A Study comparing the efficacy and safety of Metformin-Pioglitazone versus Metformin-Glimepiride in Type 2 Diabetes mellitus.

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Abstract: *Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Many trials have demonstrated that each percentage point reduction in HbA1c was associated with a 35% reduction in micro vascular complications.A combination of Metformin-Pioglitazone versus Metformin-Glimepiride was compared for better selection of drugs to reduce HbA1c, FBS and PPBS.Two groups, group A (Metformin-Pioglitazone) and Group B (Metformin-Glimepiride) each with 30 patients for 6 months were selected. After 6 months of therapy levels of HbA1c, FBS and PPBS levels were estimated and compared with baseline values.The percentage drop in the mean HbA1c in group A and group B were 20.07% and 21.49% respectively. The percentage drop in the mean FBS in group A and group B were 27.7% and 30.5% respectively. The percentage drop in the mean PPBS in group A and group B were 25.3% and 26.7% respectively.Weight gain was more in group A whereas number of hypoglycemic episodes were more in group B; both statistically not significant(p>0.05). There is better glycaemic control in group B than group A which was statistically significant (p<0.05).*
Key words*: FBS, Glimepiride, HbA1c, Metformin, Pioglitazone, PPBS.*

I. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1, 2]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels [3].It is an endocrine disorder, more than 100 million (6% of the population) of people world-wide are affected in spite of enormous facilities available to control its growth [4]. Type 2 diabetes is caused by two primary metabolic defects: progressive pancreatic β-cell dysfunction and insulin resistance [5]. β-Cell dysfunction superimposed on insulin resistance leads to hyperglycemia and subsequently to type 2 diabetes. Typically, at the time of diabetes diagnosis, nearly 50% of β-cell function has been lost and less than 60% of normal insulin sensitivity is present [6].

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications [7]. The UK Prospective Diabetes Study and other trials have demonstrated that each percentage point reduction in A1Cwas associated with a 35%reduction in micro vascular complications [8].

The guiding principle in the management of patients with type 2 DM is to correct the metabolic defects of carbohydrate and lipid metabolism to normal or near normal [9].The lifestyle modification, diet and exercise of moderate intensity are used to improve insulin sensitivity and are recommended as an integral part of treatment of type 2 diabetes [10].When the lifestyle modification, diet and exercise fails to maintain the adequate glycaemic control, oral hypoglycemic agents are introduced as a treatment approach [5,6].

Oral Hypoglycemic Agents (OHAs) can be used either alone or in combination with other OHAs or insulin. Currently, there are different classes of oral anti diabetic agents: sulfonylureas – insulin secretagogues that target β -cell dysfunction; metformin – a biguanide that reduces hepatic glucose production and improves insulin sensitivity, thiazolidinediones – insulin sensitizers that lower peripheral insulin resistance; α -glucosidase inhibitors – intestinal enzyme inhibitors that slow carbohydrate absorption; and meglitinides – rapid but short-acting, non sulfonylurea secretagogues ; GLP-1 analogs and DPP-4 inhibitors [11,12].

It has been suggested that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy. The early use of an insulin-sensitizing agent either alone or in combination is expected to improve both acute and long-term outcomes in patients with type 2 diabetes [13].

II.   Objectives Of The Study

2.1 To compare the efficacy and safety of metformin plus pioglitazone versus metformin plus glimepiride in patients with type 2 diabetes mellitus.

2.2 To compare the adverse effects in each group.

III.   Material And Methods

The present study was carried out on patients with Type 2 diabetes mellitus attending the Medicine department of GOVERNMENT GENERAL HOSPITAL, RANGARAYA MEDICAL COLLEGE, KAKINADA. The protocol regarding the present study was submitted to the Institutional Ethics Committee and the permission was taken before starting the study. Written informed consent was taken before enrollment.

3.1 Inclusion Criteria
1.   Patients diagnosed with Type 2 diabetes mellitus with HbA1c>7%to<9%,
2.   Age   40-70 years of both sexes,
3.   Body Mass Index (BMI) 25-30kg/m^2.

3.2 Exclusion Criteria
1.   Patients with Type 1 diabetes mellitus,
2.   Systolic blood pressure >170mm of Hg,
      Diastolic blood pressure>100 mm of Hg.
3.   Clinically significant renal or hepatic impairment,
4.   Any cardiac complications like congestive heart failure, Unstable/severe angina and coronary insufficiency,
5.   Any pregnant and lactating women,
6.   Chronic systemic illness,
7.   Chronic treatment with corticosteroids,
8.   Patients not willing to participate.

3.3 Methodology
63 patients fulfilling the inclusion criteria were chosen for the study (3 of the patients were lost for follow up). Out of these 60 patients, all the patients were randomly divided into two groups. Group A (metformin and pioglitazone) (1000/2mg) and group B (metformin and glimepiride) (1000/15mg).

At the time of enrollment into the study, the patients were subjected to thorough clinical examination and necessary baseline investigations were recorded. The patients were observed for weight, height and blood pressure measurement. The records of age, sex, family history and other possible associated diseases were also maintained. The records of the weight and height are helpful for the determination of body mass index. The patients were also interviewed for their initial sign and symptoms. The necessary baseline investigations were recorded(Fasting Blood Sugar,2 hr Post Prandial Blood Sugar,HbA1c,blood urea ,serum creatinine, urine routine, Electrocardiogram, Liver function tests). The study was carried out for a period of 24 weeks.

Dietary modifications were added and the patients were advised to continue the same diet that was advised. The patients were informed regarding the possibility of hypoglycemia and were educated about the recognition and treatment of hypoglycemic symptoms. Follow up measurements of FBS, 2 hr PPBS, weight gain, number of hypoglycemic episodes were done at every month interval till 24 weeks. HbA1c was repeated at the end of the study (i.e. at 6th month).

IV.   Efficacy And Safety Evaluations
The primary efficacy variable was the change in HbA1C from baseline to 6th month. Secondary efficacy outcomes included changes in fasting plasma glucose, 2-hr postprandial plasma glucose levels from baseline to 6 month after randomization of the patient into the study. Safety outcomes included adverse events, particularly hypoglycemic symptoms and changes in body weight. The patients were interviewed and asked for any type of adverse events throughout the study. The patients were specially asked for the hypoglycemic symptoms. The daytime hypoglycemic episodes are usually recognized by sweating, nervousness, tremor, and hunger while night time hypoglycemia may be without symptoms or manifest as night sweats, unpleasant dreams, or early morning headache. Any changes in body weight were also noted.

4.1Estimation of blood glucose
Estimation of blood glucose was performed by glucose oxidase peroxidase method using a HITACHI analyzer 902.

4.1.1 Principle

A hemolysed preparation of the whole blood is mixed continuously for 5 minutes with a weak binding cation exchange resin. During this time Hb A binds to the resin. After the mixing period, a filter is used to separate the supernatant containing the glycohemoglobin from the resin, where the labile fraction is eliminated; hemoglobin's are retained by a cationic exchange resin.

The glycohemoglobin percent is determined by measuring the absorbance's at 415 nm of the glycohemoglobin fraction and the total hemoglobin fraction. The ratio of the two absorbance's gives the percentage glycohemoglobin.

Haemolysed whole blood + cation exchange resin→HbA1a, 1b, 1c

4.1.2 Procedure
A) Hemolysate preparation`

100 µL of blood is added to 500 µL of lysing reagent, mixed well and allowed it to stand for 5 minutes till lysis is completed. The hemolysate is used for further assay.The hemolysate preparation is shown in TABLE-1.

Table -1 Hemolysate preparation

	Calibrator	Test
Lysing reagent	500 µL	500 µL
Calibrator	100 µL	-----
Whole blood	----	100 µL

B) Separation of glycohemoglobin

100 µL of the hemolysate is added into the ion exchange resin tubes. Filter separator is placed approximately 2 cm above the liquid level in the tube. The tube is kept on the mixer and mixed well. The filter separator is pushed until the resin is firmly packed .the supernatant is separated, read the absorbance at 415mm against water blank.

C) Total hemoglobin fraction

Mixed well and the absorbance of calibrator and sample are read at 415 nm for total hemoglobin readings. (TABLE-**2**)

Table-2 shows the quantities to be added the preparation.

	Calibrator	Test
Deionized water	5.0 ml	5.0ml
Calibrator	20 µL	-----
Sample hemolysate	----	20 µL

D) Calculation

$$Rc = \frac{Absorbance \ of \ calibrator \ (glycol \ )}{Absorbance \ of \ calibrator \ (total \ )}$$

$$Ru = \frac{Absorbance \ of \ unknown \ (glycol \ )}{Absorbance \ of \ unknown \ (total \ )}$$

% glycohemoglobin of unknown $= \frac{Ru}{Rc} \times$ Value of calibrator.

4.1.3 HbA1c values
The ranges of HbA1c in relation to diabetes are shown in TABLE-3.

Table-3 HbA1c values in relation to diabetes.

Non diabetic level	<6%
Excellent control	6-7%
Good control	7-8%
Fair control	8-9%
Poor control	>9%

4.2 Estimation of weight gain:
Estimation of weight gain was done using an electronic weighing machine.

4.3 Laboratory tests include
1. Blood sugar estimation-fasting (FBS) and 2 hr postprandial(PPBS),
2. HbA1c estimation,
3. Blood urea estimation,
4. Serum creatinine,
5. Urine routine,
6. Liver function tests,
7. Electrocardiogram.

4.4 Statistical analysis
The data is presented as mean ±S.D .The two groups are compared using student t test. The significance between groups is tested with GRAPHPAD INSTAT 3 software. The variables compared are fasting blood sugar, postprandial blood sugar, glycated hemoglobin, weight gain, frequency of hypoglycemic episodes.

V.   Results

All the results are compared between the 2 groups:

Group A -   Metformin-Pioglitazone
Group B -   Metformin - Glimepiride

5.1 Demographic Parameters Comparison in Two Groups
5.1.1 Age

The mean age group of group A is 55.4 years. (Range of 40 to 70 years).The mean age group of group B is 53.5 years (range of 40 to 70 years).

In both the groups no statistical difference is noted in the mean age group where p value is 0.3943 (p>0.05 so not significant) and the patients are comparable in relation to their mean age group. This data is represented in Table-4 and Fig-1.

Table – 4 represents the mean age group in two groups.

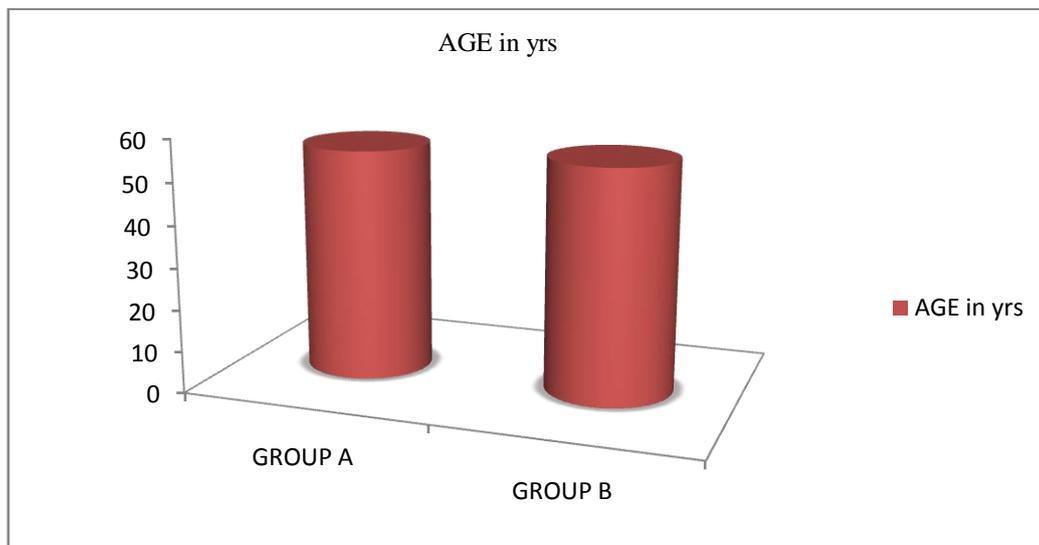| GROUPS	AGE (yrs) Mean± S.D
Group A	55.4±7.85
Group B	53.5±8.05

Fig -1 represents the mean age group in two groups.

5.1.2 Gender distribution

Out of 30 patients in group A, 18 are males and 12 are females. In group B, Out of 30 patients, 17 are males and 13 are females. There was no major gender difference in between the groups. This data is represented in TABLE-6 and Fig-2.

Table – 6 represents gender distribution in the two groups.

GROUP	SEX	
	MALE	FEMALE
Group A	18	12
Group B	17	13

Fig–2 represents gender distribution in the two groups.

5.2 Anthropometric Measurements Comparison In Two Groups
5.2.1 Body Mass Index

The mean body mass index of group A is 27.82±1.18 (S.D). The mean body mass index of group B is 28.16 ± 1.33 (S.D). In both the groups no statistical difference is noted where $p > 0.05$ (not significant) and the two groups are comparable in relation to the mean body mass index. This data is represented in TABLE-6 and Fig-3.

Table – 6 represents the mean body mass index in the two groups.

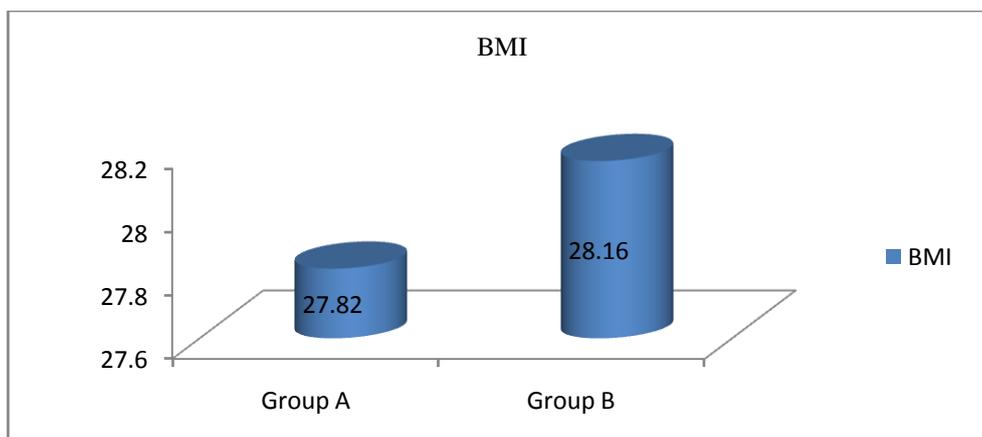| GROUP	BMI
	Mean± S.D
Group A	27.82±1.18
Group B	28.16±1.33

Fig – 3represents the mean body mass index in the two groups.

5.3 Laboratory Blood Investigations Comparison In Two Groups

5.3.1 Fasting Blood Sugar (FBS)

The mean baseline FBS in group A and group B are 190.96±12.297 (S.D) mg/dl and 190.4 ±9.485 (S.D) mg/dl respectively. There is no significant difference where p> 0.5 (i.e. p=0.842) in the mean baseline FBS values between the two groups and they are comparable.

At the end of the study, the mean FBS at 24weeks in group A and group B are 138.03±6.201 (S.D) mg/dl and 132.33±7.298 (S.D) mg/dl respectively. So there is statistically significant (S) difference at the end of the study where p<0.05 (i.e. p= 0.003) between the two groups. This data is represented in TABLE 7 and Fig-4

Table -7 represents the mean fasting blood sugars in the two groups.

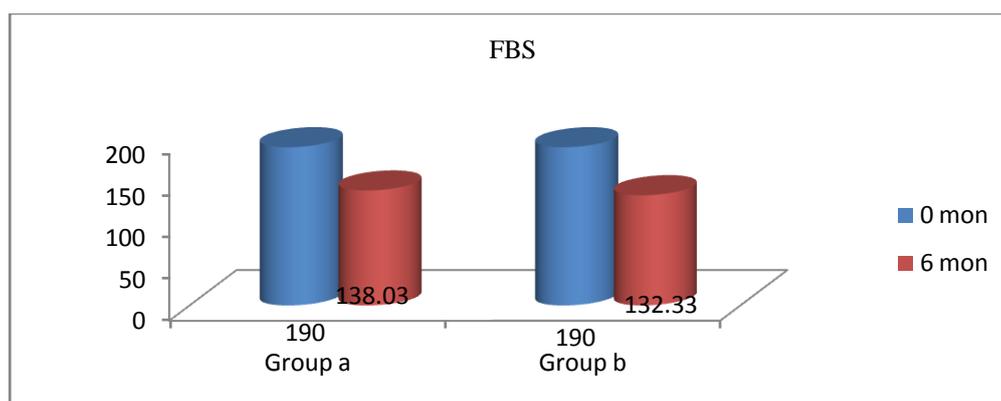| GROUP	FBS	
	BASELINE(0 MON)	AFTER 6 MON
	MEAN±S.D	MEAN± S.D
Group A	190.96±12.297	138.03±6.201
Group B	190.4±9.485	132.33±7.298
	t value=0.199 p value=0.842(NS)	t value=3.102 p value=0.003(S)

Fig -4 represents the mean fasting blood sugars in the two groups

5.3.2 Post Prandial (2hrs) Blood Sugar (PPBS).

The mean baseline PPBS in group A and group B are 263.2±23.425 (S.D) mg/dl and 254.16±28.572 (S.D) mg/dl respectively. The mean baseline PPBS are comparable in the two groups and there is no statistically significant difference between the two groups in relation to the mean baseline PPBS where p>0.05 (i.e. p= 0.1857).

At the end of the study, the mean PPBS values at 24 weeks in group A and group B are 196.53±20.316 (S.D) mg/dl and 184.93±93 (S.D) mg/dl respectively. There is statistically significant difference between the two groups at the end of the study where p < 0.05 (i.e. p= 0.026). This data is shown in TABLE-8 and Fig-5.

Table – 8 represents the mean post prandial blood sugars (PPBS) in the two groups

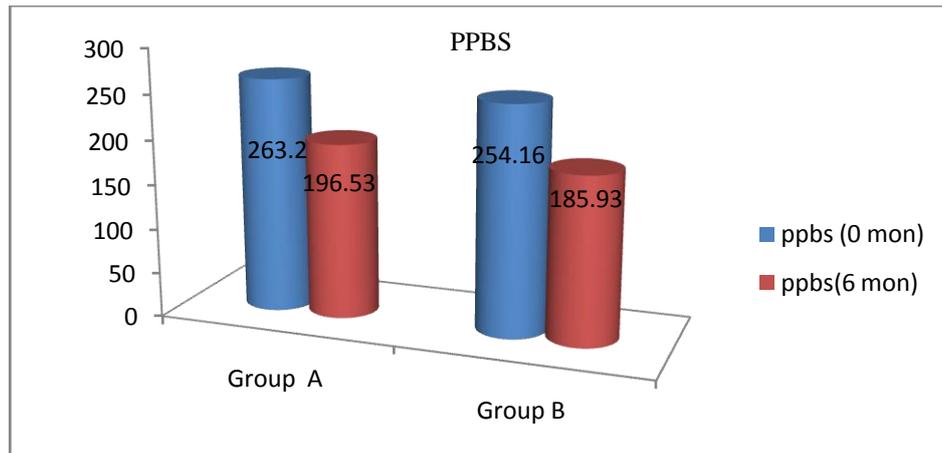| GROUPS	PPBS	
	BASELINE(0 MON)	AFTER 6 MON
	MEAN±S.D	MEAN± S.D
Group A	263.2±23.425	196.53±20.316
Group B	254.16±28.572	185.93±15.256
	t value=1.339 p value=0.1857(NS)	t value=2.285 p value=0.026(S)

Fig – 5 represents the mean post prandial blood sugars in the two groups

5.3.3   Glycated hemoglobin (HbA1c).

The mean baseline glycated hemoglobin values in group A and group B are 7.57±0.35   (S.D) % and 7.49±0.28 (S.D) % respectively. No statistically significant difference is noted between the two groups where p >0.05 (i.e. p=0.36) and both groups are comparable in relation to their mean glycated hemoglobin values.
At the end of the study, the mean glycated hemoglobin values at 6mon in group A and group B are 6.05±0.18 (S.D) % and 5.88±0.21 (S.D) % respectively. Statistical significance is observed between the two groups at the end of the study where p<0.05 (i.e. p= 0.0014). This data is represented in TABLE-9 and   Fig-6.

Table – 8 represents the mean glycated hemoglobin in the two groups.

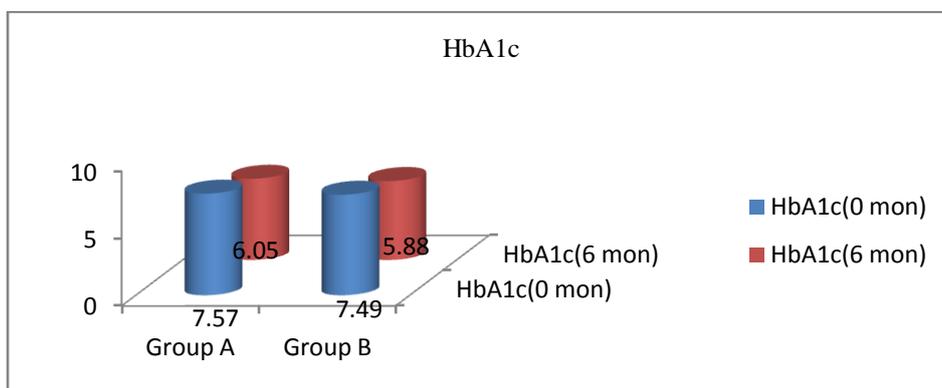| GROUPS	HbA1c	
	Baseline(0 MON)	After 6 MON
	Mean± S.D	Mean± S.D
Group A	7.57±0.35	6.05±0.18
Group B	7.49±0.287	5.88±0.216
	t value=0.9319 p value=0.36(NS)	t value=3.53 p value=0.0014(S)

Fig – 6 represents the mean glycated hemoglobin in the two groups

5.3.4   Changes in mean fasting blood sugar (FBS) in two groups

The mean FBS in Group A at 0 month is 190±9.49, decreased to 162.26±9.43 at 3rd mon and finally at 6th month was 132±7.29 mg/dl. The mean FBS in Group B at 0 month 190.96±12.29 decreased to 166.7±11.44 at 3rd month   and finally at 6th month was 138.03±6.21 mg/dl respectively. This data is represented in Table-10 and Fig-7(a).
Overall the mean drop in FBS in group A and group B are 58 mg/dl and 52.93 mg/dl respectively. The percentage drop in the mean FBS in group A and group B are 30.5% and 27.7% respectively. This data is represented in Fig-7(b).

Table – 10represents the mean FBS in the two groups during the entire study period.

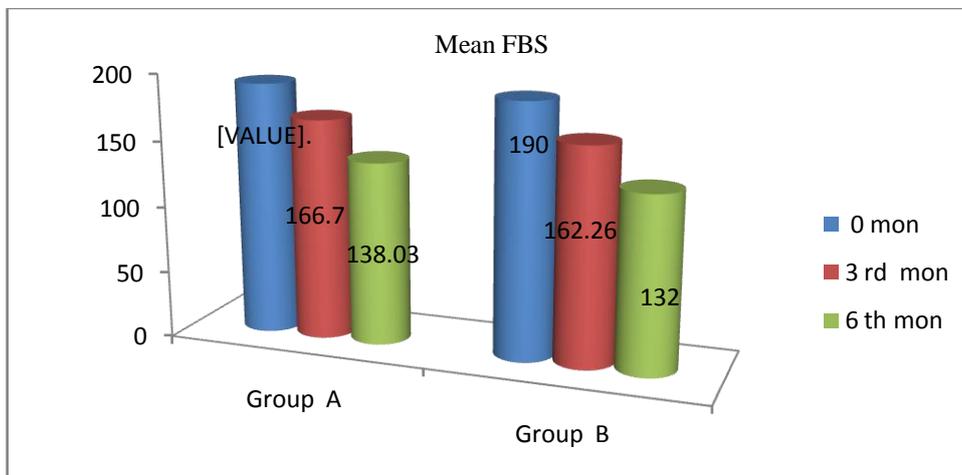| GROUPS	FBS Mean± S.D		
	BASELINE 0 month	3rd month	6th month
Group A	190±9.49	162.26±9.43	132±7.29
Group B	190.96±12.29	166.7±11.44	138.03±6.21

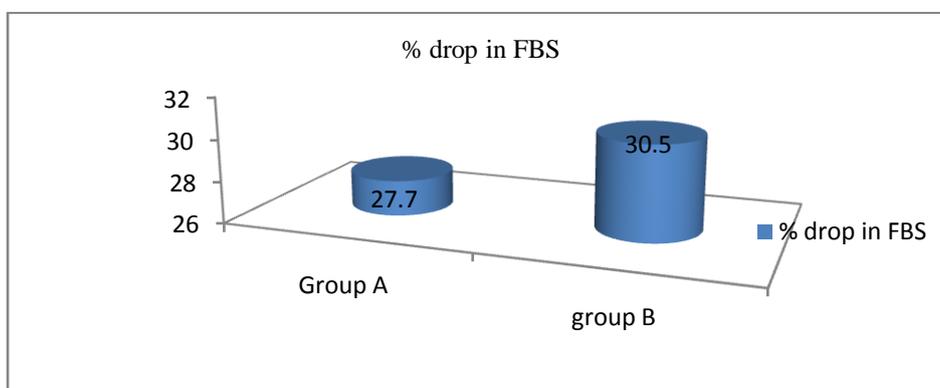Fig-7(a) represents the mean FBS in the two groups.

Fig-7(b) represents the percentage drop in FBS in the two groups.

5.3.5 Changes in Mean post prandial blood sugar (PPBS, 2 hrs) in twogroups

The mean PPBS in group A at 0 wks is 254.16±28.572, decreased to 221.23.977±41.2 at 12 wks and finally was 185.93±15.256 at 24wks mg/dl respectively. The mean FBS in group B at 0 wks is263.2±23.425, decreased to 227.3±22.167 at 12wks, and finally was 196.53±20.316 at 24wks mg/dl respectively. This data is represented in TABLE-11 and Fig-8(a).

Overall the mean drop in PPBS in group A and group B are 68 mg/dl and 66.67 mg/dl respectively. The percentage drop in the mean PPBS in group A and group B are 26.7% and 25.3% respectively. This data is represented in Fig-8(b).

Table – 11represents the mean PPBS in the two groups.

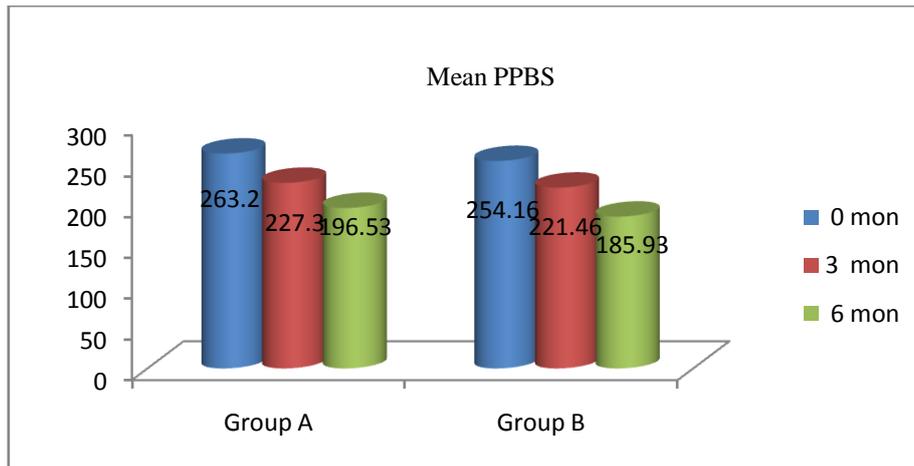| GROUPS	PPBS Mean± S.D		
	BASELINE 0 month	3rd month	6th month
Group A	254.16±28.572	221.46±23.977	185.93±15.256
Group B	263.2±23.425	227.3±22.167	196.53±20.316

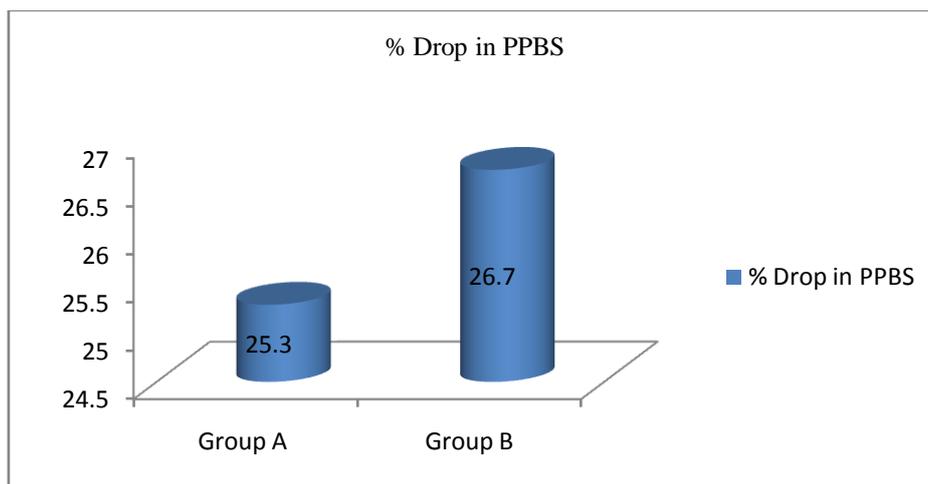Fig 8(a) represents the mean PPBS in the two groups.

Fig-8(b) represents the percentage drop in PPBS in the two groups.

5.4 Side Effects Comparison in Two Groups
5.4.1 Weight gain
      The mean weight gain in group A and group B are 1.09 and 0.9 kgs respectively. There is slightly higher weight gain in group A than group B which is not statistically significant. (p=0.0918). This data is represented in TABLE-12 and Fig-9

Table- 12 represents the mean weight gain in the two groups.

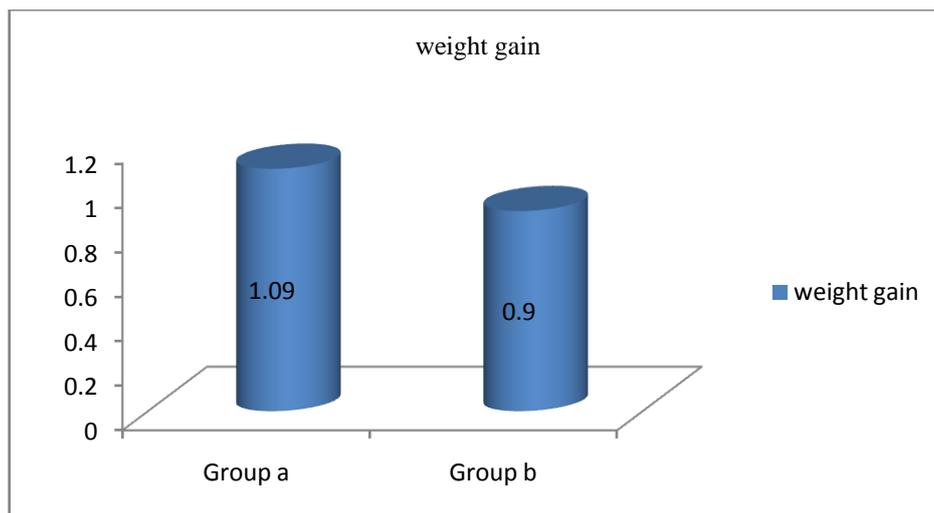| GROUPS	MEAN WEIGHT GAIN(at 24 Wks)(Kgs)
Group A	1.09
Group B	0.9
	t Value-1.714 p Value-0.0918(NS)

Fig-9 represents the mean weight gain in the two groups.

5.4.2Hypoglycemic episodes

The number of severe hypoglycemic episodes in group A and in group B is 27 and 30 respectively. There is slightly higher frequency of hypoglycemic episodes in group B   which is not statistically (NS) significant (p=0.7109). This data is represented in Table-13 and Fig -10.

Table- 13 represents the mean number of hypoglycemic episodes in the two groups.

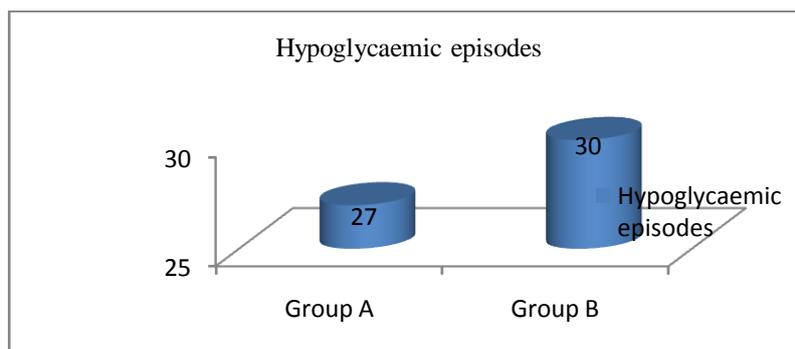| GROUPS	NO. OF HYPOGLYCAEMIC EPISODES
Group A	27
Group B	30
	t Value-0.3725 p Value-0.7109(NS)

Fig- 10 represents the mean number of hypoglycemic episodes in the two groups.

VI.   Discussion

Diabetes is a chronic illness that affects all ethnic groups globally across social and economic levels. It is characterized by insulin deficiency and insulin resistance. Both microvascular complications, such as retinopathy, nephropathy, and neuropathy, and macro vascular complications, such as myocardial infarction or stroke, are associated with chronic hyperglycemia of T2DM which present a major threat to public health and exact huge social and economic tolls (Helseth 1999,[14]Shaw 2000[15]).

Appropriate glycaemic control is a fundamental pillar in the management of type 2 DM. Adequate glycaemic control is necessary to relieve acute symptoms and to prevent, defer or reduce the severity of chronic micro vascular and macro vascular complications. Even short-term glycemic control can improve quality of life (QOL) and save health care resources (Testa 1998[16]).

It has been suggested that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy. The early use of an insulin-sensitizing agent either alone or in combination is expected to improve both acute and long-term outcomes in patients with type 2 diabetes (Bell et al 2004[13]).

The present study was done with emphasis to compare the efficacy and safety of metformin and glimepiride with metformin and pioglitazone combination therapy in patients with type 2 DM.

The present study is conducted on 63 patients diagnosedwith type 2 diabetes mellitus (3 of the patients were lost for follow up). Out of these 60 patients, 30 patients are randomly allocated to group A who are given metformin-pioglitazone and the remaining 30 patients are labeled as group B and given metformin - glimepiride.

The parameters considered in the study are Fasting Blood Sugar, 2hr Post Prandial Blood Sugar, HbA1c, weight gain and   number of hypoglycemic episodes.

The mean age, gender distribution, means body mass index are comparable between the two groups.

The results of the present study are compared with the previous studies regarding the efficacy and safety of the combination therapy. However there are only few studies with this combination of American Diabetes Association, Standards of medical care for patients with diabetes mellitus, Diabetes Care, 2003; 26, S33–S50.

6.1 In Relation To The Glycaemic Control

In the present study, there is better glycaemic control (as reflected by decrease in Fasting Blood Sugar, Post Prandial Blood Sugar and HbA1c) with the metformin and glimepiride combination therapy compared to metformin and pioglitazone combination therapy which was statistically significant ($p < 0.05$).

In the present study, the decrease in mean glycated hemoglobin in group A metformin and glimepiride is- 1.61% (decreased from 7.49% to 5.88%) and -1.52% decrease in metformin and pioglitazone (decreased from 7.57% to6.05%) which is statistically significant($p = 0.0014$). The results are similar to PIOfix study [18] were   HbA1c for metformin plus pioglitazone is -0.8±0.9% and for metformin plus glimepiride is -1.0±0.9%.

Guillermo Umpierrez et al (2006) [19] Glimepiride therapy, resulted in a more rapid decline in A1C levels at weeks 6, 12, and 20 vs. pioglitazone ($p < 0.05$). A mean A1C $\leq$ 7% was reached faster in the glimepiride group (median, 80–90 days vs. 140–150 days [$p = 0.024$]). Pravin Ingle et al (2010) [20].An HbA1c value was reduced from 9.9 ± 1.91 % at baseline to 8.1 ± 1.76 at the end of 6 months with metformin in combination with glimepiride.

In comparison with ADA (American Diabetes Association, 2008), a sulfonylurea combined with metformin constitutes an attractive option in the clinical practice. This combination can reduce HbA1c concentration up to 2% [20] In the present study we have got the similar results to decrease in HbA1c concentration at the end of 6 months.

6.2 In Relation To Hypoglycemic Episodes and Weight Gain

In the present study, the number of hypoglycaemic episodes in metformin - glimepiride is 30 and metformin- pioglitazone is 27 respectively. The frequency of hypoglycaemic episodes is slightly higher in the metformin –glimepiride group   but was not statistically significant when compared to metformin-pioglitazone. ($p = 0.7109$)

In the present study, the mean weight gain in the metformin-glimepiride group and in metformin-pioglitazone group is 0.9 and 1.09 kgs respectively. There is a slightly higher weight gain metformin-pioglitazone therapy which was not statistically significant ($p = 0.0918$).

Guillermo Umpierrez et al (2006) [18], Pravin Ingle et al (2010)[19] showed that   Glimepiride treatment was associated with an increased risk of hypoglycemia and pioglitazone with higher rate of weight gain.

VII.   Limitations Of The Present Study

1.   The sample size (30 in each group) taken in this study is small.
2.   Usually diabetes is associated with co-morbid conditions.
3.   In the present study all the co-morbid conditions were excluded.

VIII.   Summary

- The present study was done to compare the efficacy and safety of metformin and Glimepiride with metformin and pioglitazone combination therapy in patients with newly diagnosed type 2 DM.
- Age, sex, duration of diabetes, body mass index are comparable in both the groups of our study
- This 24 week long randomized controlled study of 60 patients of type 2 DM has shown a better glycaemic control in patients treated with metformin and glimepiride combination therapy compared to metformin and pioglitazone therapy which is statistically significant.
- There is a statistically significant decrease ($p = 0.003$) in mean fasting blood glucose in metformin and glimepiride combination therapy   compared to metformin and pioglitazone therapy.
- There is a statistically significant decrease ($p = 0.026$) in mean post prandial blood glucose in metformin and glimepiride therapy compared to metformin and pioglitazone therapy.
- There is a statistically significant decrease ($p = 0.0014$) in mean glycated hemoglobin in metformin and glimepiride therapy compared to metformin and pioglitazone therapy.

IX.   Conclusion

The diabetes epidemic continues to grow unabated; with a staggering toll in micro and macro vascular complications, disability and death. The chronic hyperglycemia of type 2 DM is associated with these complications. So the corner stone in the management of type 2 DM is the attainment of good glycaemic control.

From the assumption described in results and discussion the present study concludes that both the combinations such as Metformin-glimepiride and Metformin-pioglitazone reduced the Glycosylated Hemoglobin level, Fasting and post-prandial plasma glucose significantly. But the metformin-glimepiride combination provided superior control of glycaemia as compared to the Metformin-pioglitazone combination throughout the study period of 24 weeks.

So, we can conclude from our study findings that combination therapy of Metformin-glimepiride is an efficacious, cost effective and compliant therapeutic regimen in comparison to the Metformin- pioglitazone in patients with type 2 diabetes mellitus

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