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STUDY OF LIPID PROFILE AND NON-HDL CHOLESTEROL AS A BIOMARKER OF CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: The reduction of cardiovascular risk by lowering low-density lipoprotein cholesterol (LDL-C) is well documented, and LDL-C remains the main target of lipid lowering therapy. However, not all patients with cardiovascular risk have elevated LDL-C. There is growing recognition that non-high density lipoprotein cholesterol (Non-HDL-C) is strongly related to cardiovascular risk. Aim: This study was done to evaluate the importance of Non-HDL C in predicting cardiovascular risk in type 2 Diabetes Mellitus. **Methods**: 100 type 2 diabetic patients were taken as subjects. Fasting and post meal blood sugar, lipid profile, and Non-HDL C was analysed in these patients. The patients were divided in two groups depending on their Non- HDL C level; ≤ 130 mg/dl and > 130mg/dl. **Result and discussion**: In this study it was seen that, age <60 years, being female, BMI >25 kg/m^2 and LDL cholesterol >100mg/dl were associated with having Non-HDL cholesterol >130mg/dl. **Conclusion**: The results showed positive correlation between Non-HDL and LDL cholesterol. It also showed significant non achievement of Non-HDL cholesterol targets of ≤ 130mg/dl even if LDL cholesterol targets were achieved i.e. <100mg/dl suggesting the importance of measuring Non –HDL Cholesterol to predict the risk of cardiovascular disease in type 2 diabetes.

KEYWORDS

Non-high density lipoprotein cholesterol, Lipid profile, Type 2 diabetes mellitus.

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the kidneys, heart, blood vessels, eyes and nerves. [1]

Diabetes is a common disease, although the exact prevalence is unknown. It is estimated that almost 250 million people currently have diabetes and by 2025 this number will reach 280 million, 80% of whom will live in developing countries. [2]

According to the most recent estimates published in the "Diabetes Atlas 2006" [3], India has the largest number of diabetic patients in the world, estimated to be 40.9 million in the year 2007 and expected to increase to 69.9 million by the year 2025. Type 2 diabetes in Asian Indians differs from that in Europeans in several aspects: the onset is at a younger age, obesity is less common, and genetic factors appear to be more common. [4]

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.[5] In addition, or perhaps as part of this high risk for CVD, patients with diabetes and pre-diabetes often have a dyslipidemic feature of metabolic syndrome.[6] Classic diabetic dyslipidemia is characterized by elevated triglycerides, decreased high density lipoprotein (HDL) cholesterol and low density lipoproteins (LDL) particles of altered composition. [7] Total cholesterol and low-density lipoprotein cholesterol (LDL-C), the major component of the former, represent key standard modifiable risk factors for atherosclerotic cardiovascular disease. The hallmark of atherogenic dyslipidemia is low levels of high-density lipoprotein cholesterol (HDL-C) as well as elevated triglycerides (TG) levels, while LDL-C level may only be marginally elevated in this setting. [8, 9]

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. [10] Researchers concluded that most of the debilitating complication of diabetes can be prevented or delayed by prospective treatment of hyperglycemia and cardiovascular risk factors.[11, 12]

It has been recently suggested that Non-HDL(NHDL) cholesterol might be a useful marker and better predictor of

CVD than LDL cholesterol in diabetic as well as non-diabetic individuals. [13] Non high density lipoprotein cholesterol reflects total cholesterol minus HDL cholesterol and encompasses all cholesterol present in potentially atherogenic lipoprotein particles (Very low-density lipoproteins [VLDL], intermediate density lipoprotein [IDL], low-density lipoproteins [LDL], lipoprotein [a]). [14]

Frieldwald's equation is generally considered to be less accurate with increasing triglyceride levels and inapplicable at triglyceride concentration >400mg/dl. The advantages of using Non-HDL cholesterol as a screening tool include the fact that it requires measurement of only total cholesterol and HDL cholesterol both of which can be measured reasonably accurately in a non- fasting sample, as opposed the LDL cholesterol measurement, which requires a fasting sample. [15]

Elevated non-HDL cholesterol signifies increased CVD risk, even if LDL cholesterol levels are at or below the National Cholesterol Education Programme goal or appear "normal". [16] In clinical trials, non-HDL cholesterol has been shown to independently predict CVD. [17, 18] Target goal for LDL and non-HDL cholesterol in patients with diabetes are <100 and < 130 mg/dl respectively.

With this preview, this study was undertaken with the aim of evaluating the importance of Non –HDL Cholesterol to predict the risk of cardiovascular disease in type 2 diabetes.

MATERIAL AND METHODS

This study was done at Indira Gandhi Govt. Medical College and Hospital, Nagpur, between March 2014 to September 2014. 100 diagnosed patients of type 2 Diabetes Mellitus in the age group of 25-75years, attending diabetic OPD were taken as cases. Patients with complications like retinopathy, nephropathy, type 1 Diabetes Mellitus, pregnancy, history of heart disease, hepatic diseases, Carcinoma or any other chronic illness were excluded from the study. The clearance was taken from the institutional ethical committee. Informed and written consent was taken from the patients, with the explanation of the procedure of the study.

Patients were divided into 2 groups depending on the level of Non-HDL Cholesterol, who have achieved target goal of ≤ 130 mg/dl and who are > 130mg/dl. Venous blood samples were collected from all the subjects after at least 8 hours of fasting and analysed for fasting plasma glucose (FPG), 2hours post prandial glucose levels (2hPG), serum total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) on autoanalyzer XL- 640 transasia. Glucose estimation was done by kit based on GOD-POD method. Sr. TG, Sr. TC estimation was done with kit based on CHOD – POD method. HDL estimation was done with kit based on precipitation method. [19] VLDL –C and LDL-C analysis was done by applying Frieldwald's formula [20] i.e. VLDL-C= TG/5 where TG is less than 400mg/dl, LDL-C was calculated as: TC- (HDL-C +VLDL-C). Non- HDL cholesterol was calculated as: TC-HDL-C.

For serum lipid reference level, National Cholesterol Education Programme (NCEP) Adult Treatment panel III (ATP III) guidelines were referred. According to NCEP-ATP III Guidelines, hypercholesterolemia is defined as TC >200mg/dl, hypertriglyceridemia as TG >150 mg/dl ,high LDL with a value of >100mg/dl and low HDL-C with a value <40mg/dl. Dyslipidemia was defined by presence of one or more than one abnormal serum lipid concentration.

RESULTS

Table 1 reveals the mean value and the range of various clinical and metabolic characters of type 2 diabetic patients. Out of 100 eligible patients studied, there were 49 males and 51 females. This table shows that the diabetics belonged to older age group, had high BMI and had elevated lipid profile except for HDL- cholesterol which was decreased.

Table.1 Clinical and metabolic characteristics of the type 2 diabetic patients.

Variable		Mean	SD	Range
Age in years		54.32	10.43	34-73
Sex	**Male**	49		
	Female	51		
BMI (Kg/ mt^2)		26.68	3.77	17.58-38.67
FBS(mg/dl)		193.42	56.92	127-399
PMBS(mg/dl)		248.86	67.18	147-485
TC(mg/dl)		215.37	25.11	167-285
TG(mg/dl)		234.35	49.85	158-395
HDL(mg/dl)		33.49	10.93	12-60
VLDL(mg/dl)		43.02	13.97	26-136
LDL(mg/dl)		135.42	19.10	90-211
Non HDL-C(mg/dl)		157.44	31.06	102-223

Table 2 shows classification of patients in 2 groups: Number of patients having Non-HDL Cholesterol ≤130mg/dl and Non-HDL Cholesterol > 130mg/dl according to age, gender, BMI and LDL- Cholesterol. Significant correlation was found between Non-HDL Cholesterol >130mg/dl and age ≤ 60years, female gender, BMI>25 Kg/m^2 and LDL Cholesterol. Unadjusted odds ratios were worked out. Age ≤60 years (OR 3.95; 95% CI = 1.5-10.47), being female (OR 3.92; 95%CI = 1.35-10.94), BMI ≥25 Kg/m^2 (OR 4.2; 95% CI = 1.47-12.36), LDL cholesterol >100 (OR 16.94; 95%CI = 5.44-92.82) were associated with having Non-HDL cholesterol >130mg/dl. Although 56 % patients achieved the target LDL of <100mg/dl, 25 (44.64%) among them had Non-HDL cholesterol above target >130mg/dl ($p<0.05$). Out of 34 patients with Non- HDL cholesterol <130mg/dl, 31 (91.17%) had LDL cholesterol below 100 mg/dl.

Table 2. Prevalence of Non-HDL Cholesterol ≤130mg/dl and Non-HDL Cholesterol > 130mg/dl according to age, gender, BMI and LDL- Cholesterol

Variable	NHDL ≤130 mg/dl (Prevalence %)	NHDL >130 mg/dl (Prevalence %)	p-value	Unadjusted Odds Ratio	95% C.I.
Age (years)					
≤60	15 (44.1)	50(75.8)	0.001, S	3.95	1.50 - 10.47
>60	19 (55.9)	16(24.2)			
Gender					
Male	10 (29.4)	39(56.1)	0.014, S	3.92	1.35-10.94
Female	24 (70.6)	27(43.9)			
BMI (Kg/m²)					
18-22.9	8 (23.5)	4(6.1)			
23-24.9	6 (17.6)	6(9.1)	0.2123 NS	2.1	0.52-8.74
≥25	20 (58.9)	56(84.8)	0.002, S	4.2	1.47-12.36
LDL (mg/dl)					
>100	3 (8.8)	41(62.1)	<0.0001,HS	16.94	5.44-92.82
<100	31 (91.2)	25(37.9)			

S-Significant, HS- Highly significant, NS- Non significant

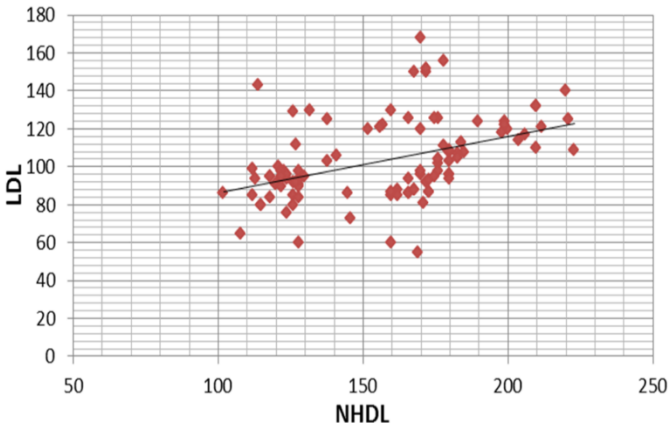
Table 3 shows, after adjusting for other covariates, LDL cholesterol >100mg/dl was independently associated with having Non-HDL C >130mg/dl (Adjusted OR 20.07; 95% CI=5.19-77.49). Similarly, age <60 years was more likely to have Non-HDL >130mg/dl (Adjusted OR 3.73; 95% CI=1.22-11.39). Having BMI>25 was more associated to have Non-HDL cholesterol >130mg/dl (Adjusted OR 2.25; 95% CI= 1.01-4.95).

Table.3 Multiple logistic regression showing predictors for Non-HDL cholesterol.

Variable	Adjusted OR	95% C.I.	p-value
LDL	1		
≤100	20.07	5.19-77.49	<0.0001, HS
(mg/dl)			
>100			
Age (years)	3.73	1.22-11.39	0.020, S
≤60			
>60	1		
BMI	1		
18-22.99			
(Kg/m²)	1.45	0.17-11.90	0.728, NS
23-24.99			
≥25	2.25	1.01-4.95	0.045, S

S-Significant, HS- Highly significant, NS- Non significant

Figure 1 shows direct and highly significant correlation between LDL-cholesterol and Non- HDL cholesterol (p value<0.0001, r=0.433). Thus severity of dyslipidemia increases in patients with increased Non- HDL Cholesterol value. Hence, elevated level of Non- HDL cholesterol can independently act as predictor of cardiovascular risk in type 2 diabetes mellitus.



r=0.433, p <0.0001, Highly Significant.

Figure. 1 Correlation between Non-HDL Cholesterol and LDL -C

DISCUSSION

Elevated non-HDL cholesterol signifies increased CVD risk, even if LDL cholesterol levels are at or below the National Cholesterol Education Programme goal or appear "normal." In current study it was seen that, age <60 years, being female, BMI >25 and LDL cholesterol >100mg/dl were associated with having Non-HDL cholesterol >130mg/dl. The results showed positive correlation between Non-HDL and LDL cholesterol. It also showed that about 25% of patients did not achieve Non-HDL cholesterol targets even if LDL cholesterol targets were achieved.

Atherogenic dyslipidaemia is associated with an increased risk of future cardiovascular complications. [21-24] The association between abnormal lipid levels and cardiovascular risk is much more evident among patients with diabetes mellitus and hypertension. [25] Current guidelines emphasise the importance of lipid goal attainment in this high-risk group. [26-32] Non-HDL cholesterol proves a better predictor of vascular events. [33] Despite LDL cholesterol being in the target range achieving Non-HDL cholesterol goal is still poor. [34-35]

A study by Liu and his colleagues concludes that non-HDL cholesterol is a stronger predictor of CHD death among those with diabetes than among those with LDL cholesterol and should be given more consideration in the clinical approach to risk reduction among diabetic patients. [36]

A study by Nanik Ram et al [37] showed a correlation between Non-high-density lipoprotein and low density lipoprotein cholesterol.

Another study by Nasser M Al-Daghri et al, aimed to determine and compare the impact of non-HDL-C versus other lipid parameters, in predicting coronary heart disease among diabetic versus non-diabetic adult Saudis. This study

supported the use of non-HDL cholesterol as the more practical and reliable target for lipid lowering therapy among the Saudi population. [38]

Grundy, in a recent report, emphasizes that there has to be strong evidence of superiority for non-HDL cholesterol to be regarded as the primary target of lipid therapy. [39]

The current study can be regarded contribution to the growing evidence of Non HDL cholesterol being superior to LDL cholesterol.

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. [40]

High BMI 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.[41]

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 association between abnormal lipid levels and cardiovascular risk is much more evident among patients with diabetes mellitus. Current guidelines emphasise the importance of lipid goal attainment in this high-risk group. Non-HDL cholesterol proves to be more sensitive and a better predictor of cardiovascular risks than LDL cholesterol. Despite LDL cholesterol being in the target range, achieving Non-HDL cholesterol goal is still poor. More aggressive lipid-lowering therapy should be implemented. Since measuring Non- HDL cholesterol in T2DM patients is simple, cost-effective and convenient, clinicians may choose Non-HDL as a routine measure in everyday practice.

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