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ASSESSMENT OF EFFICACY OF SULPHONYLUREAS AND IN COMBINATION WITH METFORMIN ON GLYCEMIC CONTROL AND LIPID PROFILE OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

The objective of the study was to assess the efficacy of sulphonylureas and in combination with Metformin on the glycemic control and lipid profile in patients with type 2 diabetes mellitus. This prospective study was carried out for a period of 6 months in patients with age more than 35 years, HbA1C >7% and fasting blood sugar level >140 mg/dl. A total of 84 patients divided into 4 groups based on their treatment. The data obtained were analyzed by using Graph pad Prism version 6.0. The statistical analysis of glycemic control and lipid profile was carried out using Paired student-t test. In monotherapy, treatment with Glimepiride ($p<0.05$) was more efficacious than Glipizide in reducing hyperglycemia. But, in combination with Metformin, Glimepiride showed more effect on HbA1C (mean reduction 1.22 mg/dl), while Glipizide (mean reduction 58.1 mg/dl) showed more effect on FBS (mean reduction 58.1 mg/dl). The monotherapy with Glimepiride ($p<0.05$) has a significant effect on lipid profile than Glipizide ($p>0.05$). When given in combination with Metformin, Glimepiride and Metformin combination had more effect on lipid profile and can be used as the drug of choice in patients with cardiovascular risk.

KEYWORDS: Sulponylurea, Monotherapy, Lipid profile.

INTRODUCTION

Diabetes mellitus is an endocrine disorder in which more than 100 million (6% of the population) of people worldwide are affected even though enormous facilities were available to control its growth.[1] It can also be easily described as a disease characterized by chronic hyperglycemia and increased cardiovascular risk.

Dyslipidemia is the major risk factor for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low high-density lipoprotein (HDL) concentration and increased concentration of low-density lipoprotein (LDL) particles. The lipid profile changes due to the increased flux of free fatty acids in case of insulin resistance.[2,3,4]

Antidiabetic drugs that reduce blood glucose levels while exerting some effect on cardiovascular risk factors should be expected to provide beneficial effects.[3] Sulphonylureas exert their activity through induction of insulin release by pancreatic-cells. Glimepiride which is more pancreas-specific does not show interaction with cardiovascular ATP-dependent potassium channels.[4]

Metformin lowers plasma glucose levels by suppressing hepatic gluconeogenesis and glycogenolysis while increasing peripheral sensitivity to insulin. Metformin can reduce HbA1C by 0.5–1.5% and exerts beneficial and modest effects on reducing blood pressure, improving lipid profile and maintaining it.[3] Individualized antidiabetic regimens can be designed by using combination therapy which is based on the pharmacological agents acting via different mechanisms and presenting differing side effects.[5]

The aim of the study was to compare the efficacy of sulphonylureas alone and in combination with Metformin in reducing the level of fasting blood glucose, glycosylated hemoglobin in patient with Type 2 Diabetes mellitus and also to assess the effect of selected oral antidiabetic agents on lipid profile of the patient with type 2 Diabetes Mellitus.

METHODOLOGY

This prospective was study conducted at Vivekanandha Medical Care Hospital, Elayampalayam. The study was approved by the Institutional Ethics Committee of Vivekanandha Medical Care Hospital. The study was carried out for the period of 6 months. Patients with age more than 35 years, of either sex, HbA1C >7% and fasting blood sugar

level >140 mg/dl were included in the study after their consent. Patients who were taking insulin and had taken insulin for more than 6 weeks in the past 3 months, who had hypersensitivity to biguanides and sulphonylureas were excluded from the study.

A total of 141 patients were screened and according to inclusion and exclusion criteria, about 84 patients were recruited in the study. As the patients were recruited for the study, they were randomized into four groups according to the treatment they received. Patients who received Glimepiride (2 mg/ day,1-0-1) alone were introduced in Group I and Glipizide (5 mg,1-0-1) alone were introduced in Group II. Patients with combination therapy of Glimepiride + Metformin (2/500 mg, 1-0-1) were in Group III and Glipizide + Metformin (5/500 mg, 1-0-1) were in Group IV. At the time, baseline data like patient's past medical history, medication history, fasting blood sugar level, HbA1C level and lipid profile were collected. Then the patients were asked to come for review after 3 months and 6 months. The glycosylated hemoglobin (HbA1C), fasting blood sugar (FBS) and lipid profile of the patients done at every review to compare the effect of mono and combination therapy.

Statistical Analysis

The statistical analysis was done by using Graph Pad Prism version 6.07. The glycemic level and lipid level before and after the drug treatment was expressed as Mean ± SD. The comparisons of glycemic status and lipid profile were carried out using Paired student t-test. $p<0.05$ was considered as statistically significant.

RESULTS

Out of 84 patients participated in the study, 48 (57.14%) were male and 36 (42.85%) were female. About 37 (44.04%) diabetic patients were overweight.

Table 1: The Baseline Characteristics of Study Population (n=84).

S.No.	Characteristics	Group I	Group II	Group III	Group IV
1.	Sex (Male/Female)	11/10	14/7	8/13	15/6
2.	Age (Years)	56.38 ± 9.11	60 ± 10.04	58.85 ± 10.36	58.19 ± 10.91
3.	BMI(kg/m2)	24.68 ± 4.00	23.86 ± 3.44	24.86 ± 2.71	26.04 ± 4.58
Lab Parameters					
1.	HbA1C (%)	8.18 ± 2.07	7.17 ± 1.86	8.73 ± 1.66	7.34 ± 1.55
2.	FBS (mg/dl)	217.23 ± 83.91	265.85 ± 93.40	257.38 ± 59.25	267.14 ± 58.3
3.	Total cholesterol (mg/dl)	146.78 ± 1.62	149.3± 3.65	150.68 ± 3.50	111.1 ± 2.49
4.	Serum Triglyceride (mg/dl)	175.89 ± 2.63	127.39 ± 3.82	180.25 ± 6.7	131.05 ± 6.54
5.	HDL(mg/dl)	40.61 ± 3.16	36.87 ± 2.67	33.26 ± 8.01	36.89 ± 6.3
6.	LDL(mg/dl)	74.46 ± 2.08	65.26 ± 1.70	60.80 ± 11.25	72.99 ± 7.15

BMI: Body Mass Index**,** HbA1C: Glycosylated Hemoglobin, FBS: Fasting Blood Sugar, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein.

Glycemic Control

The group I, group II and group IV showed the significant reduction in HbA1C from baseline ($p < 0.05$). When comparing the mean reduction of HbA1C, the group I (0.69 mg/dl) and group III (1.22 mg/dl) showed greater value in monotherapy and combination therapy respectively.

Table 2: Comparison of Glycosylated Hemoglobin Level (n=84).

S.No.	Group	Mean ± SD			Mean Reduction (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	8.14 ± 2.07	8.02 ± 1.5	7.45 ± 2.02*	0.69
2.	Group II	7.17 ± 1.86	7.05 ± 0.9	6.72 ± 1.81*	0.45
3.	Group III	8.73 ± 1.66	8.25 ± 1.1	7.51 ± 1.77^{ns}	1.22
4.	Group IV	7.34 ± 1.55	7.23 ± 0.9	7.09 ± 1.53*	0.25

*p < 0.05, ns -Nonsignificant, HbA1C - Glycosylated hemoglobin.

Fasting Blood Sugar - All the 4 groups except group II showed a significant reduction in FBS level ($p<0.05$). In monotherapy, group I showed the more mean reduction of FBS (36.71 mg/dl) and in combination therapy, more reduction was shown by group III (56.91 mg/dl).

Table 3: Comparison of Fasting Blood Sugar Level (n=84).

S.No.	Group	Mean ± SD			Mean Reduction (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	217.23 ± 83.91	201 ± 65.3	180.52 ± 76.62*	36.71
2.	Group II	265.85 ± 93.40	257.8 ± 87.31	250.04 ± 97.49 ^{ns}	15.81
3.	Group III	257.38 ± 59.25	228.35 ± 61.05	200.47 ± 75.17*	56.91
4.	Group IV	267.14 ± 58.31	233.90 ± 68.11	209.04 ± 78.23*	58.1

*p < 0.05, ns -Nonsignificant, FBS - Fasting Blood Sugar.

Lipid Profile

Total Cholesterol – The reduction of total cholesterol in all the groups (both monotherapy and combination therapy) were found to be statistically similar ($p<0.05$). After 6 months of drug therapy, the group I (41.6 mg/dl) and group III (32.8 mg/dl) showed more reduction of total cholesterol.

Table 4: Comparison of Total Cholesterol Level (n=84).

S.No.	Group	Mean ± SD			Mean Reduction (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	149.3± 3.65	131.72 ± 8.1	107.7 ± 3.15*	41.6
2.	Group II	146.78 ± 1.62	146.11 ± 1.12	147.36 ± 1.85	- 0.58
3.	Group III	150.68 ± 3.50	144.62 ± 9.21	118.4 ± 5.59*	32.8
4.	Group IV	131.05 ± 6.54	116.34 ± 7.41	102.68 ± 6.8*	28.37

*p < 0.05.

Serum Triglycerides – Group III (38.62 mg/dl) showed a greater reduction of serum triglycerides significantly (p<0.05) when compared to group IV. In monotherapy, group I showed comparatively more mean reduction of triglycerides (18.4 mg/dl).

Table 5: Comparison of Serum Triglyceride Level (n=84).

S.No.	Group	Mean ± SD			Mean Reduction (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	127.39 ± 3.82	119.67 ± 5.78	108.99 ± 7.11*	18.4
2.	Group II	175.89 ± 2.63	174.89 ± 8.69	172.56 ± 2.44*	3.33
3.	Group III	180.25 ± 6.7	161.14 ± 8.90	141.63 ± 6.04*	38.62
4.	Group IV	131.05 ± 6.54	132.11 ± 6.99	134.69 ± 6.12 ns	- 3.64

*p < 0.05, ns – Nonsignificant.

High-Density Lipoprotein – The HDL concentration has been found to be increased significantly (p<0.01) in group I with a mean value of 7.61 mg/dl. After the data analysis, group III showed greater mean improvement of HDL (4.55 mg/dl) among combination therapy.

Table 6: Comparison of HDL Level (n=84).

S.No.	Group	Mean ± SD			Mean Improvement (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	40.61 ± 3.16	43.44 ± 2.9	48.22 ± 3.14*	7.61
2.	Group II	36.87 ± 2.67	36.87 ± 1.98	36.89 ± 2.98 ns	0.02
3.	Group III	33.26 ± 8.01	34.89 ± 5.78	37.81 ± 7.50*	4.55
4.	Group IV	36.89 ± 6.3	36.94 ± 5.78	37.19 ± 6.35*	0.3

*p < 0.05 ns- Nonsignificant HDL - High Density Lipoprotein.

Low-Density Lipoprotein – All the groups except groups III showed significant reduction of LDL (p < 0.05). In monotherapy and combination therapy, group II (0.67 mg/dl) and group IV (30.79 mg/dl) showed a more reduction of LDL respectively.

Table 7: Comparison of LDL Level (n=84).

Sl.No.	Group	Mean ± SD			Mean Reduction (mg/dl)
		Baseline	After 3 months	After 6 months	
1.	Group I	74.46 ± 2.08	74.01 ± 2.1	73.79 ± 2.07*	0.19
2.	Group II	65.26 ± 1.70	65.04 ± 0.6	65.07 ± 2.04 ns	0.67
3.	Group III	60.80 ± 11..25	49.14 ±8.9	46.67 ± 9.39*	14.13
4.	Group IV	72.99 ± 7.15	61.79 ± 9.9	42.20 ±6.91*	30.79

*p < 0.05 ns- Nonsignificant LDL - Low Density Lipoprotein.

DISCUSSION

Type- 2 diabetes occurs due to insulin resistance in muscle, adipose tissue and liver and a progressive decline in pancreatic β cell function.[6] A traditional approach to diabetes therapy involves the use of a single oral agent titrated to maximum dosage, each of which targets a single pathological defect of type 2 diabetes as its primary mechanism of action, with the requirement of poor glycemic control as an indication for the addition of a second oral agent.[7] The aim of our study was to compare the effect of sulphonylureas alone and in combination with Metformin on glycemic control and lipid profile. During the study, it has been found that type 2 diabetes mellitus is affected more in male and mostly it is pronounced at the age of 55-65.

Glimepiride showed greater mean changes from baseline in HbA1C (0.69 mg/dl) as well as FBS (36.71 mg/dl) when compared to Glipizide in monotherapy. The greater mean changes from baseline in case of HbA1C and FBS were found for Glimepiride and Metformin (1.22 mg/dl) and Glipizide and Metformin (58.1 mg/dl) respectively. These results demonstrated that the treatment with Glimepiride was more efficacious than with Glipizide in improving glycemia. But in combination with Metformin, Glimepiride showed more effect on HbA1C while Glipizide showed more effect on FBS.

In diabetic patients, there is an increased risk of cardiovascular complications followed by higher morbidity and mortality than in a non-diabetic population with coronary artery disease. Cardiovascular disease (CVD) is 2-3 times commoner in diabetics than in nondiabetics. Known risk factors are such as raised cholesterol, hypertension, hyperinsulinemia, abdominal obesity, disorders of platelet function and coagulation and degree of glycemic control only partly explained the increased risk.[8]

In monotherapy, the patients treated with Glimepiride resulted in significant reduction in the total cholesterol (41.6 mg/dl), serum triglyceride (18.4 mg/dl) and LDL cholesterol (0.19

mg/dl) while helped to increase the HDL cholesterol (7.61 mg/dl) throughout the study. So the Glimepiride can be considered as the best drug among sulphonylureas to be prescribed in patients with increased cholesterol and triglyceride concentration among monotherapy of sulphonylureas. These findings are similar to those reported by Komola Azimova et.al, which performed a Cardiovascular Safety Profile of Currently Available Diabetic Drugs.[9]

In this study, combination therapy of Glimepiride and Metformin showed a significant effect on lipid profile with reduction of total cholesterol (32.8mg/dl), serum triglycerides (38.62mg/dl), LDL (30.79mg/dl) and elevation of HDL (4.55 mg/dl). So Glimepiride and Metformin combination can be used in patients with cardiovascular risk.

CONCLUSION

Patients receiving Glimepiride showed a significant reduction of HbA1C and fasting blood sugar level, total cholesterol and improvement in the HDL when compared with Glipizide group. Glimepiride was found to be one of the most efficacious drug among monotherapy as compared to Glipizide. If the diabetes not adequately controlled, Metformin can be added to Glimepiride. It may also reduce the lipid-associated cardiovascular risks in the diabetes patients.

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DECLARATION OF INTEREST

The author has declared no conflict of interest.

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