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Association Between Apo Lipoprotein B Levels at Admission of Patients and Short-term Morbidity and Mortality After Myocardial Infarction

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ABSTRACT

Introduction: Dyslipidemia is an important risk factor in cardiovascular diseases. Different studies have shown that Apolipoprotein B (Apo B) is one of the best predictors in determining cardiovascular diseases and patients follow up after cardiovascular events. We hypothesized that there is a relation between Apo B levels and cardiovascular events in patients who have myocardial infarction (MI). In addition, Apo B may be an appropriate marker for following these patients after MI. **Methods**: In this study, 220 patients with acute myocardial infarction were allocated at their admission to the hospital. They were followed for three months after MI and their morbidity and mortality rates were evaluated. Apo B levels were measured immunoturbidimetrically. **Results**: Apo B levels were significantly higher in patients with the events including coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and malignant arrhythmias ($P = 0.001$). **Conclusion**: Apo B levels can be an appropriate indicator of cardiovascular events in patients after MI.

Introduction

In most countries, coronary artery disease (CAD) is the leading cause of death.[1] Increased amounts of low-density lipoprotein cholesterol (LDL-C) are mostly introduced as one of the major risk factors in atherosclerotic cardiovascular diseases.[2] Although plasma LDL-C is proven as a predictor of CAD, it might not be the most appropriate circulatory marker. Epidemiological studies have shown that apolipoprotein B-100 (Apo B), with or without Apo A-I, is a better predictor than LDL-C and other non-HDL lipoproteins in predicting coronary artery diseases.[3-5]

Prospective studies in different countries reported that cardiovascular mortality rates vary from 5% in Japan to 15% in Europe, according to cholesterol levels about 5.43mmol/l (210 mg/dl). This wide range of mortality rates is due to different sizes of LDL particles; as small dense LDLs (sd LDL) are more atherogenic than others.[6,7] High plasma levels of Apo B, especially elevated Apo B/Apo A-I ratio, have been established as a risk factor for CAD[3-5]; however, the relationship between Apo B levels and the short-term outcome after acute myocardial infarction are yet to be studied . This study aims to investigate the relationship between the Apo B levels at admission and the mortality and morbidity rates after acute myocardial infarction. Such a relation indicates that the elevated serum Apo B levels in myocardial infarction may be a marker necessitating secondary preventive measures.

Materials and methods

Sampling

All patients admitted to coronary care unit at Vali-asr and Mousavi hospitals in Zanjan, Iran from January 2008 to December 2008 with diagnosis of acute myocardial infarction based on WHO criteria were eligible participants. In studies of disease prevalence by the World Health Organization (WHO), MI was defined by a combination of two of three characteristics: typical symptoms (i.e., chest discomfort), enzyme rise and a typical ECG pattern involving the development of Q waves.[8] The final study population consisted of 220 patients. Written informed consents were obtained from all the patients. Interviews were conducted and the clinical data were collected using a common protocol. Serum Apo B levels ≥1.2 g/L were defined as high Apo B.[9] Hypertension was defined as resting systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. Cigarette smoking was defined as ever versus never smoked. Diabetes was defined as fasting blood glucose ≥ 7mmol/L or a diagnosis of diabetes needing diet or drug therapy. Total cholesterol ≥ 5.18mmol/L or triglycerides ≥ 2.26mmol/L and LDL ≥ 2.59mmol/L or HDL ≤ 1.16mmol/L and non-HDL ≥

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2.85mmol/L considered as abnormal limits.

5 ml blood samples were taken after a 12-hour fasting and sera were separated immediately after collection by centrifugation at 1500g for 15 minutes and stored at -70°C until analysis.

Lipids profile analysis

Cholesterol and triglycerides were measured enzymatically (Colorimeteric, Pars Azmun Co., Iran) by autoanalyzer (Selectra E2 Chemistry Analyzer, Vital Scientific Co., Netherland). In addition, HDL-C was determined after precipitation of Apo B-containing particles by phosphotungstic acid-$MgCl_2$ (Randox Co, UK/ Hitachi 902 autoanalyzer, Japan). LDL-C levels were estimated using Friedewald equation.

Apo B was assayed by an automated immunoturbidimetric method (XL-300 Biochemistry Analyzer. Erba Co.,Germany) with Apo B kit from Randox. Co, UK (Inter Assay: 4.2-7.6%, Intra Assay: 3.7-7.5%).

Determination of morbidities in patients

All patients were followed for up to three months after myocardial infarction and later they were followed by telephone interviews with the survivors. Information on hospitalization for congestive heart failure, angina pectoris, nonfatal reinfarction, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), arrhythmias were collected. Each event was recorded only once. Information on mortality and causes of death were obtained from hospital records. Reinfarction was defined as an infarct with an onset >72 hours after the index infarct that caused prolonged initial or a new hospitalization.

Congestive heart failure (CHF) was defined as an ejection fraction (EF) < 50% and classified into three groups of severe left ventricular dysfunction (LVD) with EF≤ 30%, moderate LVD with EF: 31- 40% and mild LVD with EF: 41- 50%. Major cardiovascular events were defined as CABG, PCI, malignant arrhythmias, reinfarction and death.

Ethical approval

We state that our study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol. This study with reference number: 630, was approved by Zanjan ethical committee. All authors observe ethical principles related to references. Written informed consents were obtained from all patients.

Statistical analysis

Statistical analyses were performed with SPSS for windows version 16.5. The main statistical comparisons were performed between patients who survived and the ones who died, between survivors with and without nonfatal reinfarction, between patients with and without CHF and between patients with and without a major cardiovascular event. Differences between groups were tested with Mann Whitney Test. Differences were considered significant if P values were ≤ 0.05, all P values are two tailed.

Multivariate analyses were carried out by multiple logistic regression analysis. Odds ratios were adjusted for factors known to be associated with CAD such as age, diabetes, cigarette smoking.

Results

The baseline characteristics of the 220 patients are given in Table 1. The mean age of the patients was 63±11 years and 157 subjects (71%) were male. At hospital admission, the mean plasma Apo B level was 1.22±0.36 g/L. The patients were extensively treated during the hospitalization. Thirty-nine (17%) patients underwent PCI and 23 (10%) underwent CABG during 3-month follow up period.

Apo B levels in patients who had coronary artery bypass grafting were about 156 mg/dl; a significant relation was found in patients without morbidity (P = 0.0001). However, the Apo B levels had no significant correlation with the patients with arrhythmias and reinfarction and the participants who did not suffer from these morbidities.

A total of 10 (4.5%) patients died; 6 of patients died during the initial hospitalization and 4 during the remaining follow up period. Two hundred-two (91%) of patients had LVD and were divided into three groups: mild LVD 65 (29%), moderate LVD 55 (25%), and severe LVD 82 (37%). Six of patients (2.7%) had a nonfatal reinfarction.

As shown in Table 2, in univariate analysis, Apo B levels were significantly higher in patients with one of the major cardiovascular events; Apo B 1.31±0.41 g/L (P = 0.0001). As previously stated, several baseline characteristics apart from Apo B levels predicted the outcome. If their univariate P value was <0.2, these variables were entered into multivariate logistic regression model together with Apo B plasma level.

The resulted multivariate analysis showed that there is a significant correlation between Apo B and major cardiovascular events (P = 0.0001). There was a significant correlation between the male sexuality and major cardiovascular events, hypercholesterolemia and CHF, increased non-HDL-C lipoproteins and death rate in

Table 1. Patients' characteristics at hospital admission

	Total	Morbidity and Mortality		P
		Yes	NO	
N	220	114	106	–
Age	63±11	63±12	64±12	–
Male	157(71)	84(73)	73(27)	0.76
HTN	66(30)	38(33)	28(26)	0.24
Smoker	74(33)	42(36)	32(30)	0.29
DM	100(45)	53(50)	47(41)	0.19
Apo B ≥1.2 g/L	124(56)	76(66)	48(45)	<0.001
TC ≥5.18 mmol/L	84(38)	44(38)	40(37)	0.89
LDL ≥2.59 mmol/L	122(55)	65(61)	57(50)	0.09
HDL <1.16 mmol/L	125(56)	68(59)	57(53)	0.37
Non HDL ≥2.85 mmol/L	107(72)	61(75)	68(46)	0.36

Data are means ± SD or n (%) ,TC: total cholesterol ,DM: diabetes mellitus, HTN: hypertension, LDL: low density lipoprotein, HDL: high density lipoprotein

Table 2. Association between cardiovascular risk markers at admission of patients and short-term morbidity and mortality after myocardial infarction

Parameter	CABG or PCI	P value	CHF	P value	Non fatal reinfarction	P value	Death	P value
Sex (M)	77(49)	0.03	146(93)	0.3	3(2)	0.2	7(4.5)	0.9
Smoking	38(51)	0.1	69(93)	0.5	1(1.4)	0.3	2(2.7)	0.3
DM	42(42)	0.4	94(94)	0.2	3(3)	0.8	2(2)	0.09
TC ≥2.26mmol/L	38(45)	0.8	73(86)	0.03	3(3.6)	0.5	2(2.4)	0.2
LDL ≥2.59mmol/L	48(39)	0.08	111(91)	0.6	5(4.1)	0.1	4(3.3)	0.3
HDL <1.16mmol/L	59(47)	0.3	86(90)	0.5	2(1.6)	0.2	7(5.6)	0.3
Non-HDL ≥2.85mmol/L	54(50)	0.07	100(93)	0.8	5(4.7)	0.1	2(2)	0.00
Apo B ≥1.2 g/L	68(54)	0.001	114(91)	0.9	3(2.4)	0.7	5(4)	0.07
HTN	31(47)	0.6	61(92)	0.8	2(3)	0.6	4(6)	0.4

TC : total cholesterol, DM: diabetes mellitus, HTN: hypertension, LDL: low density lipoprotein, HDL: high density lipoprotein

patients (P values were 0.03, 0.03, and 0.001 respectively), as well.

Table 3. Odd ratio of ApoB for cardiovascular morbidity and mortality events

	Odd ratio	P-value	(95%) CI
Morbidity events	2.67	0.0001	1.53-4.66
Mortality events	0.76	0.46	0.22-2.72

Discussion

Lipid profile constituents include high total cholesterol, high LDL-C, high Apo B levels and high Apo B/Apo A-I ratio representing cardiovascular risk factors in the general population.[3-5] Based on the results regarding finding an appropriate marker(s) in lipid profile, it was observed that the serum apolipoproteins are probably better markers of the balance between preatherogenic and atherogenic lipoproteins and predictors of cardiovascular risk.[4,10]

LDL particles, alone, do not provide any information on the other lipoprotein particles or their atherogenicity. On the other hand, very low-density lipoprotein (VLDL) particles, intermediate-density lipoprotein (IDL), and LDL particles covered by apolipoprotein B (Apo B) molecule, can give us more information regarding their atherogenicity; serum concentrations of Apo B contain a number of atherogenic particles.[11] Different studies have emphasized on a positive correlation between Apo B levels, specially ApoB/ApoA-I ratios, and cardiovascular morbidity.

Haidari *et al*. showed that Apo B was the best predictor of CAD in a subgroup of very young patients (age≤40, n=77, OR 8.6, $P < 0.009$). They showed that the severity of atherosclerosis correlated significantly with the serum Apo B concentration in the normolipidemic subgroup (r=0.22, $P < 0.008$) .[5]

In another study in Iran, Azizi and his co-workers showed that the concentration of Apo B was a better marker than the traditional lipids in discriminating between patients with cardiovascular disease and patients without CVD in non-diabetic patients with premature coronary artery disease.[12]

Kirmizis *et al*. in a correlation analysis showed that apolipoproteins and their ratio correlated with cardiovascular morbidity in hemodialysis patients, i.e. ApoA-I negatively and Apo B and ApoB/ApoA-I ratio positively ($r = -0.6$, $P < 0.05$; $r = 0.659$, $P < 0.01$; and $r = 0.614$, $P < 0.01$, respectively).[13] In this study, it was found that there is a relationship between Apo B and major cardiovascular events including CABG and PCI in patients after their myocardial infarction. The odds ratio of Apo B for morbidity and mortality events are represented in Table 3.

Wallenfeldt *et al*. demonstrated that the ApoB/ApoA-I ratio was associated with metabolic syndrome and with the change in carotid artery IMT (intima-media thickness) during 3 years of follow-up .[14]

Yoshida *et al*. in a prospective study showed that during follow-up period (mean 334 days), 30 (19%) coronary events (including 5% revascularization for target lesions and 14% for new lesions) were observed. They also reported that coronary events significantly increased in patients with higher ApoB/ApoA-I ratio (>75th percentile) compared to those with a lower ratio ($P = 0.001$). In addition, LRP (Lipid-rich plaque) was significantly higher in patients with higher ApoB/ApoA-I ratio in comparison with their counterparts ($P = 0.001$).

In a multivariate logistic model, after adjusting confounding and coronary risk factors, higher ApoB/ApoA-I ratio was significantly associated with LRP (OR 4.36, 95% CI = 1.81–9.48, $P = 0.001$). They concluded that elevated ApoB/ApoA-I ratio would predict higher coronary events, and is also significantly associated with LRP measured by IB-IVUS (integrated backscatter intravascular ultrasound). These results may explain the contribution of ApoB/ApoA-I ratio to the increased risk of coronary events after percutaneous coronary intervention .[15]

Corsetti *et al*. demonstrated that the 4G/5G polymorphism in the promoter region of the PAI-1 (Plasminogen Activator Inhibitor-1) gene is associated with the risk for recurrent coronary events in a subgroup of normolipidemic postinfarction patients.[16] Consequently, because of the importance of genetic variations, we suggest that it is better to study the variations of cardiovascular markers, such as PAI-1, Paraoxonase-1 (PON-1) and adipokines (such as adiponectin, leptin, e.g.) that can affect cardiovascular system in normolipemic and hyperlipemic participants

with or without CVD. As mentioned, we also carried out a study on the relationship between PON-1 gene polymorphisms and high ApoB/ApoA-I ratios in normolipemic participants. A positive relation was found between L55M polymorphism of PON-1 and high ApoB/ApoA-1 ratios ($P = 0.016$).[17]

The limitations of our study would be small sample size and rather short follow up period of patients. Therefore, studies focusing on the measurements of cardiac risk markers like Apo B and longer follow up periods are suggested.

In conclusion, this study revealed that Apo B appears to be an appropriate marker for evaluating cardiovascular events in patients after MI. Evaluation of the other cardiovascular lipid markers such as Apo A-I and Lp(a) (in addition to Apo B) in such patients is also recommended to follow the patients' morbidities.

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Conflict of interests: The authors declare no conflicts of interest.

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