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Original Research Article

Assessment of apoB and apoA-I serum levels associated with Acute Coronary Syndrome (ACS) in Babylon province

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Abstract

Acute coronary syndromes (ACS), is a term that encompasses both unstable angina and myocardial infarction (MI) with or without ST-segment elevation.It is a life-threatening disorder that remain a source of high morbidity and mortality despite advances in treatment. Risk assessment done by using risk factors and risk markers. In the present study assessment of apolipoprotein B (apoB) and apolipoprotein A-I (apoA-I) done to recognize their roles as risk biomarkers.Acase control study enrolled 160 subjects; 80 patients diagnosed as ACS patients by expert physicians and 80 controls (non-ACS) subjects. Serum levels of apoB and apoA-I was measured by using ELISA technique. The results were expressed as qi-square categorical statistics. A P value of < 0.05 was considered to be statistically significant. A concentration of apoB>1.3g/L in female and >1.5g/L in male appeared to be eleven times risky for ACS than lower levels (OR=11.2).ApoA-I showed non-significant variation between patients and controls (p>0.05). Subjects having apoB/A-I ratio between (0.6-o.79) as a female and (0.7-0.89) as a male are two times risky to get ACS than controls (OR=2.3).Concluded that apoB is a strong predictor of ACS, abnormal low apoA-I serun level does not contribute to the risk stratification of ACS in the presence of high apoB serum level, and the apo-ratio is the strongest of all lipid-related variables and is thus the best summarizing risk variable.

Key words:ACS, apoB, apoA-I, apoB/A-I-ratio, Biomarker

الخلاصة

متلازمة الشرايين التاجية الحاده, هو مصطلح يضم مجموعة من الاعراض تتراوح بين الذبحة الصدرية الغير مستقرة وصولا الى احتشاء العضلة القلبية المصحوب بارتفاع موجة STغير المصحوب بارتفاعها. وبالرغم من التطور الحاصل في مجال علاج المرض الان نسبة الاعتلال والموت الحاصلة عنه عالية جدا. يتم التنبؤ بحدوث المرض عن طريق عوامل الخطورة والواسمات الحيوية للخطورة. ضمت الدراسة ١٦٠ شخصا: ٨٠ مريضا مشخصا اضافه الى ٨٠ شخص غير مصابين بالمتلازمه مع مراعاة التماثل الديموغرافي بينهم. تم قياس مستويات كل من apoBو apoA–I في مصل الدم باستخدام تقنية الألآيزا.اظهرت الدراسة فرق معنوي في تركيز الapoBفي المرضى عن مجموعة السيطرة, فيما لم تظهر الدراسة فرق معنوي في تركيز apoA–Iبين المجموعتين , لكنها اظهرت فرق معنوي في نسبة apoB/apoA–I, مما يشير الى فعالية استخدام apoB كواسم حيوي للخطورة مع عدم فعالية استخدام apoA–I في حال وجود تركيز عالي للapoB في مصل الدم, اضافه الى فعالية استخدام نسبة apoB/apoA كأفضل مؤشر للمتغيرات المتعلقة بالدهون في الدم.

الكلمات المفتاحية:متلازمة الشرايين التاجية الحادة, apoB, apoA–I, apoB/apoA–I ratio, الواسمات الحيوية.

Introduction

Acute Coronary Syndrome

The term (ACS) is used to describe the continuum of myocardial ischemia (unstable angina pectoris) or infarction (with or without concomitant ST segment elevation) [1].

Acute Coronary Syndrome classified into two categories according to electrocardiograph (ECG) findings:

1. ST- segment elevation ACS (ST-segment elevation MI)

2. Non ST-segment elevation ACS. Because UA and non-ST segment elevation MI (NSTEMI) are characterized by the absence of ST segment elevation, may have either no changes, ST-segment depression or T-wave inversion on their ECGs so they are collectively termed non ST segment elevation ACS (NSTE-ACS) [2].

Diagnosis depends on three entities (triangle): 1) Clinical presentation and physical findings 2) ECG changes, 3) Serological findings[1]. Just two of the three criteria are enough as a tool for evaluation, hospitalization, or treating the case as ACS, whereas the history of risk factors is supportive [3].

The pathophysiologic hall mark of ACS is atherogenesis and process that leads to plaque rupture. So, understanding of this complex process is still evolving.Atherosclerosis:Is a lipoprotein-driven disease that leads to plaque creation at specific sites of the arterial tree through intimal inflammation, necrosis, fibrosis and calcification. After decades of apathetic progression, such plaques may suddenly cause life-threatening coronary thrombosis presenting as an ACS [4].

Risk factors can be categorized as: 1.Traditional risk factors. 2. Emerging risk factors. Some of these risk factors can be modified through behavioral changes or pharmacological therapy and are appropriate targets for interventional efforts to reduce the probability of developing or slowing the progression of CAD. Some risk factors cannot be easily modified, but individuals who are at high risk for developing CAD may benefit from more aggressive interventions of other risk factors such as lowering of LDL-cholesterol [5].

Dyslipidemia is one of traditional risk factors of ACS. Assessed largely by investigating lipid profile of the subject, but it seems recently that a great deal of research has been conducted into the use of apo proteins or lipid sub fractions as markers of CAD risk [6].

Lipids typically do not travel alone in the blood. Instead, it binds to a protein that transports it to its destination in the body. The complex formed by the binding of lipid to protein i.e. lipoprotein, makes lipids water soluble, which enables its transportation in blood [7].

Apo-B represents cholesterol carried on all of the potentially pro-atherogenicapoB-containing particles [primarily VLDL, IDL, and LDL as well as chylomicron remnants and lipoprotein (a), thus indicating substantial risk [33].Apo A-I, which is the chief protein component of HDL, is largely responsible for reverse cholesterol transport (RCT) through the macrophage ATP-binding cassette transporter (ABCA1) [8].

The aim of Study was to estimateapoB, and apoA-I serum levels in addition to apoB/apoA-I ratio to assesstheirability to predict ACS events.

Materials and Methods

Between 1st December 2014and 31st January 2015, 80 consecutive patients aged ≥ 40 years old, diagnosed by expert physicians to have ACS were enrolled in the study. This study was performed in the laboratories of Biochemistry Department in college of Medicine /University of Babylon. Patients were recruited from coronary care units (CCU) in Merjan Medical City and Al-Hilla Teaching Hospital in Babylon Province, Hilla City. Control group 80 subjects were collected from Consultation Clinic Department of both Merjan Medical City and Al-Hilla Teaching Hospital as they are patients for other than ischemic heart disease. The overall mean age of patients

with ACS and control were (60.28±12.02) and (58.21±11.61) years old, respectively. There was no significant mean difference between the mean age of patients and control. This study was matched for gender, the ratio of male: female was 2:1 for both sexes.

Exclusion criteria

Patients having the following conditions were excluded: D.M., renal failure, on statins or any hypolipidemic drug, hormones, or glucocorticoids, age<40 years, patients coming from outside the governorate, pregnant women, incapacity to provide informed consent, prior inclusion in the present study, patients with known history of thyroid, hepatic, or malignant disease, drug abusers and anemics.

Ethical Issues: included

a- Approval of scientific committee of the Clinical Biochemistry Department in Babylon Medical College/ University of Babylon/ Iraq.

b- Approval of Babylon Health Directorate/Ministry of Health & Information Center for Research & Development of Babylon Province.

c- The objectives and methodology were explained to all participants in the current study and their signed consent was gained.

Sample collection: Five ml of blood were obtained from each subject by vein puncture in sitting or lying position, and then pushed slowly into disposable tubes containing separating gel. Blood in the gel containing tubes was allowed to clot at room temperature for 2 hours and then centrifuged at 1000 ×g for approximately 15 minutes then the supernatant were obtained and stored at -80˚C until analysis [9].

Serum level of apoB and apoA-I estimated by applying the steps of ELISA technique according to kit directions.

Statistical analysis: All statistical analysis was performed by using statistical package for social sciences (SPSS) 20th version. Chi square (X^2) test and Fisher exact test were used to find the significance of the categorical variables. P values less than (0.05) were considered significant.

Results

Differences of Patients and control by Socio-Demographic Characteristics

The overall mean age of patients with ACS and control were (60.28±12.02) and (58.21±11.61) years old, respectively. There was no significant mean difference between the mean age of patients and control. This study was matched for gender, the ratio of male: female was 2:1 for both sexes.

Table 1: Differences of patients with ACS and control by residence, occupational status, educational status and family income.

Variable	Study Groups		χ^2	*P*-values	Odds Ratio (95% C.I.)
	Patients(%)	Control(%)			
Residence					
Urban area	43 (53.8)	44 (55.0)	0.025	0.874	0.951 (0.510-1.772)
Rural area	37 (46.2)	36 (45.3)			
Occupational status					
Employed	10 (12.5)	19 (23.8)	3.411	0.065	2.180 (0.942-5.046)
Non-Employed	70 (87.5)	61 (76.2)			
Educational status					
Illiterate	35 (43.8)	28 (35.0)			
Primary school	23 (28.8)	20 (25.0)	0.044	0.834	1.087 (0.499-2.368)
Secondary school	15 (18.8)	14 (17.5)	0.117	0.732	1.167 (0.483-2.818)
Higher education	7 (8.6)	18 (22.5)	5.190	0.023*	3.214 (1.177-8.777)
Family income					
low**	54 (56.3)	50 (62.4)			
middle	25 (31.3)	15 (18.8)	2.550	0.110	0.540 (0.253-1.150)
high	10 (12.4)	15 (18.8)	0.431	0.511	1.350 (0.551-3.307)

P<0.05 is significant **reference group

Table.1 shows the differences of patients and control by residence, occupational status, educational status and family income. There was significant difference of patients with ACS and control by educational status, control were three times more likely to have higher education.

Table2: Differences of patients with ACS and control by apoA-1 and apoBapolipoproteins

Variable		Study groups		P Values	Odds Ratio (95% C.I.)
		Patients (%)	Control (%)		
Apo-B					
Normal	Female 0.6-1.3 g/l	9(11.3)	47(58.8)		
	Male 0.6-1.5 g/l				
Abnormal	Female>1.3 g/l	71(88.7)	33(41.2)	**<0.001***	**11.24 (4.929-25.614)**
	Male>1.5 g/l				
Apo-A1					
Normal	Female 1.2-2.3g/l	50(62.5)	43(53.8)		
	Male 1.1-2.0g/l				
abnormal	Female <1.2g/l	30(37.5)	37(46.2)	0.262	1.434 (0.763-2.695)
	Male <1.1g/l				

*p value < 0.05 is significant

Table (2) revealed that there is significant difference in apoB serum level between patients and control ($p<0.05$). It was appeared that the subjects having abnormal high serum level of apoB (male>1.5, female>1.3 g/l) are eleven times at risk to get ACS than normal subjects (Odd ratio=11.24). ApoA-I showed non-significant variation between patients and controls ($p>0.05$).

Table 3: Differences of patients with ACS and control by apo-B/A-I ratio

Apo-B/A-I ratio		Study group		P value	Odd ratio
		Patient (%)	Control (%)		
Low risk	Female 0.3-0.59	40(50)	69(86.3)		
	Male 0.4-0.69				
Moderate risk	Female 0.6-0.79				
	Male 0.7-0.89	21(26.3)	11(13.8)	0.005*	2.353 (1.133-6.945)
high risk	Female 0.8-1.0				
	Male 0.9-1.1	19(23.7)	0(0.0)	0.998	0.0(0.0)

P-value<0.05 is significant

The moderate risk group showed significant difference between patients and controls ($p<0.05$) revealing that subjects having apoB/A-I ratio between (0.6-o.79) as a female and (0.7-0.89) as a male are two times risky to get ACS than controls (OR=2.3).

Discussion

The development of atherosclerosis involves theinteraction of multiple metabolic and cellularprocesses. Central to this are disorders of lipoproteinmetabolism. A number of studies have suggested that concentration of apolipoprotein A-I(apoA-I) and apolipoprotein B-100(apoB) are better predicators than measurements of plasma lipids [7].

There was no significant mean difference between the sociodemographic characters of patients and control (table:1). This sociodemographic matching helps to eliminate differences in parameters' results. The excess burden of ACS among patients appears to be primarily due to dyslipidemia that is characterized by:significant high levels of ApoB,insignificant low levels of ApoA1(table:2) and subsequent significant high apoB/apoA-I ratio (table:3).

ApoB is positively correlated to the severity of the CAD expressing the simple fact that an excess of apoB-particles always denote proatherogenic condition [10]. High apo B levels may indicate an increased number of small dense LDL particles which are easily oxidised and which promote an inflammatory response and the growth of plaques. The larger apo B- containing particles such as VLDL and IDL can enhance the risk of atherothrombosis by inhibiting the fibrinolytic system and by stimulating the cytokine production and the inflammatory response [11].Aging, dietary intake of saturated fat,cigarette smoking, and a sedentary lifestyle has been associated with high apoB serum level [12].

ApoA-I showed non-significant variation between patients and controls ($p>0.05$) as in table (2) revealing that abnormal low apoA-I serum level does not contribute to the risk stratification of

ACS in the presence of high apoB serum level, which agreed with Sierra-Johnson J et al [12] and Kunak T et al [13] who reported that apoA-I levels were high in patients with CAD. But it disagreed with Walldius et al [8] who proved that apoA-I was protective, it reflects the anti-atherogenic potential in HDL particles, the higher the value the better protection of CV risk. These observations lead to the new fact suggested the presence of non-functional HDL molecule presented by Otocka-KmiecikA et al [14]. Only the apoB and the apoB/apoA-I ratio remained significantly associated after the adjustment for traditional risk factors. So apoA-I can be used as a complement to the analysis of dyslipidemia as it is a part of apo-ratio.

In present study about 62.5% of patients had normal apoA-I level (table 2), but it seems to be nonfunctional and may be as a result of elevated oxidative stress subsequent to smoking, hypertension, abdominal obesity and aging presented as risk factors for atherosclerosis and its resultant ACS events. The idea of non-functional apoA-I is suggested by Otocka-Kmiecik A et al [14] and Dhingra R, et al [10] who conclude that oxidation or modification of certain residues of apoA-I could inhibit its anti-oxidant activity converting HDL into a dysfunctional molecule which may affect its protective properties.

In addition to that, in present study there was (37%) of patients having low apoA-I level and 46% of controls like them which coincide with a low HDL-c in our population. This observation could be presented as a result of lacking exercise -life style especially in the studied age group as the exercises increase biological half-life of apoA-I prolonging HDL survival as explained by Kunak T et al [13]. Other indirect mechanism may be implicated by inducing NO bioavailability via exercise, which may decrease oxidative modifications of apoA-I which is reported by Biazek A et al [15]. As well as tabooing of alcohol in Islam, which has an effect reported by Silva ERD et al [16] that it increase HDL-c concentration by raising transport rates of the major HDL apolipoproteinsapoA-I and –II. Both previously mentioned reasons represent two subsequent factors of this low level of apoA-I, which agreed with that reported by Middle East study by Gehani AA et al [17]. Another factor concerning women in studied group, where most of them (81%) were suspected to be menopause (age>55years), so there is subsequent low apoA-I resulted from low estrogen level, as reported by Lambrinoudaki I et al [18].

As the apo B/ A-I ratio, shows the balance between the atherogenic (apo B) and anti-atherogenic cholesterol particles (apoA-I), and has been employed in the evaluation of cardiovascular risk so, to evaluate the significance of apoB/A-I ratio in current study the study group divided into three groups; low risk, moderate risk and high risk groups (table 3) according to INTERHEART study [19], INTERHEART study [20] and AMORIS study [21].

The moderate risk group showed significant difference between patients and controls ($p<0.05$) revealing that subjects having apoB/A-I ratio between (0.6-o.79) as a female and (0.7-0.89) as a male are two times risky to get ACS than controls (OR=2.3). This finding is in consistence with Walldius G et al [22], Walldius G et al [23], Barter PJ et al [24], and van Lennep JE et al [25], where they reported that the reason for improved predictive effect of apoB/A-I ratio might be due to the fact that the ratio reflects and integrates the "cholesterol balance" between potentially atherogenic lipoprotein particles (apoB) in relation to all anti-atherogenic particles (apoA-I), the apo-ratio is the strongest of all lipid-related variables and is thus the best summarizing risk variable. This result coincide with the findings of Jung CH et al [26] who conclude that apoB/A-I ratio of >0·65 in men and 0·62 in women is a

marker of Metabolic syndrome , which in turn regarded as a risk factor for CHD.

Another study by Jing F et al [27] reported that the cut-off value for apo-B/A-I ratio is 0.85 in men and 0.80 in women represent risk factor of ACS which showed relative approximation to the present study results. Data from AMORIS [21] showed that the apo-ratio has a significantly stronger relation with MI than any other lipid-based ratio. INTERHEART study by McQueen MJ et al [20] showed that the strongest and also the most prevalent risk factor was the apo-ratio both in men and women in each of the 52 countries where the study was applied.

Dyslipidemia in term of high apoB serum level and high apoB/A-I ratio presented in this study may be caused by obesity which presented as significant high waist circumference (WC) in studied group. Another contributing factor to dyslipidemia was physical inactivity especially in old age patients, which resulted in low apoA-I level leading to high apo-ratio. Old age itself represents a contributing factor to this dyslipidemia as apoA-I concentration decrease with aging. Smoking; as a significant risk factor in the present study contributes to this dyslipidemia by rising apoB level. Cigarette smoking reportedly reduced plasma lipoprotein lipase (LPL) activity after a mixed meal. Reduced LPL activity may contribute to the reduced clearance of apoB, all these reasons agreed with, Vodnala D et al [28] and Roy S [29].

Conclusion

Dyslipidemia in term of high apoB and high apoB/A-I ratio represent prominent predictive biomarkers for ACS. Abnormal low apoA-I serun level does not contribute to the risk stratification of ACS in the presence of high apoB serum level.ApoA-I even if within normal serum levels does not exclude CAD risk.

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