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Original Article

Biochemistry Section

# Relationship between Dyslipidemia and Glycemic Status in Type-2 Diabetes Mellitus

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## ABSTRACT

**Introduction:** India has among the largest number of diabetic subjects in the world. Dyslipidemia is a lipoprotein metabolic abnormality leading to a persistent increase in the plasmatic concentration of cholesterol and triglycerides. Studies found that increased triglyceride levels and decreased HDL cholesterol levels predicted Coronary Heart Disease (CHD). HDL may be the most consistent predictor of CHD in type 2 diabetes subjects, followed by triglyceride and total cholesterol.

**Aim:** To assess the link between HDL/LDL ratio and diabetic status of patients and to compare HbA1c and FBS with HDL/LDL ratio.

**Materials and Methods:** This was a retrospective cross-sectional study done over a period of 1 year; in the clinical biochemistry department of a tertiary care rural centre. Before starting the study, the protocol was prepared and presented to Institutional Human Research Ethics Committee which was subsequently approved. The data for 101 diabetic patients and 106 non-diabetics were considered, who attended the hospital for their routine health check-up. The following were noted from the online data centre and filled into a proforma-FBS, PP2BS, HbA1c, HDL, LDL, Tc/HDL, HDL/LDL. p-value of less than 0.05 was considered statistically significant.

**Results:** There was significant increase in the levels of FBS and HbA1c in diabetic group compared to the control group. The level of HDL gradually decreased, the level of LDL increased,while the HDL: LDL ratio significantly was less in the diabetic group.

**Conclusion:** It can be concluded that diabetes mellitus type 2 is strongly associated with lower level of high density lipoprotein and higher level of low density lipoprotein cholesterol due to which there is alteration in the HDL/LDL ratio.


**Keywords:** Dyslipidemia, Glycemic status, HBA1c, Predictor, HDL/LDL ratio

## INTRODUCTION

Diabetes has been described as “One of the main threats to human health in the twenty first century [1]. US Centre for Disease Control showed that there were 5.5 million diabetics in 1980 that increased to 21.1 million in 2010. This increase mirrors the increasing prevalence of obesity. Worldwide, there is a projected increase in the prevalence of diabetes from 382 million (8.3%) in 2013 to 592 million (10.1%) in 2035 [2].

Chronic hyperglycemia, dyslipidemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[3] Secondary dyslipidemia occurs due to hypothyroidism, obstructive liver disease, obesity, diabetes mellitus, pregnancy, chronic renal failure, alcohol, cigarette, smoking, bypass surgery, stress. [4] Diabetic dyslipidemia is a condition where the good cholesterol (HDL) levels are decreased and raise triglyceride and bad cholesterol (LDL), which increase the risk for heart disease and stroke [5].

Type 2 diabetics are usually dyslipidemic even if under relative good glycemic control. Elevated triglycerides, decreased high-density lipoprotein cholesterol and elevated small dense low-density lipoprotein cholesterol are risk factors for atherosclerosis in type 2 diabetes [6].

The cardiovascular complication of diabetes is the leading cause of death in people with diabetes. Of these CVD, coronary heart disease and stroke are the most common causes [7]. There are many risk factors for CVD but the most significant is abnormal lipid values [8].

Recent study reported that insulin increases the number of LDL receptor, so chronic insulin deficiency might be associated with a diminished level of LDL receptor. In these cases also, increase in LDL particles results in increase in LDL cholesterol value in diabetes mellitus [9]. In diabetes mellitus, the rise in plasma cholesterol level is due to an increased hepatic production of VLDL or decreased removal of VLDL from the circulation [10].

Recent studies have demonstrated that in diabetic patients Triglyceride (TG) level is a risk factor for CVD independent of HDL-C level and despite glycemic control, the incidence of macrovascular disease is increased two to five-fold in diabetics as compared to non-diabetic patients. This is attributed mainly to diabetic dyslipidemia [11].

Hypertriglyceridemia often is rather modest. In non-diabetic individuals, renal disease, hypothyroidism and genetically determined lipoprotein disorders effect the lipid levels; while in T2DM, the obesity/insulin-resistance lead to lipid abnormalities independently of hyperglycemia. In T2DM, this phenotype is not usually fully corrected with glycemic control, suggesting that insulin resistance is associated with this lipid abnormality. An increase in triglyceride rich lipoproteins is commonly associated with a reduction in HDL and an increase in small dense LDL levels [12].

VLDL1 is a strong determinant of plasma triglyceride concentration and has been shown to relate to insulin sensitivity as measured by HOMA-IR. In insulin resistant individuals, VLDL1 is secreted in excess while the secretion of VLDL2 is comparable to that in insulin-sensitive individuals [13].

In the Framingham Heart Study, 13% of men and 24% of women with diabetes mellitus had increased total plasma cholesterol levels, compared with 14% of men and 21% of women without diabetes mellitus [14]. By contrast, the prevalence of high plasma triglyceride levels in individuals with diabetes mellitus (19% in men and 17% in women) was significantly higher than in those without diabetes mellitus (9% of men and 8% of women).

Many studies found that diabetes and dyslipidemia overlap and that they together accelerate the process of atherogenesis as a result. [15]. Together they increase cardiovascular risk and form a

vicious circle in which dyslipidemia worsens diabetes and diabetes worsens dyslipidemia.

The Strong Heart Study showed that there is a stepwise decrease in LDL size according to diabetic status from normal to impaired glucose tolerance, and then to diabetes. This association is more striking in women than in men, which may be the reason why diabetic women lose their sex-specific cardio-protection even at concentrations well below the National Cholesterol Education Program (NCEP) [16].

Low density lipoprotein-cholesterol is a strong independent predictor of CHD in patients with DM, particularly when components of diabetic dyslipidemia are present. A low level of HDL-C under 40 mg/dl (<1 mmol/l) is an independent risk factor for CVD. In diabetic dyslipidemia, the concentration of HDL-C is reduced and its compositions as well as distribution are changed. However, when obesity and hypertriglyceridemia were absent, HDL2-C levels in the diabetic population were not significantly different from controls [17].

At present, LDL-cholesterol remains a strong independent predictor of CVD in diabetic patients, even when the LDL level is below the national cholesterol education program target of 130mg/dl. The strong heart study observed a 12% increase in CVD risk in diabetic subjects with every 10mg/dl increase in LDL-cholesterol. Varbo A et al., showed that with each 1 mmol/l increase in non-fasting remnant cholesterol there was a 2.8 fold causal risk for ischemic heart disease, independent of HDL reduction [18,19].

Diabetics with HbA1c >8% show a 150% increased risk of death from heart disease. The Adult Treatment Panel III (NCEP) recommend treating diabetics with hyperlipidaemia [20]. A previous study concluded that increased triglyceride levels and decreased HDL cholesterol levels predicted CHD in T2DM subjects [21]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that both decreased HDL and elevated LDL predicted CHD. HDL may be the most consistent predictor of CHD in type 2 diabetes subjects, followed by triglyceride and total cholesterol [22].

Elevated HbA1c is also regarded as an independent risk factor for cardiovascular disease in diabetics as well as non-diabetics. [23]. The risk of cardiovascular disease increases by 18% for each 1% increase in absolute HbA1c. Besides this, the HbA1c and cardiovascular disease correlation is known among non-diabetic cases [24].

Considering the above scenario, it was aimed in the study, to find out the association between various clinical and laboratory parameters of diabetic patients and effects of dyslipidemia in comparison with non-diabetic patients.

## MATERIALS AND METHODS

This was a retrospective cross-sectional study done over a period of 1 year (January 2018 to December 2018). The study was done in the clinical biochemistry department, Shree Krishna Hospital (tertiary care rural centre), Pramukh Swami Medical College, Karamsad.

The study was approved by the Institutional Human Research Ethics Committee (IEC/HMPCMCE/87/Faculty/8/10/18).

Data for 101 diabetics and 106 non-diabetics were taken for the study, out of the total 278. These patients reported to the hospital for routine health check-up. The data were present online in the hospital portal. The FBS, PP2BS, HbA1c, HDL, LDL, Tc/HDL, HDL/LDL, besides the demographic information were taken and filled into a proforma.

### Exclusion Criteria

- Patients with chronic renal disease, liver cirrhosis, cancer.
- Patients taking anti-lipidemic drugs
- Patients on alcohol.

As per hospital protocol, HbA1c was measured by the Turbidometric inhibition immunoassay (TINIA), fasting blood glucose by the hexokinase method and AHDL method-Bichromatic endpoint for measuring the HDL.

## STATISTICAL ANALYSIS

Analysis was performed using the commercially available statistical software stata 14. For each analyte, Mean±SD values were presented. p-value of less than 0.05 was considered statistically significant.

## RESULTS

This study comprised of 207 individual (101 case and 106 controls). Among 101 case group had 60 males and 41 females [Table/Fig-1].

There was significant increase in the levels of FBS, HbA1c and LDL while a decrease in HDL in diabetic group [Table/Fig-2].

| Age (years) | Total | Male | Female |
|---|---|---|---|
| 20-40 | 6 | 4 | 2 |
| 41-60 | 43 | 24 | 19 |
| 61-above | 52 | 32 | 20 |
| Total | 101 | 60 | 41 |

**[Table/Fig-1]:** Age and gender distribution.

| Paratmeter | Group | Mean value | Standard deviation | p-value |
|---|---|---|---|---|
| FBS (mg/dL) | Diabetic<br>Control | 182.3861<br>93.4528 | 86.98850<br>5.86049 | <0.001 |
| HbA1c | Diabetic<br>Control | 8.2812<br>5.5792 | 1.63479<br>0.35071 | <0.001 |
| HDL (mg/dL) | Diabetic<br>Control | 45.7426<br>53.8962 | 11.36279<br>19.57497 | <0.001 |
| HDL/LDL ratio | Diabetic<br>Control | 0.5452<br>0.6132 | 0.32507<br>0.40083 | 0.18 |

**[Table/Fig-2]:** Fasting blood sugar (FBS), HbA1c, HDL, HDL/LDL ratio.

There was a significant positive linear correlation between HbA1c and fasting blood sugar (r=0.661, p=0.0001) while negative correlation between glucose and HDL-C (r=-179, p=0.0001). Negative correlation was also found between HbA1c and HDL-C (r=-175, p=0.0001).

## DISCUSSION

The present study was designed to investigate the HDL/LDL ratio and their relationship with glycemic status in the diabetes mellitus of type 2. The HDL/LDL was considered as an indicator for cardiovascular diseases. There was a significant decrease in HDL level among diabetics as compared to the control group. Lower HDL cholesterol level is attributed to triglyceride enrichment by cholesterol ester transfer protein and increased hepatic triglyceride lipase activity. Elevated lipid and lipoprotein level were found in diabetic patients which may be due to insulin resistance because impaired insulin action increase free fatty acid release from intra-abdominal adipose tissue, promoting lipoprotein lipase activity which results in reduced triglyceride clearance [10].

There was a significant positive linear correlation between elevated blood glucose and total cholesterol, triglycerides, LDL, HBA1C and negative correlation between glucose and HDL-C. This is an important finding which shows that hyperglycemia is closely associated with hypercholesterolemia, hypertriglyceridemia, elevated LDL, and reduced HDL which are all documented as risk factors for CHD.

Therefore, diabetic patients with lack of diabetic control (high FBS) have higher lipids, less HDL cholesterol. This also points to the significance of control of blood glucose in diabetic patients.

Thus the results of this study clearly indicate that there is strong association between the levels of HbA1c and HDL: LDL ratio. The levels of the Hb1Ac were found significantly higher in the diabetic

| Author name | Sample size | Findings |
|---|---|---|
| Gowtham K et al., [26] | Case-control<br>30 T2DM-30 Non diabetic | HDL and LDL cholesterol levels and correlated HDL/LDL ratio with HbA1c levels and fasting blood glucose.HDL and LDL cholesterol levels and correlated HDL/LDL ratio with HbA1c levels and fasting blood glucose |
| Lorenzo C et al., [15] | Epidemiological study<br>1107 individuals with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) | triglyceride was high in isolated IGT, and high-density lipoprotein cholesterol was low in combined IFG/IGT |
| Klisic A et al., [27] | Cross sectional study<br>275 T2DM individuals | Total cholesterol; and LDL cholesterol are independent predictors of higher HBA1c, and as they increased by 1 mmol/L each, probabilities of higher HBA1c increased by 30%, 34%, and 42%, respectively |
| Sirsikar M et al., [28] | Case-control<br>75 T2DM-75 Non diabetic | HbA1c showed direct and significant correlations with cholesterol, triglycerides and LDL and inverse correlation with HDL in cases |
| Devkar V et al., [29] | Retrospective cross sectional study<br>100 T2DM individuals | Both HBA1C and FBG exhibited direct correlations with cholesterol, TG, and LDL and inverse correlation with HDL. The levels of serum cholesterol and TG were significantly higher and of HDL significantly lower in patients with worse glycemic control as compared to patients with good glycemic control. |
| Yadav N et al., [30] | Cross sectional study<br>Group I (73 individuals with good glycemic control HbA1C 6-7 gm%), group II (69 individuals with fair glycemic control HbA1C 7.1-8.2 gm%) and group III (69 individuals with poor glycemic control, HbA1C >8.2 gm%) | TG level was maximum in group III, LDL level was highest in group III, HDL was lowest in group III. A significant positive correlation was observed between level of TG and HbA1C. a positive correlation was observed between LDL and HbA1C. a negative correlation was seen between HDL and HbA1C |
| Sreenivas Reddy A et al., [31] | 490 T2DM individuals | The level of HbA1c showed a direct significant correlation with TC, TG, LDL, but did not correlate with HDL |
| Artha IMJR et al., [32] | Retrospective study<br>140 T2DM individuals | A significant positive correlation between LDL, total cholesterol, LDL-C, TG, and TC to HDL-C ratio, triglycerides, and TC/HDL-C ratio with HBA1c level were found. A negative correlation was observed on HDL-C with the HBA1c level. |
| Patel DK et al., [33] | 50 T2DM individuals | HbA1c level showed the direct correlation with level of LDL-C, TG, and TC while it had negative correlation with high-density lipoprotein |
| Valarmathi A et al., [34] | 35 T2DM individuals | HbA1c correlated with raised LDL, raised TG and low HDL. |
| Naqvi S et al., [35] | Cross-sectional study<br>509 T2DM individuals | With HbA1c cut-off value of 7%, 74% patients had high triglycerides and showed a significant association with high triglyceride levels |
| Prabhavathi K et al., [36] | 130 T2DM individuals | HbA1c showed direct and significant correlations with cholesterol, TG and LDL |

**[Table/Fig-3]:** Compilation of similar studies with the outcomes.

group. Similarly, the ratio of HDL: LDL was also altered due to the low levels of the protective high density lipoproteins. The results were similar to the previous studies done by Indumati V et al, though they have taken LDL: HDL as the parameter because in their study the ratio was increased [25].

Patients with type 2 diabetes mellitus are at an increased risk of cardiovascular morbidity and mortality. The significant increase in Fasting blood sugar, Hb1Ac and alterations in protective HDL and bad LDL of diabetic patients when compared to the control predicts that patients with type 2 Diabetes mellitus are at a higher risk level for CHD.

The [Table/Fig-3] enlists some of the studies on diabetic dyslipidemia.

## LIMITATION

The retrospective nature of the study limits its relevance.

## CONCLUSION

High glycated hemoglobin (>7.0%) correlated with high lipid profile values and low glycated hemoglobin value (<7.0%) correlated with low Lipid profile values. Thus, HbA1c can be used as a potential biomarker for predicting dyslipidemia in type 2 diabetic patients in addition to glycemic control. Hence early diagnosis can be accomplished through relatively inexpensive blood testing and may be utilised for screening high-risk diabetic patients for timely intervention with lipid lowering drugs.

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