Original Article

موضوع أصيل

COMPARISON OF APOLIPOPROTEIN B, NON-HDL-C, AND LDL-C: TOWARDS MORE ACCURATE PREDICTOR TEST FOR ISCHEMIC HEART DISEASES IN A SAMPLE OF SYRIAN MALES

مقارنة بين Apolipoprotein B وNon-HDL-C وLDL-C: نحو اختبار تنبؤي أكثر دقة بأمراض القلب الإقفارية عند عينة من الذكور السوريين

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ملخص البحث

هدف البحث: يمثل كوليسترول البروتينات الشحمية منخفضة الكثافة (LDL-C) عبء الجسم من الشحميات المسببة للتصلب العصيدي للشرايين بشكلٍ جزئي فقط، وتشير مجموعة متزايدة من الأدلة إلى أن الكوليسترول خارج البروتينات الشحمية عالية الكثافة (Non-HDL-C) والصميم البروتيني B (ApoB) هما أكثر دقة في تقدير اختطار أمراض القلب الوعائية العصيدية المرتبطة بالشحميات كأمراض القلبية الإقفارية (IHD). تهدف هذه الدراسة إلى مقارنة كل من Apo B وNon-HDL-C وLDL-C لتحديد الاختبار الأكثر تنبؤ ودقة بأمراض القلب الإقفارية.

طرق البحث: أجريت دراسة من نمط الحالات والشواهد، حجم العينة 200 من الذكور، 100 يعانون من نقص التروية القلبية تم أخذهم من قسم أمراض القلب من مشفى المواساة الجامعي بدمشق، و100 من الأشخاص السليمين، سُجلت بيانات المشاركين (العمر، التعليم، قياسات الجسم، التدخين، استهلاك الكحول، الداء السكري وارتفاع ضغط الدم)، كما تم إجراء الفحوصات المخبرية (الكرياتينين، الألبومين، سكر الدم، الكوليسترول، الشحوم الثلاثية وHDL-C وApoB والبروتين التفاعلي CRP) وتم حساب كل من LDL-C وNon-HDL-C، وتمت مقارنة النتائج باستخدام T-test وبرنامج SPSS، ودراسة الارتباط والدقة وقيم التنبؤ.

النتائج: بينت الدراسة أنّ اختبار ApoB كان الأكثر دقة والأفضل للتنبؤ بأمراض القلب الإقفارية، تلاه Non-HDL-C في حين لم يكن لـ LDL-C قيمة تنبؤية يعتد بها.

الخلاصة: توصي هذه الدراسة بإجراء ApoB كأفضل اختبار للتنبؤ بأمراض القلب الإقفارية في حال توفره، وبحساب Non-HDL-C في جميع الحالات بشكل روتيني، أما LDL-C فلا يمكن الاعتماد عليه للتنبؤ بأمراض القلب الإقفارية.

ABSTRACT

Objective: *Low-density lipoprotein cholesterol (LDL-C) only partly represents the atherogenic lipid burden, and a growing body of evidence suggests that none high-density lipoprotein cholesterol (Non-HDL-C), and Apolipoprotein B (ApoB) are more accurate in estimating lipid-related Atherosclerotic cardiovascular disease such as ischemic heart disease (IHD). The aim of this study was to compare Apo B, Non-HDL-C, and LDL-C to identify the most accurate and predictive test for IHD.*

Methods: *A case-control study, 200 males; 100 patients suffer from ischemic heart disease were taken*

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from the Cardiology Department of Al-Mouwasat University Hospital in Damascus, and 100 healthy persons, Participants' data were taken(age, education, anthropometric measurements, smoking and alcohol consumption, diabetes and hypertension), then laboratory tests were done (creatinine, albumin, glucose, cholesterol, triacylglycerol, HDL-C, ApoB, CRP) and the values of LDL-C and Non-HDL-C were calculated. The results were compared using T test and the SPSS program, the correlation, accuracy, prediction were studied.

Results: *ApoB test was the most significant and strongest predictor for IHD, followed by Non-HDL-C, but LDL-C had not acceptable predictive value.*

Conclusions: *This study recommends perform of ApoB as the best test to predict IHD if it is available, calculate Non-HDL-C in all cases routinely, LDL-C was not reliable.*

INTRODUCTION

Atherosclerotic cardiovascular disease (IHD) is the main cause of morbidity and mortality worldwide,[1] and most deaths are in low- and middle-income countries.[2]

Lipoproteins, particularly low-density lipoprotein (LDL) and other apolipoprotein ApoB-containing lipoproteins including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and lipoprotein (a) (Lp(a)) play a fundamental role in the initiation and evolution of atherosclerosis. During atherogenesis, the cholesterol-rich, ApoB-containing lipoproteins are retained and accumulate within vascular intima of the arterial wall,[3] and together with reactive immune and inflammatory mechanisms result in atherosclerotic plaque formation and progression.[4, 5]

Increase in concentrations of ApoB containing lipoproteins, particularly LDL, are associated with an increased risk of developing IHD. Clinical trials using lipid-lowering drugs have shown that lowering LDL-cholesterol results in significant reductions in both morbidity and mortality in patients with or without established coronary heart disease, studies using aggressive plasma LDL-cholesterol reduction as secondary prevention have demonstrated increased survival rates.[6]

However, despite of reductions in LDL-cholesterol with maximally tolerated statins and newer lipid-lowering agents, many people still experience cardiovascular events and/or IHD progression,[7] which may, in part, relate to triglyceride or to cholesterol content within triglyceride-rich lipoproteins.[8,9]

As known LDL-C is a well-established risk factor for IHD, being the primary therapeutic target in both primary and secondary prevention of IHD according to global dyslipidaemia guidelines.[10-12]

But despite of what was previously believed that LDL was the most atherogenic lipoprotein and thus became the target for therapy surveillance, it is now realized that all these lipoproteins (LDL, IDL, VLDL, Lp(a)) confer some atherogenic potential. Apo-B level indicates the total number of lipoprotein particles includes LDL, IDL, VLDL, Lp(a). Since ApoB indicates most atherogenic particles, it was hypothesized that ApoB concentration should be better predictor risk factor for IHD than LDL according to earlier studies.[13]

Non-HDL-C includes all cholesterol in potentially atherogenic lipoprotein particles, (VLDL, IDL, LDL, and lipoprotein (a). A study conducted by Boekholdt et al, concluded that changes in Non-HDL-C also explained a larger proportion of the athero-protective effect of statin intervention than did LDL-C and ApoB.[14]

So, whether we measure LDL-C or obtain it Using the Friedewald equation, this ignores the important atherogenic VLDL remnants as targets for therapy. Meanwhile, the VLDL remnants, as well as the atherogenic IDL,VLDL, are accounted for using simple Non-HDL calculation which is the difference between TC and HDL.[15]

Apolipoprotein B (Apo B) analysis is recommended for risk assessment, particularly in people with high TAG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening,

diagnosis, and management, and may be preferred over Non-HDL-C and considered better than LDL-C and Non-HDL-C estimation for IHD risk assessment in people with high Triacylglycerol, Diabetes, obesity, or very low LDL-C.(16) This has created a need for identification a reliable biomarker which could help in future prediction of coronary risk. Which is better Non-HDL or apolipoprotein B as a biomarker to adopt it as a predictive risk factor for IHD instead of LDL-C? In most conditions, LDL-cholesterol, Non-HDL cholesterol and ApoB are highly correlated, but, in individuals with mild-moderate hypertriglyceridaemia and associated illnesses, such as diabetes, obesity and the metabolic syndrome, discordance between these measures may occur.[17]

These observations highlight the need for this study to compare these tests ApoB, Non-HDL-C, LDL-C for IHD risk assessment.

Aim of this study: Comparison of Apo B, Non-HDL-C, and LDL-C to identify the most accurate and predictive test for IHD.

METHODS

A Case-control study of 200 males (males to exclude HDL-C hight bias in females). Control group included 100 persons of apparently normal males who are close in terms and age to the patient group. (no clinical history of heart disease, no prior ischemic heart disease). Patient group included 100 patients suffer from an ischemic heart disease, which includes acute coronary syndrome ACS, myocardial infarction with ST-elevation STEMI, or myocardial infarction without ST-elevation NSTEMI.

Exclusion criteria: Patients on statin therapy, people with chronic diseases and long-term hospitalization, such as kidney failure, liver failure or cancer, and Those with serum triglyceride levels more than 400 mg/dl.

This study was carried out in department of laboratory medicine, medicine college, Damascus university, from October 2018 to September 2020, the samples were collected from Al-Mouwasat University Hospital, department of cardiology intensive care for patients-group, whereas control group were collected from healthy persons. All participants were given written, informed consent for this study and approval was obtained from all of them, in addition to approval of Damascus university for performing this study. Participants' details such as age, education, anthropometric measurements height and weight for body mass index, abdominal and hip circumference for waist-hip ratio, history of smoking and alcohol consumption, and history of diabetes and hypertension were taken. A venous blood sample of 5 mL was obtained from each participant after fasting for at least 12 hours. The blood samples were collected into vacutainer tubes, and after they were centrifuged, the serum was divided and transferred to two Eppendorf tubes, one stored at -40 C until Apo B, CRP analysis were done, and the other was used immediately for the analysis (creatinine, albumin, blood glucose, total cholesterol, triacylglycerol, HDL).

By using commercially available kits (Dirui), the absorbance of the samples was measured using automated spectrophotometer (Olympus), enzymatic method for albumin, creatinine, blood glucose, total cholesterol (TC), triacylglycerol (TAG) and high-density lipoprotein cholesterol (HDL-C), and immunoturbidimetric method for reactive protein C (CRP), Apolipoprotein B (Apo B). Concentration of LDL-C was calculated according to Friedewald's formula (LDL = TC – HDL– TG/5) which is internationally accepted (Friedewald et al., 1972), Non-HDL-C was calculated as the difference between the TC and HDL-C.

Statistical analysis: The results were analyzed using SPSS version 22 software of IBM, student t-test to determine the mean and standard deviation for comparisons, Pearson's correlation (coefficient with the two-tailed count of correlations) test was used to study the correlation between each of ApoB, Non-HDL-C, and LDL-C with IHD risk factors. The binary logistic regression (Exp(b)) was done to calculate odds ratio for IHD and the Area Under the Curve (AUC) for accuracy was done, p-value less than 0.05 was considered a statistically significant value.

RESULTS

The statistical study of each parameter indicated that

the data distribution was normal or close to it, with no missed or anomalous influencing values in each of the studied groups. Therefore, the results of all measured parameters were presented in the form of mean (M) and standard deviation (SD) and for the categorical variables (education level, smoking, presence of diabetes, type of ischemic heart disease) were presented as a number (percentage) as shown in Table 1.

The results shows that the ages of the participants, which ranged in control group between (45-70 years) with an average of 58.02±6.20 year, while the age of patient group ranged between (44-72 years) with an average of 57.89±7.78 years, statistical tests showed that the two study groups were compatible in age, where the t-test did not show a statistically significant difference between the averages of ages in two groups, and the p-value was greater than 0.05.

Table 1 also shows statistically significant increase

Characteristics		Control group Non IHD (100)		Patient group IHD (100)		p-value
		Number	%	Number	%	
Education level	Up to 9	4	4.0%	76	76.0%	**
	Up to 12	21	21.0%	15	15.0%	ns
	More than 12	33	33.0%	9	9.0%	**
	Postgraduates	42	42.0%	0	0.0%	
Smoking	Nonsmoker	100	100%	32	32%	**
	Smoker	0	0.0%	68	68%	
Diabetes	Number	0	0.0%	18	18%	
Ischemic Heart Disease	ACS	0	0.0%	18	18.0%	
	STEMI	0	0.0%	78	78.0%	
	NSTEMI	0	0.0%	4	4.0%	
Mean (M), Standard Deviation (SD)		M	SD	M	SD	
Age (Year)		58.02	6.20	57.89	7.78	ns
Systolic Blood Pressure (mmHg)		116.44	5.13	138.57	9.15	**
Diastolic Blood Pressure (mmHg)		74.61	4.94	89.76	11.65	**
Creatinine (mg/dl)		1.00	0.17	1.02	0.30	ns
Albumin (g/dl)		4.39	0.54	3.87	0.84	**
Body Mass Index (Kg/m^2)		25.06	1.77	30.96	2.87	**
Waist to Hip ratio		0.88	0.04	1.07	0.10	**
C-Reactive Protein (mg/l)		3.31	1.47	14.39	5.57	**
Fasting glucose (mg/dl)		91.06	8.26	177.96	36.11	**
Triacylglycerols (mg/dl)		100.05	14.55	170.34	27.97	**
Total Cholesterol (mg/dl)		161.81	8.10	207.40	24.22	**
non-HDL-C (mg/dl)		113.57	11.00	173.39	27.27	**
HDL-C (mg/dl)		48.24	3.83	34.01	7.75	**
LDL-C (mg/dl)		93.56	9.73	139.32	24.50	**
Apolipoprotein B (mg/dl)		79.78	5.96	125.43	13.55	**

Acute coronary syndrome; HDL: High-Density Lipoproteins; IHD: ischemic heart disease; LDL: low-density lipoproteins; non-HDL-C: cholesterol outside of high-density lipoproteins; NSTEMI: myocardial infarction without ST elevation; STEMI: myocardial infarction with ST elevation; TC: total cholesterol. [p-value: more than 0.05 (ns statistically insignificant); less than 0.01 (*); less than 0.001 (**)]

Table 1. The total anthropometric, clinical and laboratory data of the two study groups and the results of the comparison between them according to the t-test (P).

of values for ischemic heart disease risk factors: BMI, waist circumference/hip W/H, systolic Blood Pressure SBP, diastolic Blood Pressure DBP, triacylglycerol TAG, total cholesterol TC, LDL-C, Non-HDL- (C), ApoB and inflammatory parameter (CRP) for the patient group compared to their values in control group and decrease of HDL-C value (innocent lipoprotein of causing atherosclerosis) in the patient group.

1- Correlation of Apo B, Non-HDL-C, LDL-C with IHD risk factors: The results showed strong correlation between each of Apo B, Non-HDL-C and LDL-C with ischemic heart disease risk factors in control group, patient group separately, and in both groups together, as displayed in Table (2), the results showed that the most strong positive correlation was for Apo B with ischemic heart disease risk factors, followed by Non-HDL-C, then LDL-C, the studied risk factors for IHD includes well-known risk factors such as increasing of: blood pressure (SBP, DBP), body mass index (BMI),waist to hip ratio (W/H), fasting sugar (FG), C-reactive protein (CRP), total cholesterol (TC), triglycerides (TAG), serum cholesterol outside high-density lipoproteins (Non-HDL-C) and LDL-C, while the correlation with HDL-C was negative considering that HDL-C is a protective factor for IHD, and the p-value was statistically significant in all cases,

2- Odds Ratio of APOB, Non-HDL-C, LDL-C for predicting IHD: By comparing the odds ratio of the

Risk factor		ApoB Group			Non-HDL-C Group			LDL-C Group		
		control	patients	both	control	patients	both	control	patients	both
SBP	r	0.610	0.273	0.835	0.571	0.213	0.772	0.509	0.163	0.725
	P	0.000	0.006	0.000	0.000	0.033	0.000	0.000	0.105	0.000
DBP	r	0.603	0.275	0.693	0.559	0.230	0.654	0.497	0.180	0.612
	P	0.000	0.006	0.000	0.000	0.021	0.000	0.000	0.072	0.000
BMI	r	0.863	0.557	0.869	0.845	0.551	0.855	0.796	0.524	0.830
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
W/H	r	0.454	0.174	0.758	0.360	0.156	0.700	0.363	0.107	0.656
	P	0.000	0.083	0.000	0.000	0.121	0.000	0.000	0.287	0.000
FG	r	0.644	0.306	0.851	0.626	0.332	0.808	0.571	0.294	0.768
	P	0.000	0.002	0.000	0.000	0.001	0.000	0.000	0.003	0.000
CRP	r	0.782	0.312	0.822	0.722	0.227	0.755	0.668	0.195	0.715
	P	0.000	0.002	0.000	0.000	0.023	0.000	0.000	0.052	0.000
TC	r	0.706	0.751	0.903	0.484	0.962	0.984	0.495	0.943	0.977
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
TAG	r	0.489	0.490	0.878	0.544	0.573	0.867	0.317	0.409	0.789
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
Non-HDL-C	r	0.745	0.803	0.936				0.968	0.982	0.990
	P	0.000	0.000	0.000				0.000	0.000	0.000
LDL-C	r	0.696	0.782	0.908	0.968	0.982	0.990			
	P	0.000	0.000	0.000	0.000	0.000	0.000			
ApoB	r				0.745	0.803	0.936	0.696	0.782	0.908
	P				0.000	0.000	0.000	0.000	0.000	0.000
HDL-C	r	0.800-	0.480-	0.836-	0.832-	0.513-	0.834-	0.799-	0.509-	0.816-
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

LDL: Low-density lipoproteins; non-HDL-C: cholesterol outside of high-density lipoproteins; ApoB: apolipoprotein B; HDL-C: high-density lipoproteins; TAG: triacylglycerol; TC: total cholesterol; CRP:C-reactive protein; FG: fasting glucose; W/H: waist/hip ratio, BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; R: correlation coefficient; P: probability value

Table 2. Correlation of ApoB, Non-HDL-C, LDL-C with risk factors for ischemic heart disease.

three tests (Apo B, Non-HDL-C, LDL-C) for predicting IHD, it is evident in Table 3 that Apo B (Exp (B) = 1.287, Sig = 0.032) had the highest predictive value and statistical significant for IHD, followed by Non-HDL-C which is far a bit from statistical significance (Exp (B) = 1.545, Sig = 0.067) compared to the low-density lipoprotein cholesterol (LDL-C) whose Exp(B) value was less than one and far from statistical significance.

3- Accuracy of APOB, Non-HDL-C, LDL-C to diagnose IHD: The accuracy of each of ApoB, Non-HDL-C and LDL-C was excellent, for the area under the curve (AUC) was above 0.9 for each one of them, it was 0.994 for Non-HDL-C, 0.992 for Apo B, and 0.968 for LDL-C, diagrams shown in Figure 1.

DISCUSSION

Both of ApoB and Non-HDL-C have been proposed as markers to reflect the risk conferred by proatherogenic TG-rich VLDL in addition to LDL-C.[14-16]

Results showed that Apo B was the most correlated test with IHD risk factors followed by Non-HDL-C then LDL-C. Both ApoB and Non-HDL-C are exceeded over LDL-C as predictors for IHD, but ApoB was more significant predictor of IHD than Non-HDL-C, the predictive value of ApoB was more than one and statistically significant but the predictive value of Non-HDL-C was more than one but far a bit from statistical

	B	S.E.	Sig.	Exp(B)	C.I. for 95% EXP(B)	
					Lower	Upper
ApoB	0.252	0.118	0.032	1.287	1.021	1.621
Non-HDL-C	0.435	0.238	0.067	1.545	0.970	2.462
LDL-C	-0.471	0.258	0.068	0.624	0.377	1.035

LDL: Low-density lipoproteins; non-HDL-C: cholesterol outside of high-density lipoproteins; ApoB: apolipoprotein B; Exp(B)= odds ratio; Sig.=probability; B: barameter; S.E.: standard error; C.I.: confidence interval.

Table 3. Exp (B) of coronary heart disease of ApoB, Non-HDL-C, LDL-C.

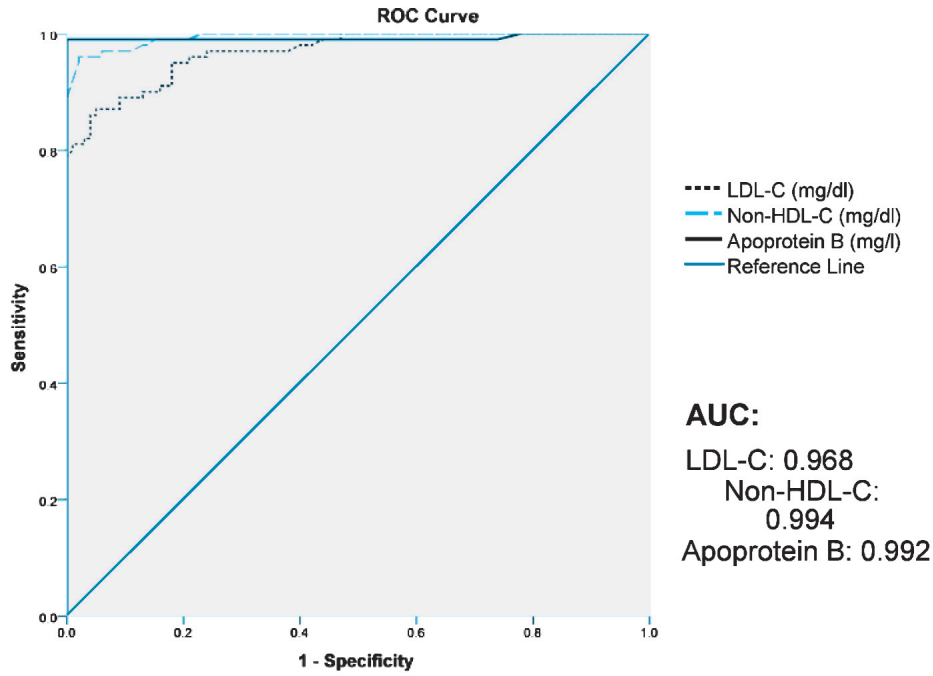

Figure 1. The receiver operating characteristic (ROC) curve and area under the curve (AUC) for Apo B, Non-HDL-C, and LDL-C tests for diagnosis and prediction of ischemic Heart Disease. Non-HDL-C: cholesterol outside high density lipoproteins; LDL: low density lipoproteins, ApoB: Apolipoprotein B.

significance, whereas LDL-C whose Exp(B) value (odds ratio) for predicting IHD was less than one and the furthest from statistical significance. All ApoB, Non-HDL-C and LDL-C were excellent for accuracy of diagnosis IHD.

And compared to the studies, our results suggest that ApoB (as a single well quantified lipoprotein measurement) is more strongly correlated to the IHD risk factors which is compatible with previous studies on ApoB.[18,19] thus it is correlated to IHD more than Non-HDL-C and LDL-C. ApoB is synthesized by the liver and secreted with VLDL, these in turn are converted in the periphery to intermediate density lipoproteins (IDL) and then to LDL. Because there is one ApoB molecule per lipoprotein particle, ApoB reflects the total number of VLDL, IDL, and LDL particles and thus the concentration of proatherogenic particles.[20]

So, may be plasma concentration of atherogenic lipoproteins is more critical to the development of atherosclerosis than the amount of cholesterol that the lipoproteins carry into the arterial wall.

Our results confirm previous observations that Non-HDL-C is superior to LDL-C in predicting cardio vascular disease.(21) probably because it also captures TG-rich atherogenic lipoproteins such as VLDL.[22]

The practical application of our findings would be the try of using ApoB instead of LDL-C (when AopB is available) for screening and treatment of IHD. Calculation of Non-HDL-C is recommended in all cases, because it is reliable, cost- free, easy calculated (the difference between total cholesterol and HDL-C) ,and serves well in predicting IHD risk factors, which is similar to results in several studies and meta-analysis which have shown the usefulness of Non-HDL-C as an effective marker of IHD risk factors, conduct by AK Badrinath, et al.(23) LDL-C was not reliable test for predicting IHD, despite of its excellent accuracy and strong correlation with IHD risk factors.

CONCLUSIONS

Based on our study, ApoB test is the best for predicting IHD; therefore, it is recommended to perform it if available it can be used as a treatment target for lowering lipid drugs. Non-HDL-C calculation is recommended in all cases, for its excellent accuracy, predictability, and strong correlation with IHD risk factors. LDL-C alone is insufficient test to depend on for predicting IHD.

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