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STUDY OF EFFECT OF METFORMIN ON LIPID PROFILE IN TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT: Type 2 diabetes mellitus poses an important health care problem because of its associated two to threefold increased risk of cardiovascular disease and its high prevalence and incidence worldwide. Dyslipidemia is an independent risk factor for severe morbidity and mortality in terms of cardiovascular risk in type-2 DM patients. Studies have shown an association between metformin and lipid profile changes although results are inconclusive. Thus, this study was done to evaluate the changes in serum lipid profiles in patients who are newly started on metformin. It was a prospective, observational and non-interventional study. 50 newly diagnosed patients of type 2 DM were enrolled and started on metformin. Lipid profile was assessed before starting treatment and then after 12 weeks. Statistical analysis was done using paired t-test. In results serum total cholesterol, triglyceride and VLDL were significantly decreased after 12 weeks of metformin therapy. The apparent change was also observed in serum LDL and HDL, but it was not statistically significant. Thus, it may be speculated that metformin has beneficial effects on lipid and lipoprotein concentration. It can be particularly more beneficial when type 2 DM coexist with hyperlipidemia. However, long term studies are needed to determine the fact that metformin will help to prevent complications of type 2 diabetes mellitus.

INTRODUCTION: Diabetes Mellitus (DM), which is one of the oldest diseases known to man is a chronic and heterogeneous metabolic disorder presenting with chronic hyperglycemia along with impairment in the metabolism of carbohydrates, lipids, and proteins [1]. The incidence of Diabetes Mellitus is pacing at an alarming rate and have become a global health issue [2]. Globally the burden of DM has affected approximately 415 million people till 2017 and is set to escalate to 642 million by the year 2040 [3].

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DM is broadly classified as Type 1 DM due to absolute insulin deficiency, Type 2 DM due to insulin resistance with an inadequate compensatory increase in insulin secretion and gestational DM, *i.e.* glucose intolerance which is first recognized during pregnancy [4, 5].

The increasing incidence of DM, in turn, leads to increased rate of complications, which is again one of the most important challenging public health issues. Complications of diabetes range from acute, life-threatening conditions such as severe hypoglycemia or ketoacidosis to chronic, debilitating complications affecting multiple organ systems, such as retinopathy, nephropathy, neuropathy, and cardiovascular disease, with cardiovascular disease being the major cause of morbidity and mortality in diabetic patients [6]. Type 2 diabetes and insulin resistance are considered to

be associated with lipid and lipoprotein abnormalities. The prevalence of dyslipidemia in type 2 diabetes is double with respect to the general population [7]. Diabetic dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C) and an increased preponderance of small, dense low-density lipoprotein cholesterol (LDL-C) particles [8]. Studies have indicated that dyslipidemia is a major cause for the development of cardiovascular disease in Type 2 Diabetes [9]. Despite Statins being the first-line treatment for dyslipidemia, a significant number of fatal and nonfatal coronary heart disease (CHD) events still occur, indicating the need to target other modifiable risk factors for CHD [10].

Metformin is one of the most popular oral glucose-lowering medications, widely considered to be the first-line treatment for patients with type 2 diabetes mellitus [11]. It inhibits hepatic gluconeogenesis, leading to reduction in fasting blood glucose levels [12]. Additionally, it has antioxidant activity that reduces risk of cancer and also improves insulin sensitivity [13, 14].

Intervention at various risk factors can decrease the incidence of cardiovascular events in Diabetes. One of these interventions can be an ideal oral anti-diabetic agent, among which metformin seems to have a promising role in the prevention of cardiovascular disease. Studies have shown an association of metformin on lipid profile in Type 2 Diabetics [15, 16, 17].

Studies have shown an improving effect of metformin on lipid metabolism, even in non-diabetics [18]. In light of the increasing problem of dyslipidemia associated with Type 2 diabetes, this study is designed to know the effect of oral hypoglycemic agents, metformin on lipid profile (TG, Total cholesterol, HDL, LDL, and VLDL) in type 2 diabetic patients. If the study shows positive effect of metformin on lipid profile, it can be considered that metformin has positive effect on outcome of cardiovascular disease and hypothesis regarding additional beneficial effects of metformin in such patients can be generated and can be tested by further appropriate method.

MATERIALS AND METHODS:

Study Design: It was a prospective, observational, and non-interventional study.

Ethical Approval: The study protocol, patient data sheet, participant information sheet and informed consent form (in English and vernacular languages) were submitted and approved by the scientific review committee and human research and ethics committee of the Institution. IEC approval no. MCS/STU/ETHICS/Approval/16649/15 Date 04/08/15.

Study Subjects: Fifty (n=50) newly diagnosed confirmed cases of type-2 DM were enrolled as study subjects from the OPD of the medicine department in a random fashion. Informed consent was obtained from the participants. Diabetes was confirmed by using WHO criteria 2010.

Confirmed DM patients were selected for the study according to the following inclusion and exclusion criteria:

Inclusion Criteria:

- Newly diagnosed type-2 DM exclusively on metformin treatment of any age & sex.
- Patient willing to give consent for the study.

Exclusion Criteria:

- Patient not willing to participate.
- Patient on hypolipidemic drugs or any other drug affecting lipid profile.
- Patients with secondary complications like
  - Nephropathy
  - Neuropathy
  - Retinopathy
  - Cardiovascular events
- Patient giving a history of smoking & alcoholism.

Study Procedure: After enrolment, the patient receives anti-diabetic drug metformin 500 mg OD. During metformin treatment, patients were on their regular diet.

Written informed consent was taken before laboratory testing. In all 50 patients, baseline lipid profile was done at the time of diagnosis of

diabetes mellitus as a routine procedure. In all subjects, 5 ml venous blood samples were collected in plain vacuity bulb. Blood samples were collected from an anti-cubital vein. After sampling, tubes were centrifuged at 3000 rpm for 10 min immediately, and the plasma separated was used for triglyceride, total cholesterol, and HDL estimation. VLDL and LDL were calculated by using Friedewald's equation respectively as below.

Serum VLDL - Cholesterol conc. (mg/dl) = Triglyceride / 5

Serum LDL - Cholesterol conc. (mg/dl) = Total Cholesterol – [HDL-Cholesterol + VLDL -Cholesterol]

Lipid profile was again done at the end of 12 weeks of metformin therapy. Note: Haemolysed samples were not taken in the study.

Statistical Analysis: Data were analyzed using SPSS 16.0 software. The results were expressed as Mean ± Standard deviation**.** The results were analyzed using paired t-test. P-value < 0.05 is considered significant.

RESULTS: Mean age of 50 patients who received metformin therapy were mean age 45 ± 10. Out of this 50 patients 35 were male and 15 were female.

TABLE 1: GENERAL CHARACTERISTICS OF STUDY POPULATION

Variable		Study group (n=50)
Age (years)		45 ± 10
Weight (kg)		65 ± 5
Sex	Male	35
	Female	15

Effect of Metformin on Serum Total Cholesterol Level: After 12 weeks of metformin therapy, Total cholesterol level decreased significantly from 204.12 ± 21.06 mg/dl to 202.34 ± 20.76 which was statistically significant as compared to baseline (*p<0.05) **Fig. 1, Table 2**.

TABLE 2: LIPID PROFILE OF NEWLY STARTED METFORMIN PATIENTS (BASELINE) AND POST METFORMIN TREATMENT PATIENTS (AT 12 WEEKS)

Variable	Baseline group (Before treatment)	At 12 weeks (After treatment)
Total cholesterol (mg/dl)	204.12 ± 21.06	202.34 ± 20.76*
Triglyceride (mg/dl)	155.68 ± 17.37	151.76 ± 9.27*
HDL (mg/dl)	34.78 ± 6.75	34.92 ± 6.21
LDL (mg/dl)	138.20 ± 24.73	137.06 ± 23.67
VLDL (mg/dl)	31.13 ± 3.474	30.35 ± 1.85*

* p<0.05 *vs*. Baseline group

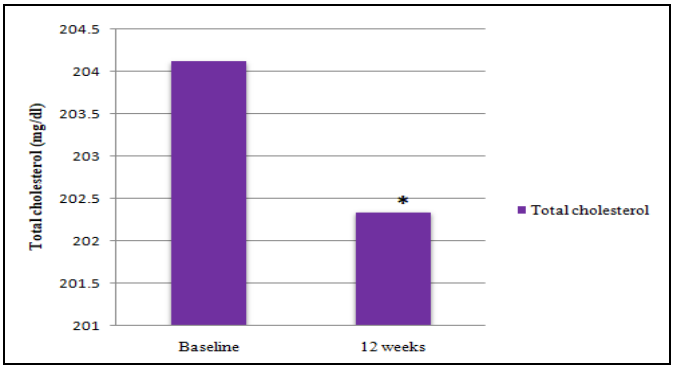

FIG. 1: EFFECT OF METFORMIN ON SERUM TOTAL CHOLESTEROL LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS. (*p<0.05 *vs*. baseline)

Effect of Metformin on Serum Triglyceride Level: After 12 weeks of metformin therapy, the Triglyceride level decreased significantly from 155.68 ± 17.37 to 151.76 ± 9.27 which was statistically significant as compared to baseline (*p<0.05) **Fig. 2**, **Table 2**.

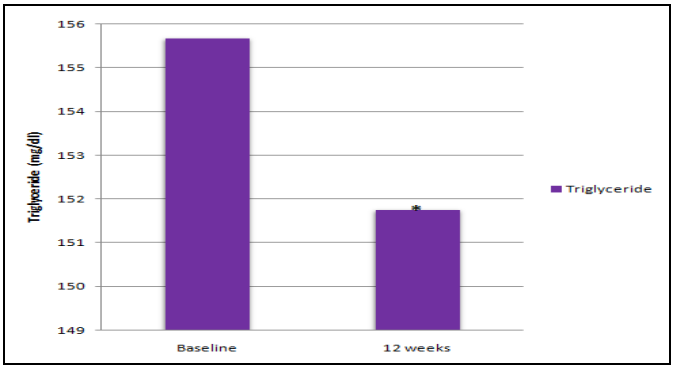

FIG. 2: EFFECT OF METFORMIN ON SERUM TRIGLYCERIDE LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS. (*p<0.05 *vs*. baseline)

Effect of Metformin on Serum HDL Level: After 12 weeks of metformin therapy, HDL level increased from 34.78 ± 6.75 to 34.92 ± 6.2, but it was not statistically significant as compared to baseline (#p>0.05) **Fig. 3**, **Table 2**.

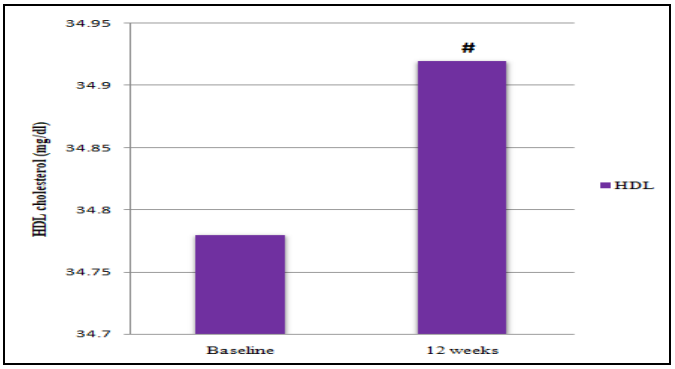

FIG. 3: EFFECT OF METFORMIN ON SERUM HDL LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS. (#p>0.05 *vs*. baseline)

Effect of Metformin on Serum LDL Level: After 12 weeks of metformin therapy, LDL level decreased from 138.20 ± 24.73 to 137.06 ± 23.67 but it was not statistically significant as compared to baseline (#p>0.05) **Fig. 4**, **Table 2**.

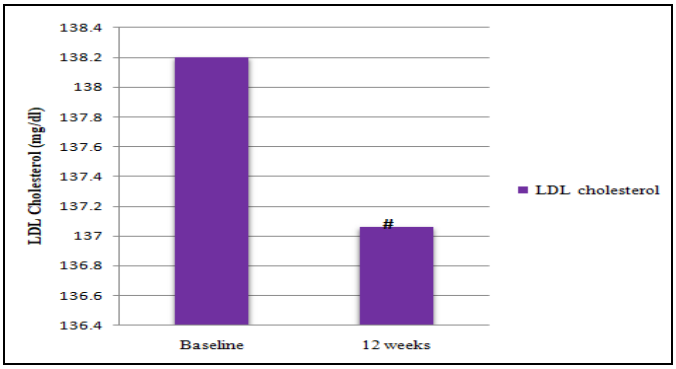

FIG. 4: EFFECT OF METFORMIN ON SERUM LDL LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS. (#p>0.05 *vs.* baseline)

Effect of Metformin on Serum VLDL Level: After 12 weeks of metformin therapy, VLDL level decreased significantly from 31.13 ± 3.474 to 30.35 ± 1.85, which was statistically significant as compared to baseline (*p<0.05) **Fig. 5**, **Table 2**.

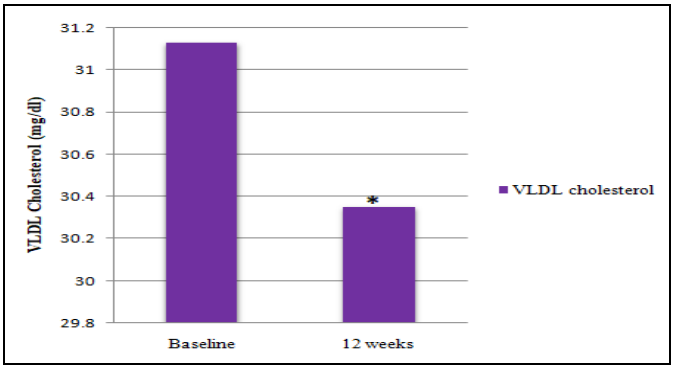

FIG. 5: EFFECT OF METFORMIN ON SERUM VLDL LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS. (*p<0.05 *vs.* baseline)

DISCUSSION: Diabetes is pacing at an alarming epidemic level and is frequently found to coexist with other conditions, such as obesity, dyslipidemia, atherosclerotic vascular disease and hypertension which contribute to morbidity and mortality [19]. The close relationship between diabetes and obesity has led to the connotation term 'diabesity, indicating that majority of patients with diabetes are obese or overweight [20]. Diabetic patients have a typical 'lipid triad' of low high-density lipoprotein-cholesterol levels, high triglyceride levels and normal or slightly raised low-density lipoprotein-cholesterol levels [7].

The complications and mortality due to cardiovascular disease is high in patients of Diabetes due to associated dyslipidemia. Most of the diabetic patients require multiple approaches along with statin therapy to reduce cardiovascular risk due to dyslipidemia [21, 22]. Moreover, studies have shown that ant diabetic agents that directly improve insulin resistance may have effects on lipid levels [23]. By keeping this in mind this study was conducted to determine effect of metformin on lipid profile in type 2 diabetes patients.

In this study, a total of 50 patients of newly diagnosed type 2 DM were enrolled. Among them 35 were male and 15 were female. The mean age of patients was 45 ± 10 years. After enrolment, they were given tablet metformin 500 mg once a day for 12 weeks. It was ensured that all the patients were glycemic all stable on the same dose for 12 weeks. Serum lipid profile (total cholesterol, triglycerides, HDL, LDL, VLDL) in type 2 DM and the effect of metformin therapy on these parameters were examined in this study. At the end of 12 weeks of metformin therapy total cholesterol, triglycerides and VLDL were significantly decreased as compared to baseline parameters. The change was also observed in plasma HDL and LDL but it was not statistically significant.

There are some studies that have shown association between metformin and lipid changes, although they have different and inconclusive results. Krishnaswami *et al*., have shown metformin to reduce LDL-C, total cholesterol, and TG levels and increase HDL-C levels [23]. Garimella *et al*., demonstrated that metformin as monotherapy reduced Total cholesterol, LDL-C, significant decrease in TG levels and increased serum HDL-C level [7]. Wulffele *et al*. reported that metformin has no intrinsic effect on HDL cholesterol and triglycerides in patients with type 2 diabetes. However, independent of its effect on glycemia, metformin reduces total and LDL cholesterol significantly [24]. Although in this study, we have found significant decrease in serum total cholesterol, triglycerides and VLDL with insignificant increase in HDL cholesterol and decrease in LDL cholesterol. Desilets *et al*., showed an association of metformin with an improvement in lipid profile and metabolic parameters even in non-diabetic patients [25].

Studies have shown that metformin may reduce low-density lipoprotein cholesterol (LDL-C) *via* an AMP-activated protein kinase pathway. In the hepatocytes metformin increases the AMP-to-ATP ratio.

All this consequently suppresses fatty acid synthesis, which leads to reduced levels of acyl-alkyl PC concentrations and LDL-C [26]. Through increasing insulin sensitivity, metformin reduces the rate of lipolysis, thereby slowing the conversion of free fatty acids to lipoprotein precursors in the liver, and by reducing plasma glucose levels, metformin lowers the fraction of irreversibly glycated LDL-C, which is removed less efficiently from the body [15].

In this study, we noted the change in lipid profile with a fixed dose of metformin 500 mg once a day. In this study patients receiving hypolipidemic drugs or any other drugs which have effect on lipid profile were excluded. Similarly patients with any of the diabetic complications were also excluded. Thus the changes observed in the study could be attributed to metformin.

A possible reason for these discrepant results may be that the clinical studies cited above-analyzed data from independent samples. In our study, this problem was avoided by paired data analysis, in which each patient was his own control thereby increasing the power of the statistical analysis.

In this study, metformin has shown a beneficial effect on lipid profile. Metformin being the first-line treatment of type 2 diabetes can serve as a useful therapeutic choice for prevention and treatment of dyslipidemia and thereby prevention of cardiovascular events. Thus, it may reduce need for lipid-lowering drugs for cases of borderline hyperlipidemia in type 2 DM. Identification of the mechanism through which metformin improves lipid profile can open new gates for research through which cardiovascular complications of diabetes can be prevented.

CONCLUSION: Treatment with metformin in newly diagnosed type 2 DM has shown a significant decrease in serum cholesterol, triglyceride, VLDL. It can be particularly more beneficial when type 2 DM coexist with hyperlipidemia.

When administered to carefully selected patients and monitored appropriately, it may prove to be valuable in altering its cardiovascular sequelae in the long term. Thus, to generalize the results of this study, study parameters need to be evaluated in larger population and for longer duration. In addition, understanding the history and identification of the mechanisms of dyslipidemia in patients with DM will stimulate research to develop new and better ways to prevent and cardiovascular complications associated with DM.

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