ASSOCIATION OF DYSLIPIDEMIAS WITH TYPE 2 DIABETES MELLITUS: A PROSPECTIVE STUDY
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ABSTRACT: Diabetes Mellitus, the most common chronic disease worldwide, has emerged as a matter of concern, because it is significantly associated with cardiovascular complications. Nearly 80% of deaths in these patients are due to these complications particularly in Asian Indians. These cardiovascular problems are mainly consequent to disturbances in lipid metabolism or more precisely Dyslipidemias which enhance the risk of macrovascular complications in the face of insulin resistance. Moreover insulin resistance itself is responsible for primarily disturbing lipid homeostasis. Our study was done to prove that Dyslipidemias are significantly associated with Diabetes Mellitus so that the former can be aggressively corrected while treating Diabetic patients as a whole. MATERIAL AND METHODS: The study was conducted at Gandhi Hospital, Secunderabad over a period of one year (April 2013 to April 2014). It was a Cross-Sectional Prospective study. 100 patients of type 2 diabetes and 100 controls were taken and their lipid profiles were assessed. CONCLUSION: Our study showed that there is considerable and significant association of Dyslipidemias with Type 2 Diabetes Mellitus. KEYWORDS: Diabetes, Dyslipidemias, Cardiovascular complications.

INTRODUCTION: Diabetes mellitus one of the most common chronic diseases globally is among the top five causes of mortality. The global prevalence of diabetes among adults is estimated to be 6.4%, affecting 285 million people, in 2010, and is expected to increase to 7.7%, affecting 439 million people by 2030. Diabetes is considered a coronary heart disease (CHD) risk equivalent and it is frequently associated with various cardiovascular (CV) complications.1 It is well-established that dyslipidemia is a major risk factor for macrovascular complications in patients with type-2 diabetes mellitus (T2DM) and affects 10%-73% of this population.23456 Approximately, 80% of deaths in patients with diabetes are attributable to cardiovascular disease (CVD). Asian Indians have higher risk of CHD than whites.7 Furthermore, data from the United Kingdom Prospective Diabetes Study suggest that both decreased High density lipoprotein -C and elevated Low density lipoprotein-C predict CHD in diabetics.8

The composition of lipid particles are more atherogenic in diabetics meaning that normal lipid concentrations themselves are more dangerous in diabetic than in non-diabetic patients. Therefore benefit of lipid lowering in type 2 diabetic patients is at least as great as in the non-diabetic population making it a very attractive target for the reduction of coronary heart disease in type 2 diabetic patients.9

Dyslipidemia literally means a disorder of lipid metabolism, including lipid and/or lipoprotein overproduction or deficiency. But more commonly Dyslipidemias have come to mean a triad of elevated total cholesterol, the "bad" low-density lipoprotein (LDL) and very low density lipoprotein cholesterol (VLDL) and the triglyceride (TG) concentrations, and a decreased "good"
high-density lipoprotein (HDL) cholesterol concentration in the blood.\textsuperscript{10} The prevalence of dyslipidemias varies according to the ethnic, socioeconomic, and cultural characteristics of distinct population groups.\textsuperscript{11} The Atherogenic Dyslipidemia Triad, rightly named is a predisposing factor for cardiovascular disease, and cannot be ignored in the face of growing evidence of its association with Type 2 Diabetes Mellitus. Diabetes is associated with increased morbidity and mortality from cardiovascular disease even in the absence of the major risk factors like cigarette smoking, hypertension, hypercholesterolemia. When these risk factors are present, the attributable risk to each factor is enhanced. In addition to hypercholesterolemia, other lipid and lipoprotein abnormalities also contribute to vascular risk. Hypertriglyceridemia often associated with low levels of high-density lipoprotein cholesterol is common in non-insulin-dependent diabetes mellitus patients, in the presence of insulin resistance. Recent studies show hypertriglyceridemia with accumulation of remnant particles and alterations in low-density lipoprotein subfractions is the basis for the existence of a strong relationship between hypertriglyceridemia and vascular risk.\textsuperscript{12} Raised serum triglycerides and low HDL-C often precede the onset of Type 2 Diabetes Mellitus for many years.

Our study was an attempt at stressing on the strong association of Dyslipidemias with Type 2 Diabetes Mellitus.

\textbf{MATERIAL AND METHODS:} The study was conducted at Gandhi Hospital, Secunderabad over a period of one year (April 2013 to April 2014). It was a Cross-Sectional Prospective study. 100 patients of type 2 diabetes and 100 controls were taken and their lipid profiles were assessed. A proforma was prepared that incorporated information relating to demographic and clinical data. Known cases of patients suffering with type 2 diabetes of age groups between 40-70 years without complications were included. Patients suffering with type 1 diabetes, complicated Diabetes mellitus and acutely ill patients were excluded.

Estimation of lipid profile including total cholesterol (Cholesterol oxidase peroxidase method), triglycerides (Proven CPO-PAP-ESPAS method), HDL cholesterol (Precipitation method), LDL cholesterol were done for all patients and controls.

The data obtained were compiled, tabulated, and analyzed. Statistical analysis of the data was done by using appropriate computer package. Wherever possible the data was arranged in tables. Prevalence is expressed in percentages and test of significance was done.

\textbf{RESULTS:} Statistical analysis showed that the levels of total cholesterol (Table 1, Chart 1), triglycerides (Table 2, Chart 2) very low density lipoproteins (Table 3, Chart 3), and low density lipoproteins (Table 4, Chart 4) were significantly raised in Type 2 Diabetic patients while levels of high density lipoproteins were lowered. (Table 5, Chart 5).

\textbf{DISCUSSION:} Different mechanisms are responsible for the development of dyslipidemia in individuals with diabetes. Defects in insulin action and hyperglycemia could lead to dyslipidemia in patients with diabetes. In the case of T2DM, the obesity/insulin-resistant state can in itself lead to lipid abnormalities independently of hyperglycemia. In T2DM, this situation is not usually fully corrected with glycemic control. Therefore conclusively insulin resistance and not hyperglycemia is the culprit. Some of the incriminating mechanisms are Insulin-controlled apoprotein production in the liver, regulation of lipoprotein lipase (LPL), actions of cholesteryl ester transfer protein (CETP) and peripheral actions of insulin on adipose tissue and muscles.\textsuperscript{13} Hyperglycemia not only causes
apoptosis of β-cells in the islets of Langerhans (Glucotoxicity) but also determines the degree of accumulation of oxidized LDLs. Moreover dyslipoproteinemia itself has a toxic effect on β-cells, but only in the presence of increased blood glucose levels, thus exponentially enhancing risk of cardiovascular disease. In fact diabetes and the lipid metabolism disorder are so tightly intertwined that ‘Diabetes Lipidus’ would be an appropriate term.14

Moreover Diabetic dyslipidemia is associated with insulin resistance, visceral obesity and liver fat content. Insulin resistance causes excessive generation of substrates like free fatty acids for synthesis of very low density lipoproteins (VLDL) in the liver. It also upregulates the production of VLDLs by other means. Also elevated apoprotein B, prolonged postprandial lipemia also worsen the condition. In addition, LDL particles are converted to smaller, perhaps more atherogenic, lipoproteins termed ’small-dense LDLs. Chronic hyperglycaemia exerts a deleterious effect on the vascular wall and, by glycation of apolipoproteins, interferes with the normal pathways of lipoprotein metabolism.15

Hypertriglyceridaemia can be found in 30%-60% of type 2 diabetics and is a frequent finding in the prediabetic state, preceding in time the onset of chronic hyperglycaemia. One major consequence of insulin resistance on lipid metabolism is the loss of the suppressive effect of insulin on fat mobilization from adipose tissue. As a result, there is an increase in free fatty acids (FFA) flux owing to reduced suppression of lipolysis. The failure to suppress FFA in the postprandial period, due to the decreased activity of lipoprotein lipase (LPL), and the rise in plasma FFA due to increased adipocyte lipolysis are key mechanisms behind the increased hepatic very low density lipoproteins (VLDL)-TG secretion.16

Overproduction of hepatic VLDL involves mainly the large buoyant VLDL1 particles, which are a dominant feature of diabetic dyslipidemia. In fact, most of the increase in triglyceride rich lipoproteins (TRLs) observed in diabetic dyslipidemia is due to VLDL1 particles.17 Moreover, the failure of insulin to suppress VLDL1 release in the postprandial phase can saturate the lipolytic pathways and contributes to postprandial lipemia.

Recent findings have helped to further clarify the regulatory steps in VLDL metabolism in the liver in type 2 diabetes n normal subjects, insulin inhibits the assembly and secretion of VLDL particles by increasing apolipoprotein B (apoB) degradation and decreasing the expression of the microsomal transfer protein (MTP) in hepatocytes.18 As a consequence, insulin inhibits hepatic secretion of VLDL-TG and apoB-100.

To summarize, diabetic dyslipidemia is a cluster of lipid abnormalities that are metabolically closely linked. Hypertriglyceridaemia, mostly due to excessive production of large, buoyant VLDL1 particles, low HDL-C, preponderance of the small dense LDL particles subclass and prolonged postprandial lipemia have been briefly reviewed, and the major role of insulin resistance has been emphasized. The most powerful atherogenic components of diabetic dyslipidemia are the small dense LDL, the elevation in remnant TRL particles, and the low HDL. The coexistence of these three factors strongly aggravates the lipid accumulation in the arterial wall and the formation of atherosclerotic plaques.

**CONCLUSION:** Our study shows that Dyslipidemias are significantly associated with Type 2 Diabetes. An already existing risk of developing Cardiovascular Disease in a background of insulin resistance is further compounded by a Dyplipemic environment. Hence correcting the lipid disturbances should be given priority while treating a patient of chronic Type 2 Diabetes Mellitus.
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The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.

**Table 1: Levels of Total Cholesterol in Type 2 Diabetics and Controls**

| Total Cholesterol | Type 2 Diabetics | Controls | Total | P value |
|-------------------|------------------|----------|-------|---------|
| <200mg/100ml      | 8                | 59       | 67    | <0.005  |
| >200mg/100ml      | 92               | 41       | 113   | <0.005  |
| **Total**         | **100**          | **100**  | **200**|         |

The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.

**Table 2: Levels of Triglycerides in Type 2 Diabetics and Controls**

| Triglycerides     | Type 2 Diabetics | Controls | Total | P value |
|-------------------|------------------|----------|-------|---------|
| less than 180 mg/dl| 10               | 39       | 49    | <0.005  |
| more than 180 mg/dl| 90               | 61       | 151   | <0.005  |
| **Total**         | **100**          | **100**  | **200**|         |

The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.

**Table 3: Levels of Very Low Density Lipoproteins in Type 2 Diabetics and Controls**

| VLDL               | Type 2 Diabetics | Controls | Total | P value |
|--------------------|------------------|----------|-------|---------|
| less than 180 mg/dl| 10               | 37       | 47    | <0.005  |
| more than 180 mg/dl| 90               | 63       | 153   | <0.005  |
| **Total**          | **100**          | **100**  | **200**|         |

The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.

**Table 4: Levels of Low Density Lipoproteins in Type 2 Diabetics and Controls**

| LDL                | Type 2 Diabetics | Controls | Total | P value |
|--------------------|------------------|----------|-------|---------|
| less than 180 mg/dl| 37               | 91       | 128   | <0.005  |
| more than 180 mg/dl| 63               | 9        | 72    | <0.005  |
| **Total**          | **100**          | **100**  | **200**|         |

The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.

**Table 5: Levels of High Density Lipoproteins in Type 2 Diabetics and Controls**

| HDL (males)       | Type 2 Diabetes | controls | Total | P value |
|-------------------|-----------------|----------|-------|---------|
| more than 35 mg/dl| 12              | 75       | 87    | <0.005  |
| less than 35 mg/dl| 88              | 25       | 113   | <0.005  |
| **Total**         | **100**         | **100**  | **200**|         |

The P value - Chi-square statistic (with Yates correction) is <0.005, considered extremely significant.
**VLDL levels in Diabetics and Controls: Chart 3**

- **Diabetics**
  - Category 1: 10
  - Category 2: 90

- **Controls**
  - Category 1: 37
  - Category 2: 63

**LDL levels in Diabetics and Controls: Chart 4**

- **Diabetics**
  - Category 1: 37
  - Category 2: 63

- **Controls**
  - Category 1: 91
  - Category 2: 9
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