



The Study of Non-HDL Cholesterol Levels Compared to LDL Cholesterol Levels in Diabetics

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Abstract

Dyslipidemia is an established risk factor for CAD in patients with type II DM, as well as in nondiabetic patients, and is likely to play a leading role in the increased CVD risk associated with diabetes. If we diagnose and treat dyslipidemia in early stage, we can decrease the risk of atherosclerotic diseases. The dyslipidemia associated with type II DM is typically more complex than simple elevation of systemic low-density lipoprotein cholesterol (LDL-C) levels. Unlike LDL cholesterol, which can be incorrectly calculated in the presence of postprandial hypertriglyceridemia, NON-HDL cholesterol (Non-HDL = LDL + VLDL + IDL + Lipoprotein (a)) is reliable when measured in the non fasting state. As NON-HDL cholesterol measures the Apo B-containing lipoproteins, it can serve as an additional tool to assess cardiovascular risk in people whose risk is not accurately identified by LDL cholesterol alone. This is especially important in patients with diabetes, in whom LDL levels may not be significantly elevated. So a prospective study was carried out in 105 diabetic patients in 20 years and above age group including both sexes irrespective of community or background who were present in inpatient department of medicine, Mata Chanan Devi hospital, New Delhi, during the time period of 2014-2016. It is a 210 bedded, tertiary care hospital in west Delhi, where the patients travel from all North India. Patients with hypothyroidism, renal failure, pregnancy, hypertension, smokers and who are on lipid lowering agent were not included in the study. After taking written informed consent fasting blood sample collected from each research participant for the analysis of lipid profile. Non-HDL-C calculated as TC minus HDL-C. LDL-C calculated by direct measurement (enzymatic colour test for the quantitative determination of LDL- Cholesterol in human serum and plasma on Beckman Coulter AU analysers). National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII) guidelines were referred to define dyslipidemia. The association between LDL and NON-HDL values were evaluated using the Pearson's Chi-Square test. P-value <0.05 was considered statistically significant .SPSS version 20.0 was used for statistical analysis.

Salient findings Out of 105 patients, there were 56 females and 49 males subjects. Minimum age is 39 years and maximum age is 81 years. Mean age in males is 56.12 ± 8.05 and in females 57.91 ± 7.13 . Mean fasting blood sugar was 184.92 mg/dl and mean post prandial blood sugar was 259.58 mg/dl as patients were on treatment for diabetes. Average duration of diabetes in present study group was 5.45 years. Mean value of triglycerides, LDL, VLDL, NON HDL, HDL were 201.99, 89.58, 41.19, 127.12, 38.5 mg/dl respectively. As per National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII) guidelines for LDL the cut off value is 100mg/dl, for NON HDL the cut off value is 130mg/dl and the cut off value for difference between NON HDL and LDL is 30mg/dl in diabetics.

In this study patients who had LDL level <100mg/dl (18%) had NON HDL level >130mg/dl (28.5%) in patients with TG >200 (46.6%) Thus in patients with TG >200mg/dl most of the patients had LDL <100mg/dl but had NON HDL >130mg/dl with a significant p value 0.012.

Our study showed that the number of patients having NON HDL and LDL difference of <30mg/dl are 39(33%) and number of patients having NON HDL and LDL difference of >30mg/dl are 66(67%) with a significant P value of

0.019. That means 67% of present study patients did not had the target of <30mg/dl difference between NON HDL and LDL.

Conclusion: In our study most of the patients did not had the target of <30mg/dl difference between NON HDL and LDL. In patients with TG >200mg/dl most of the patients had LDL<100mg/dl but had NON HDL >130mg/dl. The above point clearly says that in diabetic patients with TG >200mg/dl most of the patients had the target LDL level <100mg/dl but not had the target NON HDL level <130mg/dl. Characteristic diabetic dyslipidemia pattern i.e increased TG and NON HDL but underestimated LDL is seen in most of the patients in present study. Thus we conclude that in diabetic patients when TG >200mg/dl, NON HDL is a better target than LDL in deciding treatment for dyslipidemia.

Recommendations: NON HDL is recommended as a target other than LDL for dyslipidemia in diabetics.

In diabetic patients when TG >200mg/dl, NON HDL is a better target than LDL in deciding treatment for dyslipidemia. NON HDL is better marker than LDL for starting treatment of dyslipidemia in diabetic patients to decrease cardiovascular risk. Diabetic patients who reach the target LDL level should be seen for NON HDL level in deciding treatment for dyslipidemia. Elevated levels of NON-HDL are treatable by increasing the intensity of currently available lipid lowering agents, as well as lifestyle modification. All of the currently available lipid-lowering agents (statins, fibrates, niacin, fish-oil products, and intestinally active agents) decrease non-HDL-C levels.

As we have just compared the levels of NON HDL and LDL but not assessed the cardiovascular risk and the study population is also small we suggest further more studies in making NON HDL as a better target than LDL in diabetic patients

Introduction

Patients with diabetes mellitus have a markedly increased risk for macro vascular disease. A person with diabetes and no known cardiovascular disease (CVD) has the same risk as a person without diabetes who has already had a cardiovascular event.¹

Atherosclerosis is a multifaceted process involving interactions among immune, coagulation, hormonal, and vascular systems, and dyslipidemia is leading risk factor for atherosclerotic plaque formation and development of coronary heart disease (CHD) events.² Researchers concluded that most of the debilitating complication of diabetes can be prevented or delayed by prospective treatment of hyperglycemia and cardiovascular risk factors.^{3,4}

Diabetic patients have characteristic pattern of dyslipidemia with decreased level of high density lipoprotein cholesterol (HDL-C) and elevated triglycerides (TG) level. . In diabetes, blood glucose is not utilized by tissues resulting in hyperglycemia. Consequently fatty acids are mobilized from adipose tissue to meet the energy demands and in the process excess fatty acid accumulates in the liver leading to increased triglyceride and VLDL production.

It has been suggested that Non HDL cholesterol which consists of LDL, VLDL, IDL and Lipoprotein (a) might be a useful marker and better

predictor of CVD than LDL cholesterol in diabetic as well as non-diabetic individuals.⁵ In diabetes, low density lipoprotein cholesterol (LDL-C) which is used as one of the markers for the risk of CVD, is underestimated, as the elevated triglycerides leads to underestimation of LDL-C according to Friedewald formula

$$\text{LDL-C} = (\text{Total Cholesterol}) - (\text{HDL-C}) - (\text{Triglycerides})/5.$$

So in such cases the levels of non-HDL-C can be a stronger predictor of CVD as it strongly correlates with atherogenic lipoproteins.

Diabetics have significantly elevated ratio of total cholesterol to high density lipoprotein cholesterol (TC/HDL-C). So there is significant increase in levels of non-HDL-C which is used as marker of dyslipidemia and can also be used to predict the risk of cardiovascular disease in type 2 Diabetes Mellitus.

Objective

Our aim is to study the levels of NON HDL cholesterol in additional to LDL cholesterol in type 2 diabetes patients and to compare levels of NON HDL cholesterol to LDL cholesterol levels for making decision regarding treatment of dyslipidemia in type 2 diabetics.

Materials and Method

A prospective study was carried out in 105 diabetic patients in 20 years and above age group including both sexes irrespective of community or background who were present in inpatient department of medicine, Mata Chanan Devi hospital, New Delhi, during the time period of 2014-2016. It is a 210 bedded, tertiary care hospital in west Delhi. Patients with hypothyroidism, renal failure, pregnancy, hypertension, smokers and who are on lipid lowering agent were not included in the study. Diabetes is a self reported disease. The diagnosis of diabetes is based on American diabetic association criteria. Before starting the study, permission was taken from institutional ethical committee. After taking written informed consent fasting blood sample collected from each research participant for the analysis of lipid profile. Other baseline investigations like haematological profile, blood urea, serum creatinine, serum aminotransferase, serum uric acid, serum electrolytes was also carried out at the time of admission. LDL was measured by direct method. Blood sugar was analysed using hexokinase method. All the data and various findings including the past history, present diagnosis, blood sugar, HbA1c, fasting lipid profile of all subjects were tabulated and evaluated using Microsoft Excel. Non-HDL-C calculated as TC minus HDL-C. LDL-C calculated by direct measurement (enzymatic colour test for the quantitative determination of LDL- Cholesterol in human serum and plasma on Beckman Coulter AU analysers). National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATPIII) guidelines were referred to define dyslipidemia

The quantitative variables are expressed as mean \pm sd and compared across using unpaired t-test test. The qualitative variables were expressed as frequencies and percentages and compared across two groups using Chi-square test. The association between LDL and NON-HDL values were evaluated using the Pearson's Chi-Square test. A P-value <0.05 will be considered

statistically significant .SPSS version 20.0 was used for statistical analysis.

Result

Out of 105 patients, there were 56 females and 49 males subjects. Minimum age is 39 years and maximum age is 81 years. Mean age in males is 56.12 ± 8.05 and in females 57.91 ± 7.13 . Mean fasting blood sugar was 184.92 mg/dl and mean post prandial blood sugar was 259.58 mg/dl as patients were on treatment for diabetes. Average duration of diabetes in present study group was 5.45 years. Mean value of triglycerides, LDL, VLDL, NON HDL, HDL were 201.99, 89.58, 41.19,127.12,38.5mg/dl respectively. Difference between the mean of Non Hdl and LDL is 37 i.e. > 30 mg/dl.

The number of patients having NON HDL and LDL difference of <30 mg/dl are 39(33%)and number of patients having NON HDL and LDL difference of >30 mg/dl are 66(67%) with a significant P value of 0.019.That means 67% of present study patients did not had the target of <30 mg/dl difference between NON HDL and LDL.

Total number of patients with LDL <100 mg/dl are 74(70.47%) and NON HDL >130 mg/dl are 49 (46.6%). The number of patients who had LDL level as per ATP III guidelines i.e. <100 mg/dl are 74(70.47%), NON HDL <130 mg/dl are 51 (48.5%) and the number of patients who had LDL <100 mg/dl but had NON HDL >130 mg/dl are 23(21.9%) which is significant with a p value <0.001 making it statistically significant.

Total number of patients with TG >200 mg/dl are 52(49.5%) in that 22(20.9%) patients have NON HDL <130 mg/dl . Total number of patients with TG >200 mg/dl are 52(49.5%) in that 30(28.5%) patients have NON HDL >130 mg/dl with a significant p value 0.025.

In this study patients who had TG >200 (46.6%) ,18% had LDL level <100 mg/dl and 28.5% had NON HDL level >130 mg/dl. Thus in patients with TG >200 mg/dl most of the patients had

LDL<100mg/dl but had Non HDL >130mg/dl with a significant p value 0.012.

Table 3: Mean of Fasting, Post Prandial Blood Sugar, HbA1c, Duration of Diabetes

Table 1: Sex distribution

Male	49
Female	56
Total	105

	MEAN±S.D
FASTING	184.92±67.17
POST PRANDIAL	259.58±85.31
HBA1c	8.31±2.14
DURATION OF DIABETES in years	5.45±4.01

Table 2: Age distribution in frequency and percentage

AGE IN YEARS	Frequency	Percent
<=40	4	3.8
41-50	10	9.5
51-60	34	32.4
61-70	47	44.8
>70	10	9.5
Total	105	100

Table 4: Mean Values of Cholesterol, Triglycerides, HDL, LDL, VLDL, Non- HDL

	MEAN±SD
CHOL	166.91±35.53
TG	201.99±63.9
HDL	38.75±12.42
LDL	89.58±25.9
VLDL	41.19±14.5
NON HDL	127.12±26.14

Table 5: Showing the difference between Non- HDL and LDL with p value

Difference NON HDL - LDL	N	Mean	Std. Deviation	t-value	p-value
<=30	39	60.56	9.79	2.386	0.019
>30	66	56.35	8.08		

Table 6A : Non-HDL And LDL Distribution (in total 105 patients with P value)

		LDL		Total	Pearson Chi-Square	p-value
		<=100	>100			
NON HDL	<=130	51	5	56	24.46	<0.001
	>130	23	26	49		
Total		74	31	105		

Table 6 B: Non-HDL and LDL Frequency Distribution (in percentage of total 105 patients.)

	Frequency	Percent
LDL<100&NHDL<130	51	48.5
LDL<100&NHDL>130	23	21.9
LDL>100&NHDL>130	26	24.7
LDL>100&NHDL<130	5	4.7
Total	105	100

Table 7A: No-HDL and Triglyceride Distribution (in total 105 patients with P value.)

		NON HDL		Total	Pearson Chi-Square	p-value
		<=130	>130			
TG	<= 200	34	19	53	5.03	0.025
	>200	22	30	52		
Total		56	49	105		

Table 7B: Non-HDL and Triglyceride Frequency Distribution (in percentage of total 105 patients.)

TG group	Frequency	Percent
TG >200 & NHDL >130	30	28.5
TG >200 & NHDL <130	22	20.9
TG <200 & NHDL <130	34	32.3
TG <200 & NHDL >130	19	18.0
Total	105	100

Table 8: LDL and Triglyceride Distribution in total 105 patients divided into two groups Non-HDL <130 and >130 with P value

NON HDL	TRIGLYCERIDE	LDL		Total	Pearson Chi-Square	p-value
		<100	>100			
<130	<= 200	31	3	34	0.354	0.838
	'200 - 300	17	2	19		
	'300 - 400	3	0	3		
>130	<= 200	4	15	19	11.03	0.012
	'200 - 300	12	8	20		
	'300 - 400	3	3	6		
	>400	4	0	4		
	Total	23	26	49		

Discussion

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) defined diabetes as a CHD risk equivalent with an LDL treatment goal of <100 mg/dl.⁶ Although patients are divided into risk categories according to their levels of LDL, HDL cholesterol, and triglycerides, both the ADA and the ATP III guidelines emphasized that LDL lowering remains the top priority for lipid lowering, and non-HDL is the secondary goal of treatment when the triglyceride level is >200 mg/dl. Thus in this study focus has been done on LDL, NON HDL and Triglycerides to know the dyslipidemia pattern in type 2 diabetes patients.

The recommended NON-HDL cholesterol goal is 30 mg/dl above the LDL goal.^{7,8,9} The rationale for the 30 mg/dL gap between LDL-C and non-HDL-C goals is as follows:

- (1) Non-HDL-C constitutes LDL-C, VLDL-C, IDL-C Lp(a).
- (2) VLDL-C, the principal atherogenic lipoprotein after LDL-C, is calculated as triglycerides/5.
- (3) the upper limit of optimal triglycerides is less than 150 mg/dL and thus the optimal level of VLDL-C is less than 30 mg/dl (or 150/5 mg/dL). Thus, under conditions of optimally managed triglycerides, the non-HDL-C goal is set 30 mg/dl higher than the optimal LDL-C goal.

The present study was conducted to assess the significance of NON HDL over LDL in type 2 diabetics with triglycerides >200mg/dl and to decide whether to treat diabetics based on NON HDL value. Our study shows the number of

patients having NON HDL and LDL difference of <30 mg/dl are 39(33%) and number of patients having NON HDL and LDL difference of >30mg/dl are 66(67%) with a significant P value of 0.019. Thus most of the present study patients didn't met the criteria of having NON HDL and LDL difference of <30mg/dl. These results are in accordance to the studies conducted by Cui et al,¹⁰ Koji Sugimoto et al.¹¹

Most of the studies done are about comparing Non HDL over LDL in assessing the cardiovascular risk in diabetics. In a post hoc analysis of patients with diabetes from four prospective cohort studies—the Framingham Cohort Study, the Framingham Offspring Study, the Lipid Research Clinics Prevalence Follow-Up Study, and the usual-care group of the Multiple Risk Factor Intervention Trial—the relative risk of death for diabetic (compared with nondiabetic) patients was 7.2 for those with elevated non-HDL cholesterol (> 130 mg/dl) and low LDL (< 100 mg/dl).¹²

In our study cardiovascular assessment has not done but based on previous studies¹² NON HDL and LDL were compared to decide whether to treat the diabetics based on NON HDL value. In this study patients who had LDL levels as per ATP III guidelines i.e.<100mg/dl are 74(70%) but had NON HDL levels <130mg/dl are 23(21%) which is significant with a p value <0.001. Thus in this study patients who had LDL in normal range most of them had NON HDL above the target level. These patients are at risk of developing cardiovascular diseases if we treat diabetics only based on LDL, so lipid lowering therapy has to be

started in these patients based on NON HDL. These results are in accordance to the studies conducted by N. Ram & J. Abdul et al¹³, Raul D. Santos et al¹⁴.

In this study patients with TG >200mg/dl are 52(49.5%) in that 30(28.5%) patients have NON HDL >130mg/dl. This result signifies that in most of the patients with TG>200mg/dl had not met the NON HDL target < 130mg/dl. These results are in accordance to the studies conducted by Raul D. Santos et al¹⁴, M.Saiedullah et al¹⁵, Davidson et al¹⁶.

In this study patients with TG >200mg/dl are 49(46.6%) in that the patients who had LDL<100mg/dl are 19(18%) and NON HDL >130mg/dl in 30(28.5%) patients. It means patients who had LDL levels <100 mg/dl (18%) did not had NON HDL target <130 mg/dl (28.5%) in patients with TG >200 mg/dl (46.6%) Thus in patients with TG >200mg/dl most of the patients had LDL<100 mg/dl but had NON HDL >130 mg/dl with a significant p value 0.012. This result is in accordance to the studies conducted by Davidson et al,¹⁶ Liu et al,¹⁷ Mark L et al¹⁸.

The above findings suggest that type 2 diabetic patients have more triglyceride levels so that LDL level is underestimated but the NON HDL (total cholesterol minus HDL) levels are raised. As LDL which is the primary target in treatment of dyslipidemia is underestimated in diabetic patients an alternative NON HDL can be used as target in treating dyslipidemia in diabetics. This point was supported by a recent analysis of data combined from 68 studies,¹⁹

NON-HDL-C was the best predictor among all cholesterol measures, both for CAD events and for strokes.

Our study showed that diabetic patients who had TG levels >200mg/dl most of them had LDL<100mg/dl and the same patients had NON HDL >130mg/dl. This finding signifies that these patients are to be treated based on NON HDL value though the LDL value is normal to decrease the cardiovascular risk.

Conclusion

In our study most of the patients did not had the target of <30mg/dl difference between NON HDL and LDL. In patients with TG >200mg/dl most of the patients had LDL<100mg/dl but had NON HDL >130mg/dl. The above point clearly says that in diabetic patients with TG >200mg/dl most of the patients had the target LDL level <100mg/dl but not had the target NON HDL level <130mg/dl. Characteristic diabetic dyslipidemia pattern i.e increased TG and NON HDL but underestimated LDL is seen in most of the patients in present study. Thus we conclude that in diabetic patients when TG >200mg/dl, NON HDL is a better target than LDL in deciding treatment for dyslipidemia.

Recommendations

- NON HDL is recommended as a target other than LDL for dyslipidemia in diabetics.
- In diabetic patients when TG >200mg/dl, NON HDL is a better target than LDL in deciding treatment for dyslipidemia.
- NON HDL is better marker than LDL for starting treatment of dyslipidemia in diabetic patients to decrease cardiovascular risk.
- Diabetic patients who reach the target LDL level should be seen for NON HDL level in deciding treatment for dyslipidemia.
- Elevated levels of NON-HDL are treatable by increasing the intensity of currently available lipid lowering agents, as well as lifestyle modification. All of the currently available lipid-lowering agents (statins, fibrates, niacin, fish-oil products, and intestinally active agents) decrease non-HDL-C levels.
- As we have just compared the levels of NON HDL and LDL but not assessed the cardiovascular risk and the study population is also small we suggest further

more studies in making NON HDL as a better target than LDL in diabetic patients.

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LIST OF ABBREVIATION USED

S no.		
1.	%	Percentage
2.	<	Less than
3.	>	More than
4.	Apo	Apo lipoprotein
5.	ATP	Adult Treatment Panel
6.	DM	Diabetes Mellitus
7.	FBS	Fasting Blood Sugar
8.	HbA1c	Glycosylated Haemoglobin
9.	HDL c	High Density Lipoprotein Cholesterol
10	LDL c	Low Density Lipoprotein Cholesterol
11	NCEP	National Cholesterol Education Program
12	PPBS	Post Prandial Blood Sugar
13	TC/CH	Total Cholesterol
14	TG	Triglycerides
15	VLDL c	Very Low Density Lipoprotein Cholesterol
16	CHD	Coronary Heart Disease
17	R	Nonfasting or Random
18	F	Fasting