Original Article

Karimollah Hajian-Tilaki (PhD)
[*1]

Behzad Heidari (MD) [2]
Arefeh Hajian-Tilaki (DDS, MS) [3]
Alireza Firouzjahi (MD) [4]
Afsaneh Bakhtiari (PhD) [5]

1. Social Determinant Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
2. Mobility Impairment Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
3. Department of Orthodontics, Guilan University of Medical Sciences, Rasht, Iran.
4. Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
5. Fatemeh Zahra Infertility and Reproductive Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

* Correspondence:
Karimollah Hajian-Tilaki,
Department of Biostatistics and Epidemiology, Babol University of Medical Sciences, Babol, Iran.

E-mail: drhajian@yahoo.com
Tel: 0098 1132199936
Fax: 0098 1132199936

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Does the low-density lipoprotein cholesterol play a key role in predicting metabolic syndrome in the Iranian adult population?

Abstract

Background: The low density lipoprotein cholestrol (LDL-C) has an important role in the pathogenesis of cardiovascular disease but its association and predictive accuracy with metabolic syndrome (MetS) remains controversial. The objective of this study was to investigate the association and predictive ability of LDL-C with MetS.

Methods: We analyzed the data from a population-based cross-sectional study conducted on representative samples of an Iranian adult population. The demographic data, anthropometric measures and the lipid profiles were measured with standard methods, and MetS was diagnosed by ATP III criteria. Logistic regression model and ROC analysis were used to estimate the predictive accuracy of LDL-C and its association with MetS.

Results: The mean age (±SD) of participants with and without MetS was 47.6±12.5 years and 39.1±12.9 years, respectively (p=0.001). All anthropometric measures (body mass index, waist circumference, waist to hip ratio, waist to height ratio), systolic blood pressure, total cholesterol, triglycerides and fasting blood glucose were significantly higher in MetS, but a significantly higher difference in LDL-C was observed only in women. Accuracy of LDL-C in predicting MetS for men and women was 0.48 (95% CI: 0.43-0.54) and 0.55 (95% CI: 0.51-0.60), respectively. The unadjusted and adjusted odds ratios of different quartiles of LDL-C compared with 1st quartile did not reach to a significant level.

Conclusion: Serum LDL-C level is not significantly associated with MetS but exhibits a weak ability in predicting MetS in women.

Keywords: Low density lipoprotein cholesterol, Metabolic syndrome, Iranian adults

Metabolic syndrome (MetS) constitutes a clustering of cardiovascular risk factors including high blood pressure, increased fasting blood sugar (FBS), high serum triglycerides level (TG), low high density lipoprotein(HDL), and abdominal obesity (1, 2). It is a major risk factor for diabetes and cardiovascular event and stroke (3). Individuals with MetS have at least three times greater risk of cardiovascular complications and two times higher risk of death as compared with those without MetS (4-7). It is estimated that more than a quarter of adult population in the United States suffer from MetS (8), and its prevalence has increased dramatically in Iranian population during the two recent decades as well, and according to ethnic, geographic regions and socio-demographic characteristics, the prevalence of MetS in Iran ranges from 10- 60% (9-14). In particular, obesity and MetS are highly prevalent in geographic regions of northern Iran (15-17). Obesity, especially abdominal obesity constitutes the main components of MetS (1, 2). It has been clearly established that there is a link between obesity/central obesity and hypertension as well as other cardiometabolic risk factors in particular dyslipidemia (18-21).

Although low density lipoprotein cholesterol (LDL-C) is not a components of MetS, nevertheless, both hyperlioidemia and MetS are associated with abdominal obesity and general adiposity. It has been clearly established that LDL-C is an important risk factor of cardiovascular diseases (18-20), however, data regarding the association between LDL-C and MetS are scarce and the results of studies are controversial (21, 22).

The information in this context is very important because both LDL-C and MetS are factors for future development of cardiovascular complications which are clinically emphasized to be recognized for preventive measures. Identification of subjects with MetS based on serum LDL-C measurement, which is routinely determined in clinical practice, provides an opportunity to treat both conditions simultaneously.

Since the mainstay of treatment for dyslipidemia is based on lifestyle modifications including weight reduction and correction of abdominal obesity improves MetS and exerts additional benefits in reducing the risk of diabetes as well as cardiovascular complications. Thus, the objective of this study was to determine the ability of LDL-C in predicting MetS, independent of pre-existing components in a sample of north's Iranian adult population.

Methods

Design and study subjects: We analyzed the data of the population-based cross-sectional of Babol Lipid and Glucose study which was conducted with 1000 representative samples of urban community-dwelling individuals aged 20-70 years from April to end of December in 2012. The sampling procedure and the criteria for recruitment were described in details elsewhere (17). In brief, a random sample of 25 clusters was selected and around the center of each cluster, about 40 subjects were recruited to participate in the study. Individuals with history of atherosclerotic diseases such as myocardial infarction and cerebrovascular accidents (CVA), dementia, current cancer under radio-chemotherapy and pregnancy were excluded. All participants gave a written consent prior to participation. The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences.

Data Collection: In a household survey, first the demographic data were collected during a face-to-face interview by trained nurses. Then, the clinical examination

and anthropometric assessment were performed. Systolic, diastolic blood pressure, weight, height, waist (WC) and hip circumferences (HC) were measured with standard methods. From these anthropometric measures, body mass index (BMI), waist to hip ratio (WHR), waist to height ratio (WHtR) and abdominal volume index (AVI) were calculated. All participants were invited to central lab of the Ayatollah Rouhani Hospital with overnight fasting of 10-12 hours. The blood samples were provided and the biochemical parameters such as total cholesterol (TC), TG, LDL-C, HDL-C and FBS were measured enzymatically by automated analyzer. The MetS was confirmed by ATP III criteria. In this regard, the presence of at least three out of five components were considered as having MetS.

Statistical Analysis: The data were analyzed using SPSS software Version 18 In bivariate data analysis, we used the independent t-test for quantitative and the chi-square test for categorical data. The normality of data was examined by Kolmogrov –Smirnov test. The LDL-C was categorized based on its quartile with respect to gender. The three indicator variables were defined and the reference group was the 1st quartile. Multiple logistic regression analysis was used to estimate the unadjusted and adjusted odds ratio (OR) and its 95% confidence interval (CI).

Besides age-and-sex adjusted OR was estimated and additional adjustment was performed with pre-existing components of MetS. The receiver operator characteristic (ROC) curve analysis was used to calculate the diagnostic accuracy as defined by the area under the curve (AUC) and its 95% CI. The Pearson test was used to determine the correlation between the components of cardiometabolic risk factors. A p-value less than 0.05 as considered as the significant level.

Results

The consecutive mean (±SD) age of participants with and without MetS were 47.6±12.5 and 39.1±12.9 years, respectively (p=0.001). As shown in Table 1, in both genders, all anthropometric measures, except height, were significantly higher in MetS group as compared with those without MetS. In addition, systolic blood pressure, total cholesterol, triglycerides, HDL-C and FBS were significantly higher in both women and men. Nonetheless, LDL-C was significantly higher only in women but not in men with MetS (table 2).

Table 1. The mean (SD) of cardiometabolic risk factors of participants with and without MetS

Cardiometabolic risk factors	Male (mean±SD)			Female (mean±SD)		
	MetS	Not MetS	p-value	MetS	Not MetS	p-value
Age (year)	47.6±14.3	41.2±13.8	0.001	47.5±11.2	36.9±11.6	0..001
Weight (kg)	83.4±13.3	74.8±13.0	0.001	78.4±12.8	66.9±12.1	0.001
Height (cm)	171.6±8.3	171.9±7.7	0.76	158.4±7.3	159.7±6.8	0.036
BMI (kg/m2)	28.3±3.9	25.4±4.9	0.001	31.3±5.4	26.3±4.8	0.001
WC (cm)	102 .0±15.2	89.3±12.4	0.001	99.0±713.5	84.2±12.1	0.001
HC (cm)	106.5±11.3	99.7±12.5	0.001	114.0±11.9	104.6±13.2	0.001
WHR	0.94±0.10	0.89±0.08	0.001	0.87±0.08	0.81±0.08	0.001
WHtR	0.59±0.09	0.52±0.07	0.001	0.63 ±0.09	0.52±0.08	0.001
AVI	20.91±6.8	16.4±4.8	0.001	20.50±6.3	14.8±4.2	0.001
Diastolic BP (mm Hg)	87.9±12.5	79.5±12.1	0.001	87.6±8.16	757±11.6	0.001
Systolic BP (mm Hg)	135.4±15.1	124.1±14.4	0.001	131.9±20.3	117.4±15.0	0.001
Total cholesterol (mgr/dl)	201.6±51.0	185.9±58.7	0.001	211.5±43.7	187.2±40.6	0.001
TG (mg/dl)	256.4±151.6	151.3±115.8	0.001	208.5±136.3	110.2±64.2	0.001
LDL-C	118.8±51.1	117.5±38.3	0.75	133.2±41.9	126.1±36.5	0.037
HDL-C	32.9±6.7	37.8±10.7	0.001	37.4±12.9	39.8±11.2	0.02
FBS	125.2±43.8	98.7±22.9	0.001	125.5±54.2	94.8±16.9	0.001

BMI body mass index, WC, waist circumference, HC hip circumference, WHR waist to hip ratio, WHtR waist to height ratio, AVI abdominal volume index, BP blood pressure, TG triglycerides, LDL-C low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, FBS fasting blood sugar

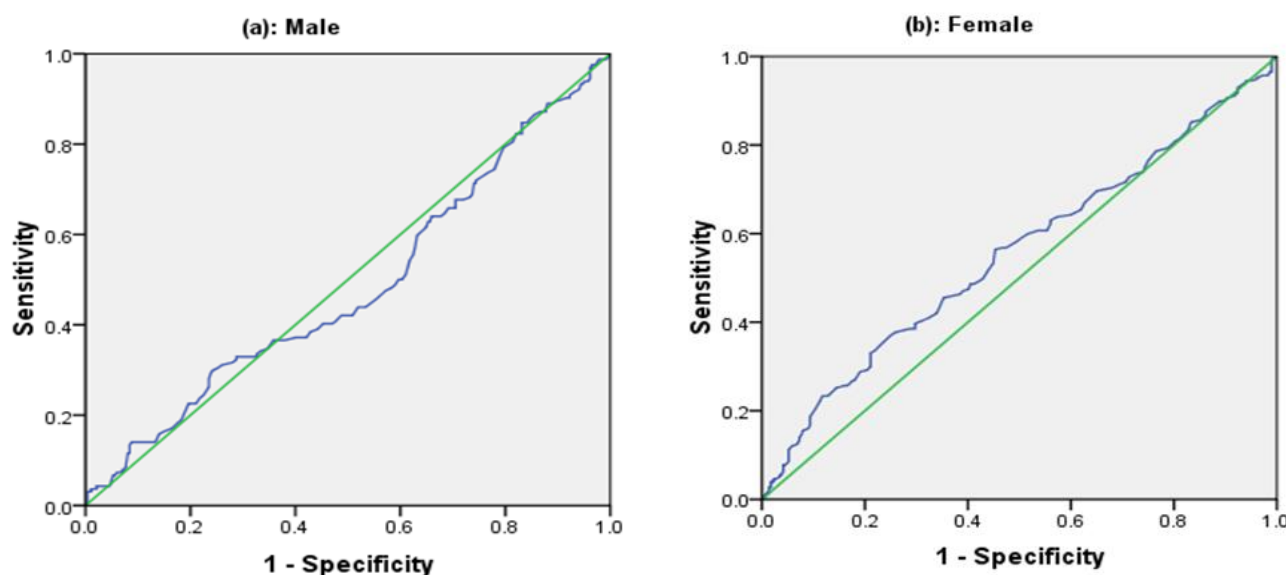**Table 2. The Pearson correlation matrix between cardiometabolic risk factors and P-value**

	CHL	TG	LDL-C	HDL-C	FBS	Diastolic BP	Systolic BP	WC	BMI
CHL Correlation	1	0.32	0.76	0.11	0.15	0.14	0.14	0.17	0.18
P-value		0.001	0.001	0.001	0.001	0.001	0.001	0.001	
TG Correlation		1	-0.16	-0.13	0.29	0.11	0.14	0.21	0.14
P-value			0.001	0.001	0.001	0.001	0.001	0.001	0.001
LDL-C Correlation			1	0.02	0.02	0.09	0.08	0.08	0.13
P-value				0.44	0.44	0.004	0.01	0.01	0.001
HDL-C Correlation				1	-0.05	0.06	0.07	0.02	0.03
P-value					0.11	0.05	0.03	0.45	0.32
FBS Correlation					1	0.15	0.19	0.02	0.07
P-value						0.001	0.001	0.45	0.03
Diastolic BP Correlation						1	0.64	0.23	0.19
P-value							0.001	0.001	0.001
Systolic BP Correlation							1	0.27	0.21
P-value								0.001	0.001
WC Correlation								1	0.62
P-value									0.001
BMI Correlation									1
P-value									

CHL cholesterol, TG triglycerides, LDL-C low density lipoprotein cholesterol, HDL-C high density lipoprotein cholesterol, FBS fasting blood sugar, BP blood pressure, WC waist circumference, BMI body mass index.

Among the components of the MetS, LDL-C was positively correlated with systolic blood pressure (r=0.08, P=0.01), BMI (r=0.13, P=0.001), and WC (r=0.08, P=0.02). Apparently there was a strong correlation between LDL-C and total cholesterol (r=0.76, P=0.001) but there was no significant correlation between LDL-C with HDL-C and FBS. Surprisingly, the correlation between LDL-C and TG was negative. Regarding the data presented in figure 1, the LDL-C has no diagnostic ability in predicting MetS among

men (AUC=0.48, 95% CI: 0.43-0.54), but there is a significant and low predicting ability for MetS in women (AUC=0.55, 95%CI: 0.51-0.60).

Nonetheless, the result of multiple logistic regression analysis (table 3) showed that the unadjusted and adjusted odds ratios (adjusted through age and gender, and additional adjustment for preexisting component of the MetS) of the 4th, 3rd and 2nd quartiles of LDL-C versus the 1st quartile did not indicate a statistically significant association.

AUC (95%CI), p-value:0.48 (0.43-0.54), 0.57 for men

AUC (95% CI), p-value: 0.55 (0.51, 0.60), 0.03 for women

AUC: area under the curve

Figure 1. ROC curves and accuracy index of LDL-C for predicting of in men (panel a) and women (panel b)

Table 3. The unadjusted and adjusted odds ratio (OR) and its 95% confidence interval (CI) of different quartiles of HDL-C using multiple logistic regression model

LDL-C	Unadjusted OR (95%CI)	P-value	Adjusted* OR(95% CI)	P-value	Adjusted** OR(95%CI)	P-value
1st Quartile	1	0.09	1 (-)	0.12	1 (-)	0.70
2nd Quartile	0.92 (0.65, 1.31)	0.65	0.92 (0.63, 1.34)	0.68	1.06 (0.63, 1.80)	0.82
3rd Quartile	0.80 (0.56, 1.14)	0.21	0.65 (0.44, 0.95)	0.03	0.79 (0.46, 1.33)	0.41
4rth Quartile	1.25 (0.88, 1.78)	0.21	0.93 (0.63, 1.36)	0.17	1.02 (0.60,1.77)	0.96

* Adjusted by age and sex

**Full adjusted by age, gender, BMI, and all pre-existing components of MetS. LDL-C low density lipoprotein cholesterol, OR odds ratio

Discussion

The findings of this study demonstrated significant differences regarding all demographic and biochemical factors of coronary artery disease between subjects with and without MetS. The values of BMI, WC, WHR, WHtR, AVI,

FBS, TC, TG, systolic and diastolic blood pressure in individuals with MetS were higher and the level of HDL-C was lower in both women and men. Whereas, the level of LDL-C was significantly higher only in female with MetS

but not in males. Based on the value of the area under the ROC curve, LDL-C yielded a weak ability in prediction of MetS only in women. Both LDL-C and MetS are prevalent in the general population, and are associated with increased risk of cardiovascular mortalities and CVS (23, 24). Many chronic medical conditions, like obesity, diabetes, dyslipidemia and hypertension are related with MetS. Hence, coexistence of these conditions with MetS poses these subjects at greater risk of cardiovascular events. The cardiovascular risk in MetS and LDL-C is comparable, and thus, coexistence of two conditions yields the risk of cardiovascular by sum of the two risk factors (21).

In a study of patients with MetS the patients at very higher risk of cardiovascular death had greater LDL-C and non-HDL-C levels than those with medium or high risk of cardiovascular death (25). So, the reduction of LDL-C in MetS confers the beneficial effect against cardiovascular diseases. In practice, reduction of LDC-C to target level by proper treatment reduces the risk but does not prevent subsequent attacks. This may be related to the presence of other risk factors such as MetS, which may reduce the effectiveness of treatment (26). High level of LDL-C and low level of HDL-C are risk factors of coronary artery disease. Patients with MetS are at greater risk of dyslipidemia(14).

Low level of HDL-C is a component of MetS, but data regarding LDL-C and MetS are lacking. A study of Japanese population showed a relationship between LDL-C and MetS; in this study LDL-C predicted development of MetS, independent of BMI, or MetS components (22). In another follow-up study of 1702 participants without MetS at baseline, individuals who developed MetS, had significantly higher LDL-C, apolipoprotein B, C-reactive protein and lower HDL-C (27). In another study, by Ying et al, the LDL- C independently predicted the MetS (28). Nonetheless, in a 7-year follow -up study of Iranian cohort comprised of first degree relatives of diabetic patients, LDL-C did not yield a predictive ability for MetS independent of age or the pre-existing components of the MetS (23).

Similar to most components of Mets, LDL-C is also associated with insulin resistance (29). Similarly, the ratio of TG to HDL-C is an indicator of insulin resistance. This was shown in a longitudinal study of Iranian cohort followed for a median duration of 6.5 years (30). In reality, the risk of cardiovascular disease is determined by the direct measurement of LDL and HDL particles. The magnitude of cholesterol especially LDL per particle varies across different persons. In patients with low HDL, the risk of cardiovascular disease may be related to unrecognized excess of LDL particles (31).

The LDL-C and size are often accompanied with low HDL-C and high TG levels (26). TG/HDL-C ratio is an indicator of MetS and insulin resistance and development cardiovascular events (32). Small dense LDL with elevated TG and low HDL-C concentrations constitute the atherogenic lipoprotein phenotype which is a feature of diabetes type 2 and MetS. Small dens LDL assessment may be helpful in predicting cardiovascular risk in MetS (32).

The results of this study showed a weak predictive ability of LDL-C for MetS in women but not in men, which is partly in agreement with Tehrani et al. who have shown no association between LDL-C and coronary heart disease or cardiovascular disease in the MetS group (33).

The present study has limitations. The cross-sectional nature of the study does not indicate causality. Additionally, we did not exclude subjects who are on treatment of antihyperlipidemic agents as a possible confounder. Nevertheless, the distribution of subjects who were taking treatment is expected to be similar across the comparison groups. As a conquence, the results are subjected to be less confounded.

Yet, the strength is a population-based with standard sampling technique and large sample size, using appropriate criteria for definition of MetS and standard methods of data collection and analysis techniques. In addition, the study population was recruited among the general population with similarities in many characteristics such as lifestyle, ethnicity, and socio-demographic features. Thus, the study population can be considered as representative of the general population.

In conclusion although LDL-C correlates with a number of MetS components, but the level of LDL-C in subjects with and without MetS was not significantly different and as a result the LDL-C did not yield predictive ability in detecting MetS except a weak predictive ability in women. At any rate, this issue needs to be confirmed further in a prospective longitudinal study.

Conflict of Interest: The authors declare that they have no conflict of interest.

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