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Potentiality of a newer oral Anti hyperglycemic combination therapy over conventional therapy in type 2 diabetes

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ABSTRACT

Over the last decade, diabetes mellitus has emerged as an important clinical and public health problem throughout the world. The aim of the study is perceive the Potentiality of a newer oral Antihyperglycemic combination therapy over conventional therapy in type 2 diabetes. The prospective study was conducted over a period of six months in the department of Medicine, Guntur City Hospital. The prevalence of type2 diabetes was high in male 65.79 % than female 34.21%. Majority of the patients (23.68 %) belonged to age group of 51–55 years. Majority of patients (55.26%) having a family history of Diabetes. Majority of patients receiving Combination of Glibenclamide + Metformin (60.53%), evaluated for effect on FPG for both combinations. The mean changes in FPG were noted. In the same way effect on HbA_1c also noted. Mean changes in for every month HbA_1c will be noted. Our study reveals that Combination therapy with Metformin plus Glimepiride is more effective than Glibenclamide plus Metformin; in improving glycemic control in type 2 diabetes, while also allowing a reduction of the dosage of each drug.

Keywords: Diabetes Mellitus, ADA, HbA_1c, FPG, Glibenclamide, Metformin, Glimepiride.

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INTRODUCTION

The term diabetes mellitus describes a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs[1].

Etiologic Classifications of Diabetes Mellitus[2]

1) Type 1 diabetes mellitus

A) immune-mediated diabetes

B) Idiopathic diabetes

2) Type 2 diabetes mellitus 3) other specific types

a) Genetic defects of beta-cell function

b) Genetic defects in insulin action

c) Diseases of the exocrine pancreas

d) Endocrinopathies e) Drug or chemical Induced f) Infection g) Uncommon forms of immune-mediated diabetes.

4) Gestational diabetes mellitus

Untreated or improperly treated diabetes leads to complications. Diabetes is the only metabolic disorder, which can affect almost every organ of the body. The organ most commonly affected are eyes, kidneys, nerves and blood vessels. Statistics reveal that people with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30-40 times more likely to develop myocardial infarction and twice as likely to suffer a stroke than non-diabetics. As per United Kingdom Prospective Diabetes Study (UKPDS), approx. 50% patients present with complications.

Causes of Complications[3]

Glucose is converted to sorbitol in presence of Aldose reductase. Sorbitol causes neurotoxicity and also has tendency to precipitate in small blood vessels resulting in vascular disfunctioning. Excess glucose binds to proteins leading to protein glycation Glycosylated proteins can cause

Changes in cellular function

Produce free radicals that can further damage the cell

Eventually protein glycosylation leads to the formation of Advanced Glycosylation End products [AGEs]. AGEs are released in to the circulation which: -

- Alter the vascular function

- Cause increase in vascular permeability
- Affect coagulation status of the endothelium
- Thus causes vascular dysfunction

Diagnostic Criteria for diabetes[4]

According to American Diabetes Association recommendation

Normal fasting plasma glucose levels are less than 110 mg per dL (6.1 mmol per L). and normal 2 hr PPG levels are less than 140 mg per dL Blood glucose levels above the normal level but below the criterion established for diabetes mellitus indicate impaired glucose homeostasis.

Persons with fasting plasma glucose levels ranging from 110 to 126 mg per dL (6.1 to 7.0 mmol per L) are said to have impaired fasting glucose, while those with a 2hrPPG level between 140 mg per dL (7.75 mmol per L) and 200 mg per dL (11.1 mmol per L) are said to have impaired glucose tolerance.

The study of prescribing pattern is a component of medical audit that does monitoring and evaluation of the prescribing practice of the prescribers as well as recommends necessary modifications to achieve rational and cost-effective medical care and it helps to evaluate and suggest modifications in prescribing practices of medical practitioners so as to make medical care rational.

This study also attempts to analyze the current prescription patterns of drugs used in the treatment of type 2 diabetes mellitus patients. The findings of this study are expected to provide relevant and useful feedback to physicians. The diabetes mellitus patients are generally treated with many pharmacological agents. In addition to the blood glucose control, treatment of concurrent illnesses and cardiovascular protective agents generally leads to poly pharmacy and the chance to drug related problems in the prescriptions

Oral Anti-hyperglycemic Agents[5,6]

The alarming spread and rising incidence prompted the formulation of guidelines by a reputed organization like the Indian Council Of Medical Research (ICMR) in collaboration with WHO and ratified by a team of experts in the field.

The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes recommends a target hemoglobin A1c concentration of 7.0% or less for all patients with diabetes and, for those in whom it can be safely achieved, a target hemoglobin A1c concentration in the normal range (usually < 6.0%) .Although no pharmacologic therapy (e.g., diet, exercise and weight loss) remains a critical component in the treatment of diabetes, pharmacologic therapy is often necessary to achieve optimal glycemic control.

Orally administered Anti hyperglycemic agents (OHAs) can be used either alone or in combination with other OHAs or insulin. In the absence of contraindications, metformin should be preferred over other agents for a number of reasons. Compared with insulin secretagogues in general, metformin has equal potency and a low risk for hypoglycemia and causes less weight gain. In obese patients, there is strong clinical evidence of reduced micro vascular and macro vascular outcomes. In the presence of contraindications or intolerance to Metformin or when metformin alone does not result in optimal control, thiazolidinedione's should be used

Combination Therapy in Type 2 Diabetes[7]

The UKPDS (United Kingdom Prospective Diabetes Study) confirmed what was already evident to most Physicians in type 2 Diabetes i.e. eventually most patients will not be able to maintain glycemic control with a single agent. Diabetes is a chronic progressive disorder. The progression of diabetes results from a vicious cycle of insulin resistance and p-cell failure. Excess circulating glucose in turn itself is damaging to the p- cell (Commonly referred to as glucotoxicity) and may further Diabetes is a chronic progressive disorder. The progression of diabetes results from a vicious cycle of insulin resistance and β cell failure. Excess circulating glucose in turn itself is damaging to the β cell (Commonly referred to as glucotoxicity) and may further accelerate the progression of the disease. Thus, loss of β-cell function is inevitable in patients with diabetes regardless of the treatment modality8. The UKPDS indicated that by 6 years after the diagnosis of diabetes more than half of the patients needed more than 1 pharmacological agent to maintain glycemic control. Pharmacological agent to maintain glycemic control.

Rationale behind the combination of a Sulfonylurea and Metformin[8,9]

Sulfonylurea and Metformin have different mechanisms of action. Sulfonylurea mainly decrease blood glucose levels by stimulating insulin release from the pancreatic β cells whereas Metformin reduces blood glucose levels predominantly by improving hepatic and peripheral tissue sensitivity to insulin i.e. decreases hepatic and peripheral insulin resistance by decreasing affinity of insulin receptors towards insulin and by increasing the number of insulin receptors. Thus, decreases hyperinsulinemia. Decreases hepatic gluconeogenesis thereby decreasing high glucose output. Reduces intestinal absorption of glucose. Reduces blood glucose levels (fasting and post-prandial). Decreases weight thereby improves insulin resistance. Metformin also has beneficial effects on serum lipid levels and fibrinolytic activity, thereby decreasing the cardiovascular risk. Because of their complementary mechanisms of action, combination therapy with sulfonylurea and Metformin -is rational and is associated with additive beneficial effect on the glycemic control.

MATERIALS AND METHOD

A prospective observational study was carried out for the duration of six months among the patients under inclusion criteria[10]. All the patients above 45 years of age of either sex and the patients admitted in the medicine ward were included in the study. For data collection and documentation Patient profile form

was designed which includes information on patients demographic details (e.g. (e.g. Patient's Name, Age, Sex, educational status, employment, date of admission and date of discharge), presenting complaints, provisional/confirmed diagnosis, social history, past medical/medication history, current medications, discharge medications, laboratory test reports.

The collected data were analyzed by using SPSS Software.

RESULTS AND DISCUSSION

A total of 38 diabetes mellitus patients were enrolled in the study, out of which 65.79% were Males and 34.21% were Females.

Table: 1 Sex Group of Patients

S.No.	Sex	No. of Patients	Percentage (%)
1	Male	25	65.79
2	Female	13	34.21

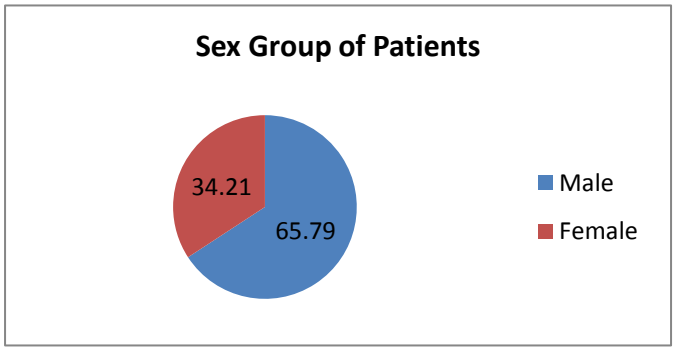

Figure 1 Sex Group of Patients

In this study middle age group people were found more. Above 45 years were maximum in number. The mean age 56 ± 12 year were observed in study group. which is shown in Table 2 and Figure 2 denote the Age group of patients.

In this study n = 22 (57.89%) were non-vegetarians and n = 16 (42.11%) were taking vegetarian food. Which is shown in Table 3 and Figure 3 gives the idea about food habits.

Patients are categorized based on diabetic family background & non-diabetic family. n = 21 (55.26%) patients were observed under category of having known family history of diabetes in their family. which is shown in Table 4 and Figure 4 indicate Family history of diabetic patients. n

=17 (44.74%) patients were observed from non-diabetic family history. Diabetes duration were observed (5.5 ± 3.5) years.

Table: 2 Age Group of Patients

S. No.	Age group	No. of Patients	Percentage (%)
1	41-45	3	07.89
2	46-50	9	23.68
3	51-55	9	23.68
4	56-60	8	21.05
5	61-65	8	21.05
6	66-70	1	02.63

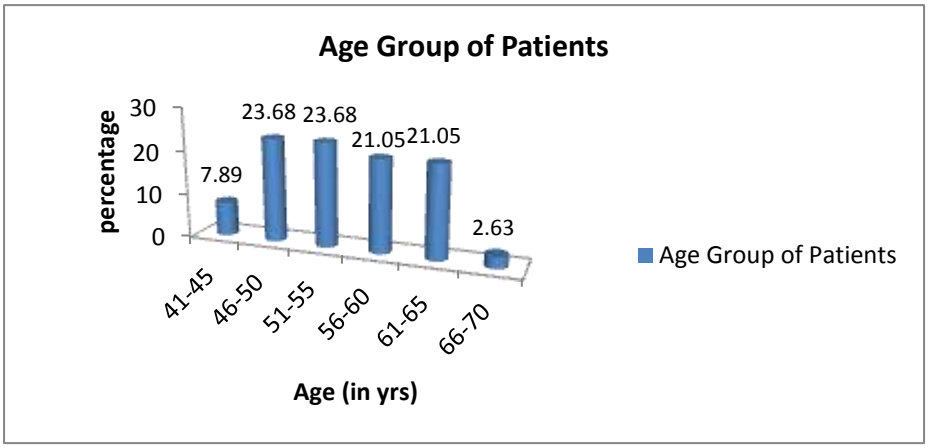

Figure: 2 Age Group of Patients

Table 3 Food habits of patients

S. No.	Food Habit	No. of Patients	Percentage (%)
1	Vegetarian	16	42.11
2	Non-vegetarian	22	57.89

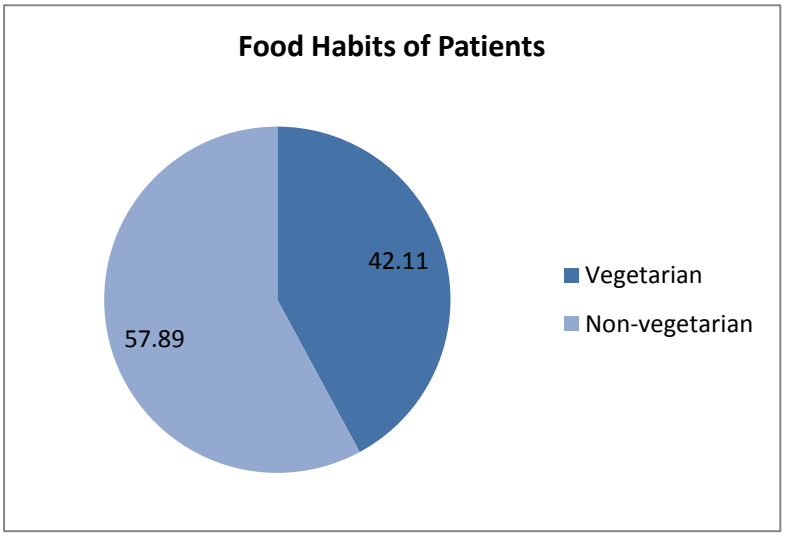

Figure: 3 Food Habits of Patients

Table: 4 Family Histories of Diabetes Patients

S. No.	Family History	No. of Patients	Percentage (%)
1	Non-Diabetic family	17	41.74
2	Diabetic family	21	55.26

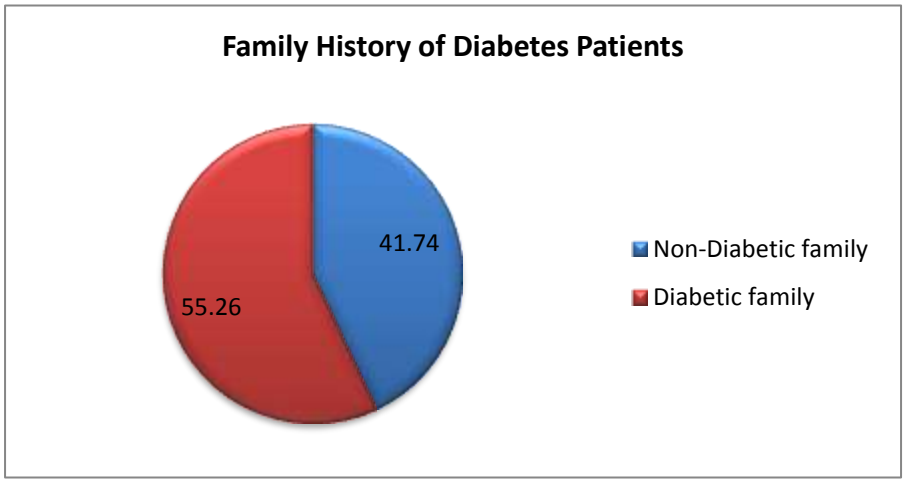

Figure: 4 Family History of Diabetes Patients

Table : 5 Patients receiving combination therapy

S. No.	Combination therapy	No. of Patients	Percentage (%)
1	Glibenclamide+ Metformin	23	60.53
2	Glimepiride+ Metformin	15	39.47

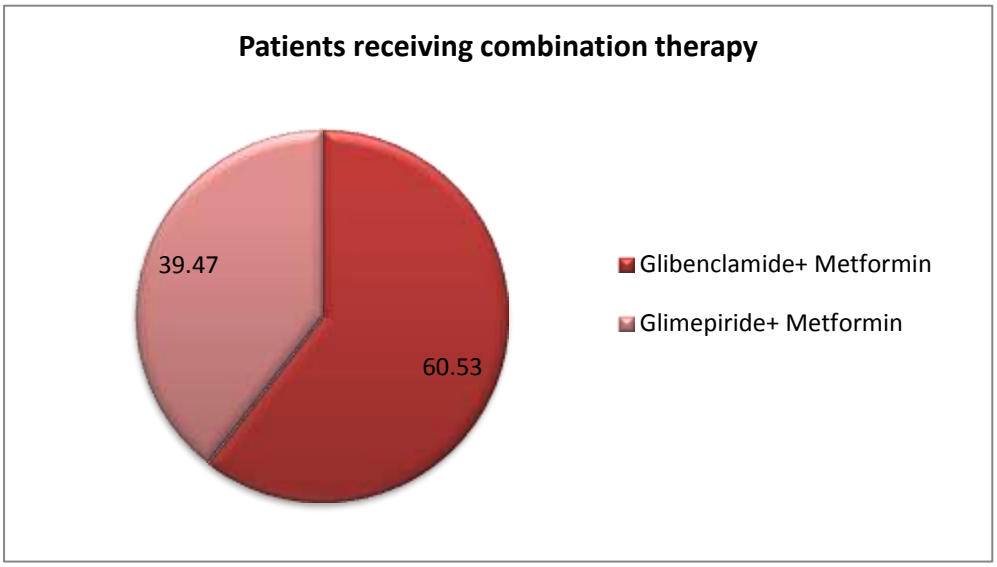

Figure: 5 Patients receiving combination therapy

During the study n = 23 (60.53%) patients were receiving Glibenclamide plus Metformin combination therapy; whereas rest of patients (39.47%) were receiving Glimepiride plus Metformin combination therapy. which is shown in Table 5 and Figure 5 signify the number of patients receiving the two varied combination therapy.

Table 6 (A) The effect on fasting plasma glucose (FPG) after every month (n = 23) of Glibenclamide plus Metformin combination therapy. In the whole group mean FPG decreased during the therapy significantly, from 193 ± 51 to 163 ± 45 mg/dL.

Table 6(B) shows mean changes that occurred in FPG after every month. A Significant positive correlation was noted between baseline & FPG change.

Table 6 (C) Glimepiride plus Metformin combination therapy effect on fasting plasma glucose (FPG) after every month, (n = 23). In the whole group mean FPG decreased during the therapy significantly, from 201 ± 56 to 157 ± 54 mg/dL. significantly, from 201 ± 56 to 157 ± 54 mg/dL.

Table 6 (D) Shows mean changes in FPG after every month. A Significant positive correlation was noted between baseline & FPG change. At the end of study, the decrease in fasting plasma glucose Concentration was -40.97 ± 14.46 mg/dL.

Figure 6 (A) Sulfonylurea plus Metformin combination therapy effect on (FPG) after every month. In the Glibenclamide plus Metformin combination therapy (n = 23) group FPG decreased during the treatment significantly up to -49.06 mg/dL during the 6 months of study period. In the Glimepiride plus Metformin combination therapy I (n = 15) group FPG decreased during the therapy significantly up to Concentration was -40.97 ± 14.46 mg/dL.

Figure 6 (B) Mean change in (FPG) at the end of 4 months; In Glibenclamide plus Metformin combination therapy change occurred up to -30 mg/dL. In Glimepiride plus Metformin combination therapy change occurred up to •44 mg/dL.

Table 7 (A) Shows that patients receiving Glibenclamide plus Metformin combination therapy effect on Glycosylated Hemoglobin (HbA1c) after every month (n = 23). In the whole group mean (HbA1c) decreased during the treatment significantly from 9.2 ± 0.8 to 8.2 ± 1.5 %.

Table 7 (B) Shows that changes occurred in (HbA1c) after every month. A Significant positive correlation was noted between baseline & FPG change. At the end of study the decrease in (HbA1c) concentration was -0.56 ± 0.34 % (i.e. -0.22 to -0.90 %).

Table 7(C) Shows that the patients receiving Glimepiride plus Metformin combination therapy effect on (HbA1c) after every one month. (n= 15). In the whole group mean (HbA1c) decreased during the therapy significantly, from 9.5 ± 1.2 to 7.85 ± 1.25 %.

Table 7 (D) Shows mean changes occurred in (HbA1c) after every month. A Significant positive correlation was noted between baseline & FPG change. At the end of study, the decrease in (HbA1c) concentration was -0.75 ±0.53%.

Figure 7 (A) Refers to effect on (HbA1c) at 4 months; in those patients receiving Sulfonylurea plus Metformin combination therapy. In the Glibenclamide plus Metformin combination therapy (n »

23) group (HbA1c) decreased during the therapy significantly; up to -0.90 % in 4 months of study period. to -1.28% in 4 months of study period.

Figure 7 (B) Refers to mean change in (HbA1c) during the 4 months; In Glibenclamide plus Metformin combination therapy change occurs up to 1.0 % (n - 23).In Glimepiride plus Metformin combination therapy change occurs up to 1.65% (n = 15).

Table 8 Signify that Sulfonylurea plus Metformin combination therapy distribution of (HbA1c) at the end of study. In this study patients were categorized in 4 groups based on their (HbA1c) level at the end of study period. In Glimepiride combination therapy more patients were observed those having < 8% of HbA1c (60.00 %) as compared to Glibenclamide combination therapy (39.13%).

Table 9 Change in Lipid Profile. Significant positive correlations were noted between baseline lipid profile. In whole group of this study reduction in total and LDL cholesterol occur significantly, but the reductions in these variables are relatively small.

Table 10 Change in Body mass index (BMI). In the Glibenclamide combination therapy group mean BMI decreased during the treatment significantly, from 30.21 ± 5.01 to 30.54 ±5.18. In the Glimepiride combination therapy group mean BMI decreased during the treatment significantly, from 30.79 ± 3.18 to 30.11 ± 2.68. In this study those patients having higher BMI at baseline showed minute reduction in BMI at end of study period; specially shown in obese patients.

Table : 6 (A) Glibenclamide plus Metformin combination therapy effect on FPG (mg/dL) after every month.

Pt .No		Monthly reading of FPG during study (mg/dl)			
	Before	1	2	3	4
1	219	190	189	162	154
2	237	210	191	182	190
3	208	192	168	180	169
4	239	195	181	175	178
5	241	222	191	170	152
6	244	209	187	191	207
7	197	187	160	139	119
8	231	199	184	174	186
9	201	189	172	151	124
10	193	178	161	152	146
11	167	140	133	120	119
12	232	210	193	200	208
13	220	211	193	189	200
14	149	141	119	127	130
15	163	151	141	143	121
16	189	173	159	144	134
17	174	161	142	121	123
18	157	149	136	127	118

19	239	218	201	182	196
20	142	121	118	109	118
21	211	197	173	151	139
22	204	190	192	174	165
23	198	179	148	135	138

Table: 6 (B) Mean changes occur in FPG after every month

S. No.	Combination therapy	months	Change in FPG (mg/dL)
1	Glibenclamide+ Metformin	1	-19.58
2		2	-36.10
3		3	-46.28
4		4	-49.06

Table: 6 (C) Glimepiride plus Metformin combination therapy effect on FPG (mg/dL) after every month

Pt. No	Monthly	reading of FPG during study (mg/dl)			
	before	1	2	3	4
24	170	152	130	119	107
25	156	125	117	102	104
26	189	178	161	141	110
27	254	219	200	202	194
28	256	232	219	210	211
29	145	136	121	109	104
30	210	194	163	127	119
31	240	210	187	174	170
32	201	181	161	150	141
33	179	147	139	110	111
34	204	178	196	189	178
35	193	162	151	140	146
36	257	211	201	193	204
37	247	201	239	211	207
38	148	117	102	114	103

Table: 6(D) Mean changes in FPG after every month.

S. No.	Combination therapy	months	Change in FPG (mg/dL)
1	Glimepiride+ Metformin	1	-26.51
2		2	-36.72
3		3	-49.97
4		4	-55.44

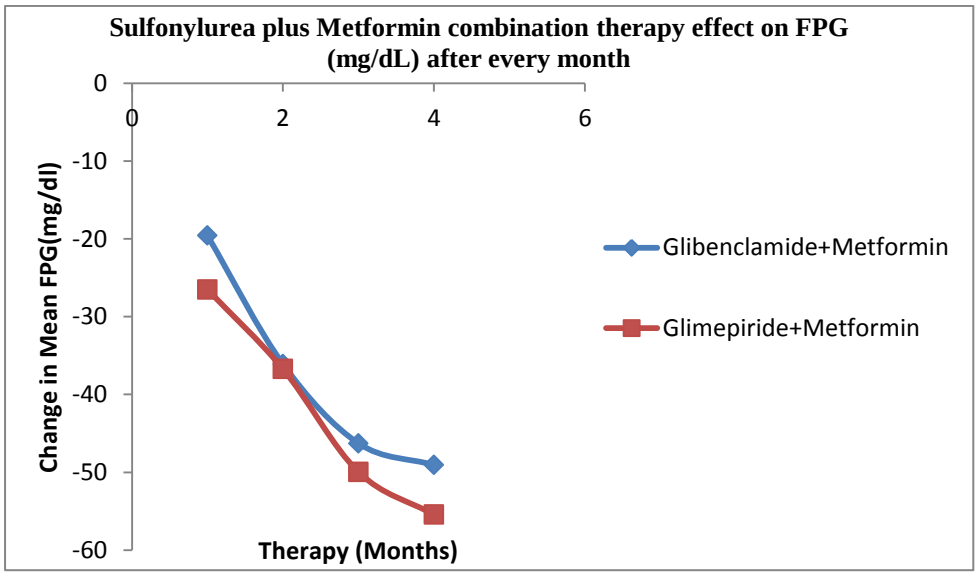

Figure 6 Sulfonylurea plus Metformin combination therapy effect on FPG (mg/dL) after every month

Table : 7 (A) Patients receiving Glibenclamide plus Metformin combination therapy effect on HbA1c (%) after every month.

Pt. No	Monthly reading of FPG during study (mg/dl)				
	before	1	2	3	4
1	9.1	8.9	8.5	8.2	7.9
2	9.7	9.6	9.4	9.0	8.7
3	8.9	8.8	8.6	8.6	8.4
4	9.6	9.7	9.3	9.2	9.0
5	9.4	9.0	9.4	9.2	8.8
6	10.0	9.9	9.7	9.4	9.5
7	8.6	8.2	8.0	7.6	7.8
8	9.9	9.9	9.4	9.0	9.1
9	8.9	8.7	8.4	7.9	7.8
10	8.9	8.9	8.7	8.4	8.0
11	8.4	8.0	7.8	7.2	6.7
12	10.0	9.8	9.8	9.6	9.7
13	10.0	10.0	9.6	9.3	9.1
14	9.0	9.0	9.2	8.8	8.4
15	9.2	9.1	9.0	8.7	8.9
16	9.8	9.4	9.0	8.9	8.6
17	8.7	8.3	8.2	8.4	8.0
18	8.8	8.4	8.2	8.0	7.9
19	10.0	9.9	9.5	9.1	9.2
20	8.6	8.2	7.8	7.4	6.9
21	9.7	9.4	9.0	8.7	8.8
22	9.6	9.6	9.2	9.0	8.7
23	9.1	8.9	8.6	8.2	8.0

Table: 7 (B) Mean changes in HbA1c after every month

S. No.	Combination therapy	months	Change in HbA1C(%)
1	Glibenclamide+ Metformin	1	-0.22
2		2	-0.45
3		3	-0.73
4		4	-0.90

Table : 7 (C) Patients receiving Glimepiride plus Metformin combination Therapy effect on HbA1c (%) after every month.

Pt. No	Monthly change in HbA1C (%)				
	before	1	2	3	4
24	8.9	8.4	7.9	7.3	6.9
25	8.4	8.2	7.9	7.6	6.6
26	8.9	8.1	7.8	7.4	7.7
27	9.4	9.1	8.9	8.5	8.0
28	10.2	10.1	9.8	9.4	9.1
29	8.3	8.4	8.2	8.0	7.9
30	9.7	9.2	9.0	8.5	7.9
31	10.1	9.9	9.5	9.2	8.9
32	10.0	9.8	9.4	9.0	8.7
33	8.6	8.6	8.3	7.9	7.5
34	9.9	9.5	9.2	9.0	8.8
35	8.9	8.8	8.4	8.0	7.8
36	10.7	10.2	9.8	9.5	9.0
37	9.8	9.7	9.2	8.7	8.3
38	8.7	8.4	8.0	7.9	7.7

Table : 7 (D) Mean changes in HbA1c after every one month.

S. No.	Combination therapy	months	Change in HbA1C (%)
1	Glimepiride+ Metformin	1	-0.22
2		2	-0.57
3		3	-0.88
4		4	-1.28

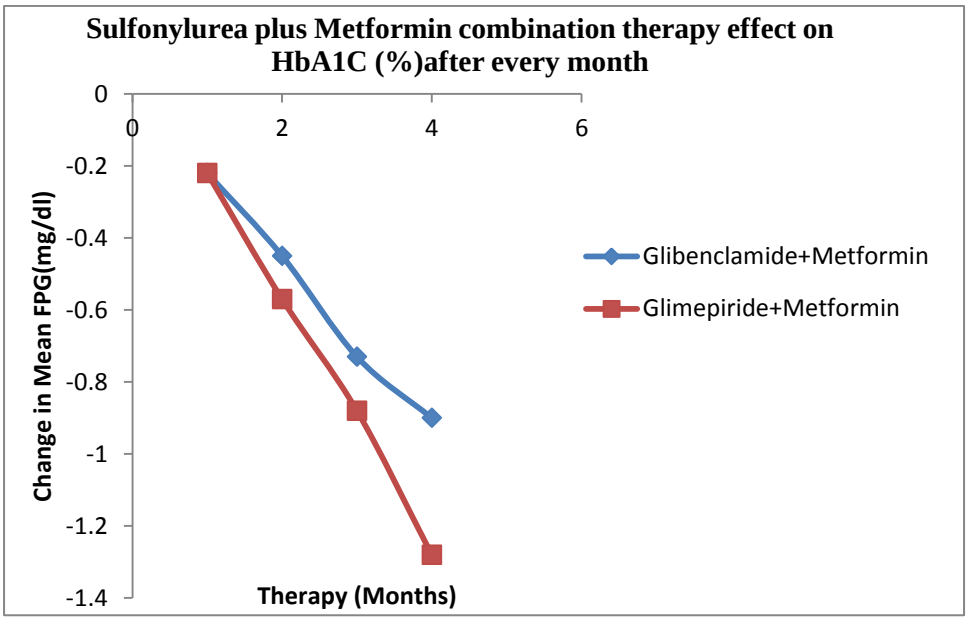

Figure: 7 Sulfonylurea plus Metformin combination therapy effect on HbA1C (%) after every month.

Table: 8 Sulfonylurea plus Metformin combination therapy distribution of HbA1c (%) at end of study (4 Months).

S. No.	Distribution of HbA1c (%)	Glibenclamide+ Metformin Patient group (%)	Glimepiride+ Metformin Patient group (%)
1	<7.00	08.70	13.33
2	7.0-8.0	30.43	46.67
3	8.1-9.0	39.13	26.67
4	>9.00	21.74	13.33

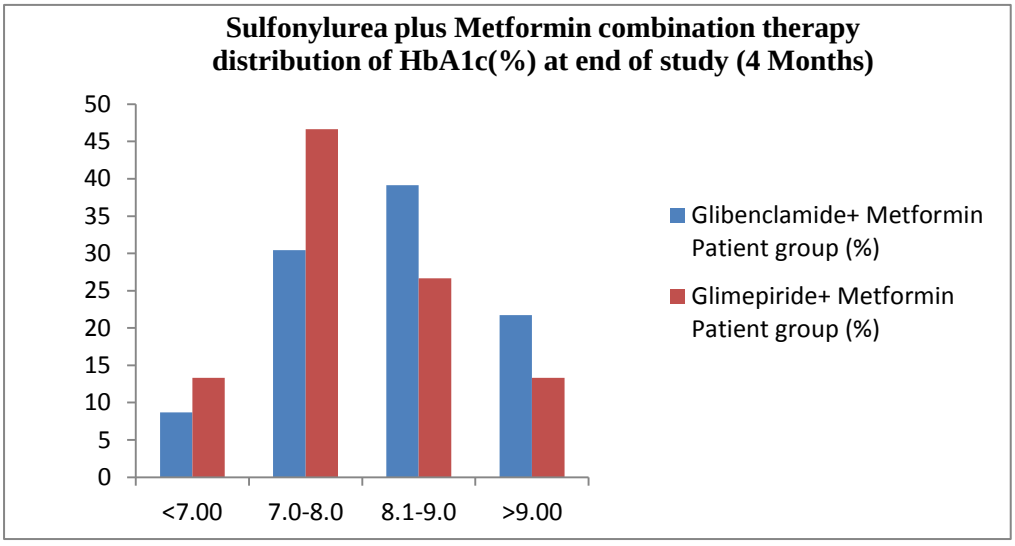

Figure 8: Sulfonylurea plus Metformin combination therapy distribution of HbA1c(%) at end of study (4 Months)

Table: 9 Change in Lipid Profile

S.No	CHOl	TG'S	HDL	VLDL	LDL	TCH/ HDL	CHOl	TG'S	HDL	VLDL	LDL	TCH/ HDL
1	198	117	45	17	145	5.0	194	110	49	19	147	5.0
2	228	230	32	19	140	5.7	220	210	39	22	132	5.5
3	234	235	32	09	145	6.2	230	232	37	07	140	6.1
4	219	214	27	17	141	5.1	210	207	29	19	134	5.1
5	186	109	45	29	82	3.9	183	100	49	27	80	3.8
6	215	154	52	29	98	4.5	209	149	49	34	82	4.6
7	223	186	37	15	151	5.3	212	174	41	18	144	5.1
8	209	227	34	11	141	5.5	202	229	37	17	140	5.5
9	229	235	30	09	145	5.9	209	216	37	15	139	5.6
10	212	175	30	18	96	4.4	209	176	33	24	92	4.4
11	228	230	32	12	140	5.8	210	224	38	23	135	5.6
12	220	198	30	13	142	5.8	212	190	36	27	140	5.6

Table: 10 Change in Body mass index (BMI)

Pt.No	**Body Mass Index (BMI)**	
	Before study	After study
1	35.22	35.71
2	33.26	31.77
3	27.41	27.57
4	29.97	29.52
5	31.31	31.07
6	27.83	27.61
7	30.08	30.24
8	28.48	27.41
9	28.76	28.62
10	26.86	25.97
11	28.11	27.75
12	27.62	27.42
13	28.76	28.43
14	27.41	27.28
15	27.88	27.58
16	25.20	25.36
17	31.25	31.03
18	31.36	32.15
19	30.61	30.26
20	31.76	32.38
21	33.65	34.76
22	32.18	33.13
23	32.33	31.58
24	29.49	28.95
25	31.76	32.63
26	33.96	33.58
27	32.18	32.79
28	28.19	27.88
29	29.86	29.59

30	31.95	31.05
31	30.60	29.90
32	32.39	31.78
33	28.38	28.79
34	32.18	31.41
35	30.76	30.50
36	29.00	28.25
37	32.00	32.66
38	27.62	27.42

CONCLUSION

The study have shown that majority of the patients with type 2 diabetes in Guntur City Hospital were managed with Combination therapy. Combination therapy with Metformin plus Glimepiride is more effective than Glibenclamide plus Metformin; in improving glycemic control in type 2 diabetes, while also allowing a reduction of the dosage of each drug. The findings of this study suggest that Metformin plus Glimepiride combination therapy is beneficial adjunct to diet/exercise in management of type 2 diabetes mellitus. At the end of study, In Glimepiride combination therapy more patients were observed those having < 8% of HbA_1C (60.00 %) as compared to combination therapy (39.13 %). The findings of this study are expected to provide relevant and useful feedback to physicians.

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