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Importance of measuring non-HDL cholesterol in type 2 diabetes patients.

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ORIGINAL ARTICLE

Importance of measuring Non-HDL cholesterol in type 2 diabetes patients

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Abstract

Objective: To study the correlation between Non-high-density lipoprotein and low-density lipoprotein cholesterol in patients with Type 2 diabetes mellitus and the proportion of patients achieving Adult Treatment Panel III recommended goals.

Methods: The cross sectional study was conducted at the Diabetic Clinic, Aga Khan University Hospital, Karachi. Data of Type 2 diabetes mellitus patients who attended the clinic bewteen 2007 and 2011 was reviewed. All Type 2 diabetic patients of either gender with fasting lipid profile irrespective of taking lipid lowering therapy were included. Type-1 DM, gestational diabetes, type 2 diabetes patients with pregnancy and those with incomplete data were excluded. Correlation between the low-density lipoprotein and Non- high-density lipoprotein was assessed by applying Cramer V and phi. Proportion of patients achieving Adult Treatment Panel III recommended goals was checked. Multivariable regression was done to identify common factors associated with elevated Non- high-density lipoprotein cholesterol.

Results: A total of 1352 patients fulfilling the eligibility criteria were included in the study. Mean age of the patients was 54.5±11.3 years; 797 (59%) were males; 1122 (83%) had Body Mass Index above 25; and 1016 (75%) had HbA1c ≥7%. Mean Non-high-density lipoprotein cholesterol was 129±42mg/dl. Mean low-density lipoprotein cholesterol was 100±37mg/dl. Both low-density lipoprotein ≤100 and Non-HDL ≤130 mg/dl was achieved in 645 (48%) patients. It is important to note that although 728 (53.8%) patients achieved target LDL cholesterol of ≤100mg/dl, among them 83 (11.4%) had Non-high-density lipoprotein cholesterol still above the target >130mg/dl (p<0.05). Out of 752 patients with Non-high-density lipoprotein cholesterol ≤130mg/dl, 645(86%) had low-density lipoprotein cholesterol below 100mg/dl. Cramer V and Phi showed that correlation between Non-high-density lipoprotein and low-density lipoprotein cholesterol was 0.71 (pvalue<0.01). After adjusting for other covariates, low-density lipoprotein cholesterol >100mg/dl was independently associated with having Non-high-density lipoprotein cholesterol >130mg/dl (Adjusted Odds Ratio 38.6; 95% Confidance Interval = 28.1-53.1). Similarly, age ≤60 years was 60% more likely to have Non-high-density lipoprotein cholesterol> 130 mg/dl (Adjusted Odds Ratio 1.6; 95% Confidance Interval = 1.01 - 2.3). Whereas having obesity Body Mass Index >25 was 3.6 times more associated to have Non-high-density lipoprotein >130mg/dl (Adjusted Odds Ratio 3.6; 95% Confidance Interval = 1.6-7.7). In patients with coronary artery disease, combined goal achievement of low-density lipoprotein ≤70mg/dl and Non-high-density lipoprotein cholesterol ≤100mg/dl was seen in 59(35%). Among patients with high-density lipoprotein ≤70mg/dl, 8(10%) had Non-high-density lipoprotein >100mg/dl (p <0.05).

Conclusion: The study showed a correlation between Non-high-density lipoprotein and low-density lipoprotein cholesterol. As measuring Non-high-density lipoprotein cholesterol in Type 2 DM patients is simple, cost-effective and convenient because it does not require 12-hour fasting which may be a risk for hypoglycaemia in these patients, clinicians may choose Non-high-density lipoprotein as a routine measure in everyday practice.

Keywords: Type 2 diabetes mellitus, Non-high-density lipoprotein (Non-HDL) cholesterol, Low-density lipoprotein (LDL) cholesterol, Coronary artery disease. (JPMA 64: 124; 2014)

Introduction

Non-high-density lipoprotein (Non-HDL) cholesterol has been shown to be superior predictor of cardiovascular risk,[1] because it contains cholesterol of all atherogenic particles, including low density lipoprotein (LDL), Lipoprotein A, very-low-density lipoprotein (VLDL),VLDL remnant and intermediate-density lipoprotein.[2,3]

Currently LDL cholesterol is the primary treatment target of lipid-lowering therapy in primary and secondary prevention of cardiovascular diseases.[4,5] However, despite achieving the LDL goal, patients still develop recurrent coronary artery disease (CAD).[6] One possible explanation of this residual risk could be a still high Non-HDL cholesterol in these patients despite achieving the LDL target. Adult Treatment Panel-III (ATP-III) guidelines recommend a Non-HDL cholesterol as a secondary treatment target among those with triglycerides level above 200md/dl.[7] However, no triglyceride cut-off level was defined by the American College of Cardiology Foundation and the American

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Diabetes Association (ADA).[8]

Apolipoprotein B100 (Apo B) molecule is present in all major atherogenic particles (VLDL, IDL, LDL). Therefore, estimating Apo B has been shown as a superior indicator of cardiovascular risk than total or LDL cholesterol.[9] Apo B measurement is not readily available of cost-effective,[10] but the correlation co-efficient for Non-HDL and Apo B is significantly better than that of LDL and Apo B.[11] Now it is well recognised that non-HDL and Apo B are closely related metabolically and they can substitute each other.[9]

Non-HDL cholesterol (NHDL-C) is calculated from lipid profile by subtracting HDL-C from total cholesterol. It is simple, inexpensive and, most important, does not require a 12-hour fast because it can be calculated on random serum sample. Therefore, the current study was planned to determine the correlation between Non-HDL and LDL cholesterol. If correlated, physicians can use Non-HDL cholesterol as a close marker of Apo B.

Treatment goal for Non-HDL is 30mg/dl above the LDL target. For diabetic patients without CAD, treatment target for LDL and Non-HDL is <100mg/dl and <130mg/dl respectively. For diabetic patients with CAD, treatment target for LDL is <70 and Non-HDL cholesterol is <100mg/dl.[7]

Targeting Non-HDL cholesterol in diabetic patients is even more important because these patients often have atherogenic dyslipidaemia characterised by low HDL cholesterol and high triglycerides with resultant increase in Non-HDL cholesterol than elevated LDL alone.[12] Many diabetic patients are not at recommended levels for Non-HDL and LDL cholesterol.

The primary objective of the present study was to determine the correlation between Non-HDL and LDL cholesterol in type 2 diabetes mellitus (T2DM) patients. Secondary objectives were to identify proportion of T2DM patients achieving ATP III-guideline recommended goals and factors associated with elevated Non-HDL cholesterol.

Patients and Methods

The cross-sectional study was conducted at the Diabetic Clinic of Aga Khan University Hospita, Karachi, and comprised data of patients having visited the clincs between 2007 and 2011. Patients ≥18 years of age, already diagnosed to have known diabetes visiting endocrine/diabetes clinic were identified from hospital medical records. AKUH is a largest tertiary care hospital in the metropolitan city of Karachi with a population of 18 million. Information about demographic characteristics, clinical presentations and laboratory biochemical parameters were collected. The study was approved by the hospital ethical review committee.

All T2DM patients of either gender with fasting lipid profile irrespective of receiving lipid-lowering therapy were included. Exclusion criteria were type 1 diabetes, gestational diabetes, and T2DM patients with pregnancy.

A structured questionnaire was used for data collection. Complete demographic and clinical history, including, hypertension, CAD, body mass index (BMI), HbA1C, Non-HDL and LDL cholesterol were identified. BMI 18-22.9 Kg/m^2 was defined as normal; 23-24.9 Kg/m^2 as overweight; and ≥25 Kg/m^2 as obese, according to an Asian cutoffs; HbA1c ≥7 as uncontrolled T2DM; and <7 as controlled T2DM according to ADA criteria; Non-HDL cholesterol, according to ATP-III, target was ≤130mg/dl in T2DM patients without CAD; with CAD target was ≤100mg/dl;[13] target for LDL cholesterol in T2DM patients without CAD was 100mg/dl; and with CAD was 70 mg/dl,[13] hypertension was defined as blood pressure ≥140/90mmHg or patients maintained on oral anti-hypertensive medication.

Data was entered and analyzed in SPSS version 17.0. Mean±SD, ranges were calculated for continuous variables and proportions for categorical variables. To see the difference between two groups independent student t-test, chi square or Fisher exact was used where appropriate. Continuous variables were checked for their linearity by doing quartile and Box Tidwell analysis. The trends in values of Exp (β) i.e. log of odds of outcome, either increasing or decreasing and confidence interval (CI) either overlapping or not were checked. If the CI was found to be overlapping with increasing or decreasing Exp (β) trend, then it was taken as continuous variable. Along with this for every continuous variable higher order terms were made like log, quadratic, cube and box-Tidwell transformation. All those variables found to be insignificant were kept as a continuous one. However, in our case, the values for BMI, and age came to be significant, hence, we formed categories. Correlation between the LDL and NHDL was assessed by applying Cramer V and phi. Multicolinearity was checked among independent variables, between nominal variables it was checked through Cramer's V and phi, between nominal and continuous through eta, and between continuous variables it was checked through Pearson correlation. The cutoff of 0.8 was considered as an Interco relation among independent variables. A univariate logistic regression analysis was conducted to assess the (crude) association of the prognostic factors for Non-HDL. Biological

significance and a value of p≤0.25 were considered significant at univariate analysis. Biological plausible interactions among variables and confounding factors were also checked. Multivariable logistic regression was done and results were expressed as odds ratios (OR), along with 95% CI.

Results

A total of 1352 patients fulfilling the eligibility criteria were included in the study. Mean age of the patients was 54.5±11.3 years; 797 (59%) were males; 1122 (83%) had BMI above 25; 335 (24.8%) had HbA1c <7%; 630 (46.6%) had HbA1c 7-9%; while 386 (28.6%) patients had HbA1c >9%. There was history of hypertension in 540 (40%) patients (Table-1). Mean Non-HDL cholesterol was 129±42mg/dl. Mean LDL cholesterol was 100±37mg/dl. Both LDL ≤100mg/dl and Non-HDL ≤130mg/dl targets were achieved in 645 (48%) patients. Although 728 (53.8%) patients achieved the target LDL of ≤100mg/dl, 83 (11.4%) among them had Non-HDL cholesterol above target >130mg/dl (p<0.05). Out of 752 patients with Non-HDL cholesterol ≤130mg/dl, 645(86%) had LDL cholesterol below 100 mg/dl. Cramer V and Phi showed that correlation between Non-HDL and LDL cholesterol was 0.71 (p<0.01).

Unadjusted odds ratios were worked out (Table-2). Age ≤60 years (OR 1.8; 95% CI = 1.4-2.4), being female (OR 1.2; 95% CI = 1.1-1.5), BMI ≥25 (OR 2.5; 95% CI = 1.4-4.5) and HbA1c >9% (OR 1.6; 95% CI = 1.2 - 2.2) were associated with having Non-HDL cholesterol >130mg/dl. After adjusting for other covariates, LDL cholesterol >100mg/dl was independently associated with having Non-HDL >130mg/dl (Adjusted OR 38.6; 95% CI= 28.1-53.1). Similarly, age ≤60 years was 60% more likely to have Non-HDL >130mg/dl (Adjusted OR 1.6; 95% CI= 1.01-2.3). Having BMI>25 was 3.6 times more associated to have Non-HDL cholesterol >130mg/dl (Adjusted OR 3.6; 95% CI= 1.6-7.7).

In patients with CAD, combined goal achievement of LDL ≤70 and Non-HDL ≤100 was seen in 59(35%) patients. Among these patients with LDL ≤70mg/dl, 8(10%) patients had Non-HDL >100mg/dl (p <0.05) (Table-3).

Table-1: Prevalence of Non-HDL <130 and Non-HDL > 130 mg/dl according to Age, Gender, BMI, HBA1C, LDL cholesterol and history of hypertension.

Variable	NHDL ≤130	NHDL >130	P-Value	Unadjusted odds ratios	95% CI
Age					
≤ 60	492 (65.4)	469 (78.2)	< 0.001	1.8	1.4-2.4
> 60	260 (34.6)	131 (21.8)		Ref	
Gender					
Male	463 (61.6)	335 (55.8)	0.03	Ref	
Female	289 (38.4)	265 (44.2)		1.2	1.1-1.5
BMI					
18-22.9	51 (6.8)	16 (2.7)	0.001	Ref	
23-24.9	81 (10.8)	80 (13.3)		3.1	1.6-5.9
≥ 25	620 (82.4)	504 (84)		2.5	1.4-4.5
HbA1c					
< 7	203 (27)	132 (22)	0.001	Ref	
7-9	365 (48.5)	266 (44.3)		1.1	0.8-1.4
> 9	184 (24.5)	202 (33.7)		1.6	1.2-2.2
LDL					
≤ 100	645 (85.8)	83 (13.8)	0.000	Ref	
>100	107 (14.2)	517 (86.2)		37.5	27.5-51.1
HTN					
No	420 (55.9)	394 (69.7)	< 0.001	--	
Yes	332 (44.1)	206 (34.3)		--	

Non-HDL: Non-High Density Lipoprotein. BMI: Body Mass Index. HbA1c: Glycated Haemoglobin. LDL: Low Density Lipoprotein.

Table-2: Adjusted Odds along with 95% Confidence Interval showing predictors for Non-HDL cholesterol >130mg mg/dl.

Variable	Adjusted ORs	95% CI	P-value
LDL			
≤100	1		
>100	38.6	28.1 - 53.1	0.00
Age			
> 60	1		
≤60	1.6	1.01- 2.3	0.03
BMI			
18-22.9	1		
23-24.9	2.6	1.1 - 6.2	0.00
≥25	3.6	1.6 - 7.7	

Non-HDL: Non-High Density Lipoprotein. LDL: Low Density Lipoprotein. BMI: Body Mass Index.

Table-3: Coronary Artery Disease Patients Characteristics (n=169).

Variable	NHDL ≤100 N (%)	NHDL > 100 N (%)	P-Value
Age			
≤60	39 (43.8)	49 (61.3)	0.02
> 60	50 (56.2)	31 (38.8)	
Gender			
Male	67 (75.3)	50 (62.5)	0.07
Female	22 (24.7)	30 (37.5)	
BMI			
18-22.9	10 (11.2)	3 (3.8)	0.18
23-24.9	8 (9)	7 (8.8)	
≥25	71 (79.8)	70 (87.5)	
LDL			
≤70	59 (66.3)	8 (10)	0.00
> 70	30 (33.7)	72 (90)	

Non-HDL: Non-High Density Lipoprotein. BMI: Body Mass Index. LDL: Low Density Lipoprotein.

Discussion

Correlation between Non-HDL and LDL cholesterol at 71%

was observed in the current study, which emphasise the importance of measuring and targeting it in T2DM patients. Non-HDL and LDL cholesterol combined target was achieved in 48% of T2DM patients. Despite LDL level ≤100mg/dl, 11% of patients had Non-HDL cholesterol above the target range.

Atherogenic dyslipidaemia is associated with an increased risk of future cardiovascular complications.[14-17] The association between abnormal lipid levels and cardiovascular risk is much more evident among patients with diabetes mellitus and hypertension.[18] Current guidelines emphasise the importance of lipid goal attainment in this high-risk group.[7,13] Non-HDL cholesterol proves a better predictor of vascular events.[19] Despite LDL cholesterol being in the target range, achieving Non-HDL cholesterol goal is still poor.[20,21]

Patient need 12-14 hour fasting for measuring LDL cholesterol which may cause risk of hypoglycaemia in a diabetic patient. Non-HDL cholesterol calculated from random serum sample, simple, convenient, cost-effective and, most importantly, it is a valid surrogate marker of Apo B in diabetic patients.[9]

A study reported 64.6%, 71.5% patients with diabetes not achieving LDL ≤100md/dl and Non-HDL ≤130mg/dl respectively.[21] Another study examined the LDL and non-HDL goal in coronary heart disease patients. It found that 74% of the patients attained LDL goal while only 51% achieved combined non-HDL and LDL cholesterol in range.[22] The current study observed combined LDL<70mg/dl and Non-HDL<100mg/dl in 35% of patients with diabetes and CAD, while another study reported 13% of such goal achievement in very high-risk CAD patients.[22]

In a study from Saudi Arabia, 77% T2DM patients had LDL> 100md/dl[23] while San Antonio heart study found 50% of patients with T2DM had high-risk LDL cholesterol level.[24]

Possible explanations for poor Non-HDL goal achievement are Non-HDL cholesterol not reported in routine lipid profile panel, lack of physicians/healthcare provider awareness regarding its importance, how to calculate Non-HDL cholesterol, failure to intensify lipid lowering therapy once LDL cholesterol is in target to achieve Non-HDL cholesterol level.

It has been suggested that direct reporting of Non-HDL-C on standard lipid profile result would improve goal achievement.[25]

High BMI, high HbA1c and younger age group were independently associated with high Non-HDL cholesterol in our study. Similar results have been identified in a high-risk group of patients.[26]

There were certain limitations in our study. Due to observational nature of the study, there was no data on use of statins, so we were unable to determine the effect of statin and therapeutic lifestyle changes on Non-HDL and LDL cholesterol goals. Similarly, cause and effect relationship could not be ascertained.

Conclusion

The results showed correlation between Non-HDL and LDL cholesterol. As measuring Non- HDL cholesterol in T2DM patients is simple, cost-effective and convenient because it does not require 12-hour fasting, which may be a risk for hypoglycaemia in these patients, clinicians may choose Non-HDL as a routine measure in everyday practice. It also showed that about 44% of patients did not achieve Non-HDL cholesterol targets. More aggressive lipid-lowering therapy, as such, should be implemented.

References

1. Virani SS. Non-HDL Cholesterol as a Metric of Good Quality of Care: Opportunities and Challenges. Tex Heart Inst J 2011; 38: 160-2.
2. Grundy MD, Scott M. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. Am J Cardiol 1998; 81: 18B-25B.
3. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. Circulation 2002; 106: 2526-9.
4. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279: 1615-22.
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
6. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al.Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495-504.
7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
8. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008; 51: 1512-24.
9. Hermans MP, Sacks FM, Ahn SA, Rousseau MF. Non-HDL-cholesterol as valid surrogate to apolipoprotein B100 measurement in diabetes: Discriminant Ratio and unbiased equivalence. Cardiovasc Diabetol 2011; 10: 20.
10. Alla VM, Kaushik M, Mooss A. Targeting residual risk: the rationale for the use of non-HDL cholesterol. South Med J 2010; 103: 434-7.
11. Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C. Correlation of non-high-density lipoprotein cholesterol with

apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. Am J Cardiol 2001; 88: 265-9.
12. Bittner V. Non-high-density lipoprotein cholesterol and cardiovascular disease.Curr Opin Lipidol 2003; 14: 367-71.
13. Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-39.
14. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, PROVE IT-TIMI 22 investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J AmColl Cardiol 2008; 51: 724-30.
15. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation 2008; 117: 3002-9.
16. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. Pharmacol Ther 2010; 126: 314-45.
17. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, et al. The residual risk reduction initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol 2008; 102: 1K-34K.
18. Assmann G, Schulte H. The Prospective Cardiovascular Munster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. Am Heart J 1988; 116: 1713-24.
19. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009; 302: 1993-2000.
20. Vulic D, Lee BT, Dede J, Lopez VA, Wong ND. Extent of control of cardiovascular risk factors and adherence to recommended therapies in US multiethnic adults with coronary heart disease: from a 2005-2006 national survey. Am J Cardiovasc Drugs 2010; 10: 109-14.
21. Malik S, Lopez V, Chen R, Wu W, Wong ND. Undertreatment of cardiovascular risk factors among persons with diabetes in the United States. Diabetes Res Clin Pract 2007; 77: 126-33.
22. Virani SS, Woodard LD, Landrum CR, Pietz K, Wang D, Ballantyne CM, et al. Institutional, provider, and patient correlates of low-density lipoprotein and non-high-density lipoprotein cholesterol goal attainment according to the Adult Treatment Panel III guidelines. Am Heart J 2011; 161: 1140-6.
23. Habib SS. Frequency distribution of atherogenic dyslipidemia in Saudi type 2 Diabetic patients. Pak J Physiol 2006; 2: 20-3.
24. Wei M, Mitchell BD, Haffner SM, Stern MP. Effects of cigarette smoking, diabetes, high cholesterol, and hypertension on all-cause mortality and cardiovascular disease mortality in Mexican Americans. The San Antonio Heart Study. Am J Epidemiol 1996; 144: 1058-65.
25. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA.The importance of non-HDL cholesterol reporting in lipid management. J ClinLipidol 2008; 2: 267-73.
26. Pirro M, Del Giorno R, Lupattelli G, Mannarino MR, Roscini AR, Covelli D, et al. Cardiovascular risk factors and recommended lipid goals attainment among patients referred in a tertiary care lipid clinic. Eur J Intern Med 2011; 22: 412-7.