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Original Research Article

A HOSPITAL BASED PROSPECTIVE STUDY TO DETERMINE THE SIGNIFICANCE OF NON-HDL CHOLESTEROL IN DIABETIC POPULATION AND TO FIND OUT ITS RELATION TO CARDIOVASCULAR RISK AT NEWLY ESTABLISHED TERTIARY CARE CENTER

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Abstract

Background: Cardiovascular disease is the leading cause for mortality in global census. A major contributor to the increased CVD among with type 2 diabetes is dyslipidaemia. NCEP ATP III emphasis the role of LDL-C in the pathogenesis of cardiovascular disease, but it has been recently suggesting that raised levels non-HDLc may be better in predicting risk associated with cardiovascular disease. The aim of this study is to determine the significance of Non-HDL cholesterol in diabetic population and to find out its relation to cardiovascular risk at newly established tertiary care center. **Materials & Methods:** A hospital based prospective study done on 50 diabetic patients who are all diagnosed as type 2 diabetes mellitus as per ADA 2015 criteria and attending diabetic clinic at Government Medical College & Hospital, Barmer, Rajasthan, India during one-year period. Atherosclerotic Cardiovascular Risk score (ASCVD risk score) system proposed by American Heart Association (AHA) /American College of Cardiology (ACC) based on scoring system estimates 10-year risk for atherosclerotic cardiovascular disease. **Results:** This study was conducted among 50 diabetic patients with age ranging from 40 years to 79 years with mean age was 56.54 years. The smoking, fasting blood sugar and post prandial blood sugar was not statistically significant (P>0.005 NS). In these 29 subjects, 28 subjects have elevated 10-year risk for cardiovascular disease as calculated through ASCVD risk scoring system. They are statistically significant with a P value of 0.0001 (<0.05). This study shows results after dividing the study population based on the TGLs concentration above and below 200 mg /dl. The results show, in population with TGLs concentration less than 200 mg / dl both LDLc and non- HDL cholesterol was good in assessing CVD risk while in population with TGLs concentration more than 200 mg/dl only non-HDL cholesterol was very good in assessing CVD risk but LDLc was not significant in assessing CVD risk. Thus, in both groups non –HDL cholesterol was very good in anticipating 10-year risk for cardiovascular disease. **Conclusion:** We concluded that non-HDL cholesterol may be a better alternative and useful tool in assessing risk of CVD. This is a very simple, cost-effective tool and also not influenced by fasting state. Thereby early intervention can be planned and introduced to prevent cardiovascular disease predisposed individuals.

INTRODUCTION

Cardiovascular disease is the most leading cause for mortality in global census. It is estimated that around 17.5 million died due to CVD and its about 31% of all death globally.[1,2] The underlying mechanism for CVD is atherosclerosis and may be caused by high blood pressure, diabetes, smoking, physical

1316

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inactivity, obesity, excessive alcohol consumption, improper diet, increased blood cholesterol.[3]

Type 2 diabetes mellitus is a very commonly associated lipid abnormality. The prevalence of dyslipidaemia in type 2 diabetes was found through many studies ranging from 70 to 85 percent.[4] With high prevalence of lipid abnormalities all diabetic population have elevated risk for cardiovascular related disease.

Dyslipidaemia in type 2 diabetes were not restricted only quantitative values, but it was also qualitative with kinetic in nature.[5] Many factors contribute to abnormality in lipid metabolism associated with type 2 diabetes mellitus which includes increased insulin resistance, relative deficiency in insulin levels, role of adipo cytokines like adiponectin, and hyperglycaemia itself.[6]

The characteristic quantitative abnormalities include hyper triglyceridaemia, prolonged postprandial hyperlipidaemia, raised levels in the remnant lipo protein particles and reduced HDL-cholesterol levels.[3]

The qualitative nature of abnormalities which is atherogenic includes raise in large VLDLc particle size, an increase in proportion of small, dense LDLc particle, susceptibility nature of LDLc to the oxidation, an raise in triacyl glycerol content in both LDLc and HDLc. So LDLc levels may be normal among type 2 diabetes patients.[6]

The lipid abnormalities in diabetes exhibit both quantitative as well as qualitative defects in lipoprotein metabolism which are more kinetic in nature mainly due altered response of insulin.[7] The well-known quantitative abnormalities include raised levels of triglycerides and reduced HDLc.

National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III emphasis the role of LDL-C in the pathogenesis of cardiovascular disease, but it has been recently suggesting that raised levels non-HDLc may be better in predicting risk associated with cardiovascular disease.[1]

Non –HDLc includes all potential atherogenic lipo protein particles like VLDLc, IDLc, LDLc, and LIPO PROTEIN (A). LDLc is calculated using friedwald equation which is considered as less accurate with increasing TGL level as in diabetes patient.[1]

The lipid abnormalities in type 2 diabetes population would have been present well before the diagnosis. This is because of fact that insulin resistance plays major role in development of this abnormalities.[8]

The aim of this study to determine the significance of Non-HDL cholesterol in diabetic population and to find out its relation to cardiovascular risk at newly established tertiary care center.

MATERIALS AND METHODS

A hospital based prospective study done on diabetic population who are all diagnosed as type 2 diabetes mellitus as per ADA 2015 criteria and attending diabetic clinic at Government Medical College & Hospital, Barmer, Rajasthan, India during one-year period.

Inclusion Criteria

People diagnosed as type 2 diabetes mellitus of age more than 40years and less than 79 years.

Exclusion criteria

- People with known thyroid disorder
- People with known hereditary lipid abnormalities
- Acute illness/infection
- People taking anti lipid drugs

Methodology

People who were diagnosed with type 2 diabetes mellitus and attending diabetic clinic in the outpatient department of Government Medical College & Hospital, Barmer were included in this study.

Venous blood was drawn from the subjects separately and samples were sent for blood sugar, Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides level estimation. Patient details regarding the general information, clinical findings and investigation results are all filled in specially designed proforma for this study.

Operational Guidelines

1. Diagnosis of diabetes mellitus was based on ADA criteria: HbA1C > 6.5% or Fasting blood sugar > 126mg/dl or 2-hour plasma glucose > 200mg/dl during an oral glucose tolerance test or Symptoms of hyperglycemia and a casual plasma glucose > 200mg/dl

2. National cholesterol educational program adult treatment panel III: Total cholesterol > 200mg/dl, Triglycerides > 150mg/dl, HDL cholesterol ≤ 35 mg / dl, Non – HDL cholesterol = TC – HDL cholesterol, LDL cholesterol ≥ 100 mg / dl

3. Joint national committee (JNC – 8) Systolic blood pressure ≥ 140 mm Hg Diastolic blood pressure ≤ 90 mm Hg

4. Atherosclerotic Cardiovascular Risk score (ASCVD risk score) system proposed by American Heart Association (AHA) /American College of Cardiology (ACC) based on scoring system estimates 10-year risk for atherosclerotic cardiovascular disease.

Statistical Analysis

Statistical analysis was done by using SPSS 21.0v software. Quantitative data was expressed in mean, median, mode and standard deviation. Qualitative data was expressed by Chi-square test. The difference was considered statistically significant when p value < 0.05.

RESULTS

This study was conducted among 50 diabetic patients with age ranging from 40 years to 79 years with mean age was 56.54 years. Male preponderance as compared to females (table 1).

The results of individual parameters and its relationship with cardiovascular risk assessed by using ASCVD RISK calculator. Female subjects in this study were not smoking. All 17 subjects who

were smoking in this study population belong to male gender and 14 among them have elevated cardiovascular risk. In this study among 50 diabetic population studied, 10 subjects had fasting blood sugar less than 130 mg / dl and remaining 40 subjects is having blood sugar more than 130 mg/dl. 8 subjects in the former group and 26 subjects in the latter group had elevated cardiovascular risk calculated by ASCVD risk scoring system. The smoking, fasting blood sugar and post prandial blood sugar was not statistically significant (P>0.005 NS) (table 2).

Systolic blood pressure more than 140 mmhg were considered to be hypertensive and statistically analyzed. Results showed 17 patients among 50 study population were hypertensive and 16 patients among them had elevated cardiovascular risk. These results were found to be statistically significant (P<0.05*) (table 2).

Diastolic blood pressure more than 140 mmhg were considered to be hypertensive and statistically analyzed. 14 patients among them had elevated cardiovascular risk. These results were found to be statistically significant (P<0.05*) (table 2).

10 patients had low HDLc level (<35mg/dl) and remaining 40 patients had HDLc level above 35mg/dl. Among 10 patients, 9 patients have elevated CVD risk calculated by ASCVD risk calculator, which was statistically significant (P<0.005*) (table 2).

This study group of 50 diabetic population were divided into two groups and statistically analysed based on NCEP ATP III guidelines which has suggest non-HDL cholesterol as secondary target after LDL cholesterol in subjects with raised TGLs more than 200mg/dl. Non-HDL cholesterol target was LDL cholesterol plus 15 which is calculated as 130 mg/dl. So, among 50 diabetic populations studied 29 subjects had non-HDL cholesterol more than 130 mg / dl and remaining 21 subjects had levels below 130 mg/ dl. Elevated 10-year cardiovascular risk calculated through ASCVD risk scoring system were present in 28 subjects among 29 subjects with raised non –HDL levels which is also statistically significant with P value of 0.0001** (table 2).

Table 1: Distribution of patients according to age groups

Age Groups (yrs)	Male	Female	Total
40-50 yrs	9	6	15
51-60 yrs	15	10	25
61-70 yrs	3	7	10
Total	27	23	50

Table 2: Correlation with cardiovascular risk assessed by using ASCVD RISK score

Risk factors		Low risk (N=16)	Elevated risk (N=34)	P-value
Smoking	Yes	3	14	>0.005
	No	13	20	
Fasting blood sugar	<130 mg/dl	2	8	>0.005
	>130 mg/dl	14	26	
Post prandial blood sugar	<200 mg/dl	1	1	>0.005
	>200 mg/dl	15	33	
Systolic B.P.	<140 mm Hg	14	18	<0.005*
	>140 mm Hg	1	16	
Diastolic B.P.	<90 mm Hg	15	20	<0.005*
	>90 mm Hg	1	14	
HDL Cholesterol	Normal	15	25	<0.005*
	Abnormal	1	9	
Non-HDL cholesterol	<130 mg/dl	15	6	<0.001**
	>130 mg/dl	1	28	

DISCUSSION

Non – HDL cholesterol estimation in the clinical practice is gaining importance nowadays.[9] It is because of the concept that LDL cholesterol is only calculated value that can be affected by other parameters especially raised TGLs levels. Elevated TGLs level is commonly found in patients with diabetes mellitus in clinical practice. LDL cholesterol can be accurately calculated only fasting sample. So, in this busy world, a patient has to spend one more day for investigation for LDLc estimation.[5] This limitation is overcome by estimation of non-HDL cholesterol which can be estimated in non-fasting samples. Its value is not affected by other parameters like TGLs levels. Another most important factor, it

includes all atherogenic lipo proteins like VLDL and other lipo protein remnants which was already proved in many clinical trials to be associated with atherosclerosis.[10]

NCEP ATP III guidelines suggested non –HDL cholesterol as secondary target for lipid lowering therapy to prevent atherosclerosis.[1] There are many clinical trials and studies which has already proven relationship of raised non-HDL cholesterol with cardiovascular risk. In this study of 50 diabetic population, 29 subjects had non-HDL cholesterol above their target as mentioned earlier. In these 29 subjects, 28 subject has elevated 10-year risk for cardiovascular disease as calculated through ASCVD risk scoring system.[11] They are statistically significant with P value of 0.0001 (P<0.05).

1318

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Several previously conducted studies based on non-HDL cholesterol as a predictor of cardiovascular risk prove its predictive value in assessing atherosclerotic cardiovascular disease. A study done by ORAKZAI et al [2009],[12] to assess the relationship of non - HDL cholesterol, LDLc, HDLc, and TGLs levels with calcium deposition in coronary arteries which acts as a marker for atherosclerotic vascular disease. After adjustment done to neutralize confounding factors like age, sex, race, cigarette smoking, hypertension, obesity, family history of premature CVD, and raising quartiles of lipid values, only non-HDL cholesterol levels are significantly related to calcium scores of coronary arteries which are statistically significant with P value of 0.002(<0.05). In another study LIU et al,[13] which was done from Framingham cohort who were all initially without any CVD, raised VLDLc predicted CVD risk after adjusted for LDLc, that study further proceeded with comparing non-HDL cholesterol for particular LDLc values, which showed non-HDL cholesterol levels predicted CVD events, but LDLc did not predict CVD events in particular non – HDL cholesterol values. Similarly, they also assessed the predictive value in the presence TGLs less than 200 mg/dl and more than 200 mg /dl separately. In the former group both non-HDL cholesterol and LDLc predicted CVD events better than latter group. In the latter non- HDL cholesterol predicted better than LDLc. Hence, they concluded that non-HDL cholesterol is better predictor of CVD and can be used irrespective of TGLs level.

This study also shows similar results when assessing the significance of LDLc and non-HDL cholesterol with 10-year risk for cardiovascular disease separately after dividing the study population based on the TGLs concentration above and below 200 mg /dl. The results show, in population with TGLs concentration less than 200 mg / dl both LDLc and non-HDL cholesterol was good in assessing CVD risk while in population with TGLs concentration more than 200 mg/dl only non-HDL cholesterol was very good in assessing CVD risk but LDLc was not significant in assessing CVD risk. Thus, in both groups non –HDL cholesterol was very good in anticipating 10-year risk for cardiovascular disease.

In another follow –up study in which they analyzed the relationship of CVD and different lipoprotein, which was conducted for 19 years follow up period by "The Lipid Research Clinics Program". Results of study showed non-HDL cholesterol was better in predicting CVD death in both males and females, in which a 30 mg/dL raise in non-HDL cholesterol level will result in 19% raise in CVD death in males and 15% in females.[14]

Numerous studies done using non-HDL cholesterol proves that it is a very good predictor of CVD death among diabetic individual (Liu et aI., 200515; Lu et aI., 20037) as well as in non-diabetic individual (AI-Daghri et aI., 2007).[16]

As demonstrated by numerous studies elevated level of non-HDL cholesterol is an important and very good predictor of the risk for CVD, and also based on extensive review on the literature and theoretically also non- HDL cholesterol which includes all atherogenic lipoproteins comprising LDLc, IDLc, and VLDLc remnant, it must be good in predicting risk for non-fatal CVD when compared with LDLc (ORAKZAI et aI., 2009,[12] LIU et aI., 2006.[13])

Based on various literatures, non–HDLc level will be useful in identifying people with atherogenic lipo protein phenotype which is commonly found in individual with metabolic syndrome and diabetic individual. As those individuals are characterized by raised TGL rich lipo proteins like VLDLc and IDLc, and reduced HDLc level.[12]

Further, various studies evidently prove independent association with raised TGLs level and CVD which proves atherogenic nature of VLDLc.

Unlike cholesterol, TGLs is not usually deposited on the atherosclerotic plaques. The mechanism of formation of atherosclerotic plaques raised TGLs have been explained by the accumulation of TGLs rich VLDL remnant and also by the structural variation in LDLc and HDLc particles due raised TGLs levels.[17] Some studies say atherogenicity of VLDLc may be due to formation of more foam cells after taking up TGLs by macrophages and thereby fastening up the atherosclerosis (LU et aI., 2003).[7]

Smoking was one of the well-known and very important risk factors for development of atherosclerotic cardiovascular disease which was strongly proved in so many clinical trials and many literatures this statement. In this study smoking is not significantly related to CVD risk. The above result may be due to the culture in India where smoking is not common among women. As in our study population, nearly half of the subjects were women. So, in this study absence of smoking among women population acts as a confounding factor.

Hypertension is very well studied in a lot of clinical trials as a significant risk factor for the development of cardiovascular disease. In our study both systolic blood pressure and diastolic blood pressure when raised were significantly related to cardiovascular risk which was assessed individually.

CONCLUSION

The result of this study suggested that non-HDL cholesterol may be superior in predicting cardiovascular disease especially in people with diabetes where triglycerides are elevated. Even though NCEP ATP III guidelines have suggested LDLc as primary target for lipid lowering therapy. There are many individuals with diabetes mellitus and metabolic syndrome where their CVD risk was underestimated due to normal LDLc levels. So, in these situations non-HDL cholesterol may be a better alternative and useful tool in assessing risk of CVD. This is a very simple, cost-effective tool and also not influenced by fasting state. Thereby early

1319

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intervention can be planned and introduced to prevent cardiovascular disease predisposed individuals.

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1320

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