نستنتج عدم وجود علاقة بين كل من انترلوكين–33 والتروبونين والبروتين التفاعلي سي وبين مستوى الدهون.علاقة الانترلوكين–33 بالبروتين التفاعلي سي والتروبونين ليست ذات دلالة احصائية.

Introduction

Coronary artery disease (CAD) means narrowing of the coronary arteries (arteries that supply blood to the heart). This narrowing is due to a bulid up in the walls of the arteries of plaque (deposits made up of cholesterol, other fats, and calcium)—a process called atherosclerosis (hardening of the arteries). If a plaque becomes delicate and breaks, a blood clot will quickly form that can block blood flow in the artery and may lead to myocardial infarction (death of the heart muscle area supplied by the blocked artery), often referred to as a heart attack [1]. Coronary heart disease was initially thought to be a disease of modern humans, with the cause being attributed to contemporary lifestyles [2]. Patients are considered stable if they are asymptomatic or if their symptoms are controlled by medications or revascularization [3, 4].

Interleukin-33 is a recently discovered cytokine that belongs to the IL-1 superfamily and is mainly expressed by different types of structural cells [5, 6]. IL-33 binds to a specific receptor named T1/ST2 (also known as ST2) that belongs to the toll-like receptor (TLR)/IL1R superfamily [7]. Interleukin-33 transcript and protein is widely expressed in different cell types including in cells of both hematopoietic as well as non-hematopoietic origins such as macrophages, dendritic cells, fibroblasts, adipocytes, smooth muscle cells, endothelial cells, bronchial, osteoblast and intestinal epithelial cells [8,9]. IL-33 is a cytokine that is constitutively expressed in the nuclei of endothelial and epithelial cells [10,11]. The full-length of IL-33, pro-IL-33, serves as a gene regulator that is localized in the nuclei [12], whereas mature IL-33 serves as a cytokine after release into the extracellular space at the onset of tissue injury [13,14]. C-reactive protein (CRP) is an acute-phase protein that serves as an early marker of inflammation or infection. The protein is synthesized in the liver and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, CRP levels rise rapidly within the first 6 to 8 hours and peak at levels of up to 350–400 mg/L after 48 hours [15]. CRP binds to phosphocholine expressed on the surface of damaged cells, as well as to polysaccharides and peptosaccharides present on bacteria, parasites, and fungi. This binding activates the classical complement cascade of the immune system and modulates the activity of phagocytic cells, supporting the role of CRP in the opsonization (i.e. the process by which a pathogen is marked for ingestion and destruction by a phagocyte) of infectious agents and dead or dying cells [16]. When the inflammation or tissue destruction is resolved, CRP levels fall, making it a useful marker for monitoring disease activity [17]. Cardiac troponin biomarkers are an essential component used to diagnose acute MI [18]. In the late 1980s, cTnI was proposed as marker of cardiac cell death, and is now widely used and established as the guideline-recommended marker in order to assist in the diagnosis of myocardial injury in clinical pathologies, such as post-surgery myocardium trauma, chemotherapy cardiotoxicity and many other diseases related to cardiac muscle injury [19].

This study aims to measure serum levels of IL-33, CRP and troponin in CAD patients.

Materials and methods

Sample collection

The samples were composed of fifty CAD patients (27 male and 23 female) aged between 3 months and 70 years and thirty genetically unrelated, healthy volunteers (17 men and 13 women) aged between 22 and 46 years. The blood samples collection extended through the period of October 2018 to February 2019. Blood samples of patients were collected from Ibn Al-Bitar Specialized Center for Cardiac Surgery, Baghdad- Iraq. All patients gave their informed written approval to participate in the

study. The diagnosis was confirmed by experienced doctors. The entire participants were of unrelated Iraqi origin and had similar geographic data.

Blood sample collection

Blood samples were collected from CAD patients and healthy controls by using a 10 ml disposable syringe in gel-containing tubes, left to clot at room temperature (20-25 ºC) for 10 minutes, then centrifuged at 5000 rpm for 5 minutes to obtain serum. Serum was separated after centrifugation and divided into three Eppendorf tubes to avoid multiple freezing and thawing and kept frozen for further experiments.

Laboratory methods

Serum levels of IL-33, CRP and troponin was determined by using enzyme-linked immunosorbent assay (ELISA). The lipid profile was analyzed according to the results of laboratory tests ordered during outpatient visits, which included cholesterol levels, triglycerides, HDL and LDL [20].

Statistical analysis

Analysis of data was carried out by using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the differences of different means (quantitative data) was tested by using Students t-test for the differences between two independent means, while Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) was either positive (direct correlation) or negative (inverse correlation) with a value of <0.3 representing no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. In addition to correlation, the r2 was calculated (The coefficient of determination), i.e. when the value of r=0.58, then r2=0.34, this means that 34% of the variation in the values of y may be accounted for by knowing values of x or vice versa [21].

Result and Discussion

Lipid profile

The concentrations of lipid profile compounds of eighty individuals (50 CAD patients and 30 controls) are presented in Table-1. The mean concentration of cholesterol in CAD patients compared to controls was 157.92±45.28 versus 165.37±30.35mg/dl, respectively, while for triglyceride was 127.22±72.87 versus 96.50±70.59mg/dl, for LDL was 91.50±40.87 versus 93.37±22.59 mg/dl. The differences were not significant (P > 0.05). While, the HDL mean concentration was 40.58±12.52 versus 52.70±15.28mg/dl and this difference was statistically significant (P < 0.05).

Table 1- Lipid profile of CAD patients and healthy control

Parameters	CAD Patients (n=50)	Controls (n=30)	Probability
Cholesterol(mg/dl)	157.92±45.28	165.37±30.35	0.427
Triglyceride(mg/dl)	127.22±72.87	96.50±70.59	0.069
HDL(mg/dl)	40.58±12.52	52.70±15.28	0.0001*
LDL(mg/dl)	91.50±40.87	93.37±22.59	0.819

Serum level of IL-33

The serum level of IL-33 was significantly higher (P=0.004) in patients experiencing CAD as compared to controls (115.33±116.20 versus 59.72±52.53pg/ml respectively), as shown in Table-2.

Table 2-IL-33 level of CAD patients compared to controls

Groups	No.	IL-33concentration pg/ml(Mean±S.D)	Probability
CAD	50	115.33±116.20	0.004*
Control	30	59.72±52.53	

*Significant difference P< 0.05

The association of IL-33 with lipid profile

The results of the correlation of IL-33 with cholesterol, triglyceride, HDL, and LDL in the patients and the control group are illustrated in Table-3. The results showed that the correlation coefficient r of cholesterol was higher in CAD patients than in the controls (0.053 versus -0.070, p=0.715 versus 0.712), while the r-value of triglyceride was -0.002 versus -0.112, p=0.989 versus 0.557. In addition, the r value of HDL was -0.105 versus 0.052, p=0.469 versus 0.783 and that for LDL was 0.103 versus -0.060, p=0.475 versus 0.752. The differences were not statistically significant ($p > 0.05$ and $r < 0.3$).

Table 3-Correlation of IL-33 with Lipid profile

Lipid profile		IL-33(pg/ml)	
	Correlation coefficient and probability	**Patients**	**Controls**
Cholesterol(mg/dl)	**r**	0.053	-0.070
	p	0.715	0.712
Triglyceride(mg/dl)	**r**	-0.002	-0.112
	p	0.989	0.557
HDL(mg/dl)	**r**	-0.105	0.052
	p	0.469	0.783
LDL(mg/dl)	**r**	0.103	-0.060
	p	0.475	0.752

Serum level of CRP

Table-4 shows the mean distribution of CRP in CAD patients compared to healthy controls. The results showed an increased level of CRP in CAD patients compared to control (0.07±0.04 versus 0.03±0.03mg/ml, respectively), while the difference was statistically significant (P=0.0001).

Table 4-CRP level of CAD patients compared to controls.

Groups	**No.**	**CRP concentration mg/ml(Mean±S.D)**	**Probability**
CAD	50	0.07±0.04	0.0001*
Controls	30	0.03±0.03	

*Significant difference P< 0.05

The association of CRP with lipid profile

The correlation relationship of CRP with cholesterol, triglyceride, HDL, and LDL in patients and control groups is illustrated in Table-5. The results showed that the correlation coefficient values of cholesterol in CAD patients versus controls were(-0.170 versus -0.185, p=0.239 versus 0.3 28, for triglyceride was -0.330 versus -0.178, p=0.019 versus 0.345. In addition, the r value for HDL was -0.151 versus -0.102, p=0.295 versus 0.592 and for LDL was -0.031 versus -0.068, p=0.830 versus 0.722. The results were not statistically significant ($p > 0.05$ and $R < 0.3$)

Table 5-Correlation of CRP with lipid profile

Lipid profile		**CRP(mg/ml)**	
	Corrlation coefficient and probability	**Patients**	**Controls**
Cholesterol(mg/dl)	**r**	-0.170	-0.185
	p	0.239	0.328
Triglyceride(mg/dl)	**r**	-0.330*	-0.178
	p	0.019	0.345
HDL(mg/dl)	**r**	-0.151	-0.102
	p	0.295	0.592
LDL(mg/dl)	**r**	-0.031	-0.068
	p	0.830	0.722

Serum level of troponin

Table-6 shows the mean distribution of troponin in CAD patients compared to healthy controls. The results did not show relative changes in the level of troponin in CAD patients compared to the control (6.83±1.88 versus 6.30±0.50 mg/ml), where the difference was not statistically significant (P= 0.136).

Table 6-Troponin level of CAD patients and controls

Groups	No.	Troponin concentration mg/ml (Mean±S.D)	Probability
CAD	50	6.83±1.88	0.136 NS
Controls	30	6.30±0.50	

NS = non significant P > 0.05

The association of Troponin with lipid profile

The correlation relationship of troponin with cholesterol, triglyceride, HDL, and LDL in patient and control groups is illustrated in Table-7. The results showed that the correlation coefficient of cholesterol in CAD patients to controls was -0.109 versus -0.114, p= 0.453 versus 0.547, while for triglyceride was(-0.204 versus -0.203, p= 0.155 versus 0.282. In addition, the r value for HDL was -0.041 versus 0.021, p= 0.778 versus 0.914 and for LDL -0.032 versus -0.041, p= 0.827 versus 0.830. The results were not statistically significant (p > 0.05 and r < 0.3).

Table 7-Correlation of Troponin with lipid profile

Lipid profile		Troponin (ng/ml)	
	Correlation coefficient and probability	Patients	Controls
Cholesterol(mg/dl)	r	-0.109	-0.114
	p	0.453	0.547
Triglyceride(mg/dl)	r	-0.204	-0.203
	p	0.155	0.282
HDL(mg/dl)	r	-0.041	0.021
	p	0.778	0.914
LDL(mg/dl)	r	-0.032	-0.041
	p	0.827	0.830

The association of IL-33 with CRP and Troponin

The correlation of IL-33 with CRP and Troponin between patient and control group is illustrated in Table-8. The results showed that the correlation coefficient r of CRPl was higher in CAD patients than in the controls (0.228 versus 0.071 p=0.112 versus 0.710), whereas the r-value of troponin was -0.048 versus -0.118, p=0.743 versus 0.923. The results were not statistically significant (p > 0.05 and r < 0.3)

Table 8-Correlation of IL-33 with CRP and troponin.

		IL-33(pg/ml)	
	Correlation coefficient and probability	Patients	Controls
CRP	r	0.228	0.071
	p	0.112	0.710
Troponin	r	-0.048	0.018
	p	0.743	0.923

Discussion

In the current study, we investigated the concentrations of IL-33, CRP, troponin and lipid profile components in eighty individuals of Iraqi people, including fifty CAD patients and thirty apparently healthy volunteers. We investigated the association between IL-33, CRP, and troponin with lipid profile as well as the relationships among IL-33, CRP, and Troponin.

The results showed a high level of IL-33 in CAD patients. Nuclear IL-33 is released from necrotic human coronary artery's smooth muscle cells, human adult cardiac myocytes and cardiac fibroblasts *in vitro* and, therefore, cell damage induces the release of IL-33 [22]. Also, a high serum concentration of IL-33 was observed in IHD [23]. In the present study, CRP concentration was also higher in CAD patients than the healthy controls. CRP is considered as an excellent biomarker of inflammation, while it is non-specific for certain diseases including the risk of MI, stroke, peripheral arterial disease, and sudden cardiac death [24]. A recent study reported that there is a strong association between serum CRP levels and coronary artery disease risk [25]. Troponin can be released into the bloodstream as a result of myocardial injury. Troponin plays a vital role in the diagnosis of Non-ST Segment Elevation Myocardial Infarctions (NSTEMIs). It is imperative to keep in mind the multiple non-ischemic and non-cardiac causes and potential factors that may lead to elevations of troponin levels [26]. High levels of hsTnI are associated with the underlying burden of coronary atherosclerosis, more rapid progression of CAD, a higher risk of all-cause mortality, and incident cardiovascular events [27]. Troponin concentration in CAD patients in the present study was within the normal range, and this disagrees with the previously reported association with increased CVD risk, which may be due small sample size or medications intake [28]. The lipid profile analysis showed only a significant association between HDL and CAD There is a clear inverse relationship between serum high-density lipoprotein-cholesterol (HDL-C) concentrations and the risk for coronary heart disease (CHD), even at low-density lipoprotein-cholesterol (LDL-C) levels below 70 mg/dL [29]. High HDL-C, reduced HDL phospholipid content, and cholesterol efflux capacity are associated with the paradoxical development of CAD [30]. Moreover, there was no significant association between IL-33, CRP, or troponin with lipid profile in CAD patients and controls. This is the first study that investigates the association of IL-33, CRP, and troponin together with lipid profile in CAD. A non-significant association was found between adipose tissue IL-33 and circulating lipids (total cholesterol, LDL, HDL, and TG) in glycemia disease [31]. Another study showed a highly significant elevation in lipid profile in a diabetic postmenopausal group [32]. CRP was also shown to be raised with the increase of TG, with the possibility to use it as a marker to predict the future risk of CAD [33]. Another study reported that there was no association between CPR and lipid parameters [34], while a non-significant association was reported between CRP level and dyslipidemia [35]. In addition, in subjects with chest pain, total cholesterol, triacylglycerol, and low-density lipoproteins levels were higher in the subjects with a positive troponin than those with a negative troponin [36]. In addition, subjects who develop chest pain due to a cardiac event, confirmed by positive troponin test, had significantly greater levels of TC.TG, LDL when compared to those levels in subjects without cardiac events, as indicated by negative troponin test [37]. To our knowledge, this is the first study that found a negative correlation between IL-33 , CRP and Troponin. Interestingly the investigated relationship between serum levels of these molecules indicated non-significant differences, which is in disagreement with Abbas [38] who found that IL-33 is positively correlated with CRP in Celiac disease (CD) in Iraqi women. However, there were no literatures found investigating the relationship between IL-33 and Troponin.

Conclusion

In summary, it was found that IL-33 and CRP were statistically associated with CAD, while troponin levels showed no statistically significant differences as compared to the control group. Moreover, testing the lipid profile showed a significant increase in HDL level, whereas no significant differences were obtained among cholesterol, triglycerides and LDL levels between CAD patients and controls. Moreoverno correlation was found between IL-33, CRP or troponin with lipid profile. In addition, there was no correlation between IL-33, CRP and troponin. Taking into consideration the limitations of the present study, represented by the small sample size, further studies are recommended with a higher sample size.

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