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ORIGINAL RESEARCH

COMPARATIVE EVALUATION OF ORAL HYPOGLYCEMIC AGENTS IN TYPE 2 DIABETES ALONG WITH SIX MONTHS OF LIFESTYLE MODIFICATION

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Abstract: The present study was conducted in a tertiary care hospital, "Noida International Institute of Medial Science, Greater Noida" in 60 OPD patients diagnosed with type 2 diabetes over a period of 6 months. In this study, we compared the efficacy and safety of Glimepiride and Pioglitazone separately and in combination with Metformin. It was found that all the four groups reduced the glycemic parameters significantly. Pioglitazone, Glimepiride, Metformin has favorable effect on lipid profile but the effect was best seen with pioglitazone and metformin group. So it was observed from the study that the combination of pioglitazone and metformin was better in all the parameters than other groups.

INTRODUCTION: Diabetes Mellitus comprises a group of common metabolic disorders that share the same phenotype of hyperglycemia 1,2 and is caused by a complex interaction of genetics, environmental factors and lifestyle changes. Depending upon the etiology of diabetes mellitus, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose usage and /or increased glucose production.1,3 An improved understanding of the pathogenesis and natural history of the complex metabolic disorder has facilitated the application of new therapeutic agents, attainment and maintenance of near normal glycemic control while minimizing the risk of iatrogenic hypoglycemia is a central long term objective of the therapy however this is often difficult to achieve in practice. The prevalence of type 2 diabetes mellitus in India has been steadily increasing in India from 4.6% in 1996 to 12% in 2000 4 ,5 and now it has further increased to 14% presently.it can be recognized clinically by presence of symptoms such as polydipsia, polyphagia and polyuria, otherwise unexplained weight loss or presence of complications associated with/or attributable to the disease. Its management includes good metabolic control, prevention of complications and at the same time enabling the patients to live a normal life span. This is possible with diet management, exercise, a variety of oral hypoglycemic agents and in advance cases with insulin 6. With the advances in the field of pharmacotherapeutics newer oral hypoglycemic agents in the various categories are being developed with proposed better efficacy. This poses a rather difficult task in selecting particular oral hypoglycemic agents. Hence there is a need to access relative efficacy of some of the newer and more commonly used agents either alone or in combination.

METHODOLOGY: A total number of 60 patients diagnosed according to ADA criteria were included in the study and observed for duration of 1 year. It was a prospective study done in uncomplicated type 2 diabetes mellitus patients.

ADA criteria(6): Random plasma glucose concentration>200mg/dl, fasting plasma glucose>126mg/dl, 2hour postprandial plasma glucose level>200mg/dl. Symptoms like polyuria polydipsia and unexplained weight loss. Patient unresponsive to diet modification and lifestyle changes. Only patients who were on the drugs in current study were included. Patient with type 1 DM, lactating and pregnant females, elderly>65 year of age, presence of any acute or chronic illness, patients having hypersensitivity to glimepiride, pioglitazone and metformin were excluded. Also patients with hepatic, biliary or renal disease, known case of CVD, any history of acute or chronic metabolic disorder, patients on concurrent

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use of drugs like beta blocker, corticosteroid, ethanol, anabolic steroid, rifampicin, phenylbutazone, sulphonamides, diuretics, sympathomimetics etc were also excluded. Patients were divided into four groups of 15 each as:

Group (G) - On Glimepiride

Group (P) – On Pioglitazone

Group (G+M) - On Glimepiride and Metformin

Group (P+M) – on Pioglitazone and Metformin

Patient were first put on lifestyle modification, for 6 months and then on pharmacotherapy then followed up for 6 months for their blood sugar fasting and postprandial, glycosylated hemoglobin, lipid profile, CBC and urine analysis.

OBSERVATIONS :

TABLE 1: SYMPTOMS ENCOUNTERED

Symptoms	No of cases
Polyuria	29
Polydipsia	37
Nocturea	19
polydipsia	19
Recurrent UTI	16
Delayed wound healing	3
Arthritis	1
URTI	5
LRTI	10
Other Infection	8
Weight Loss	15
Weakness/Fatigue	49

TOTAL NO OF SYMPTOMS=211

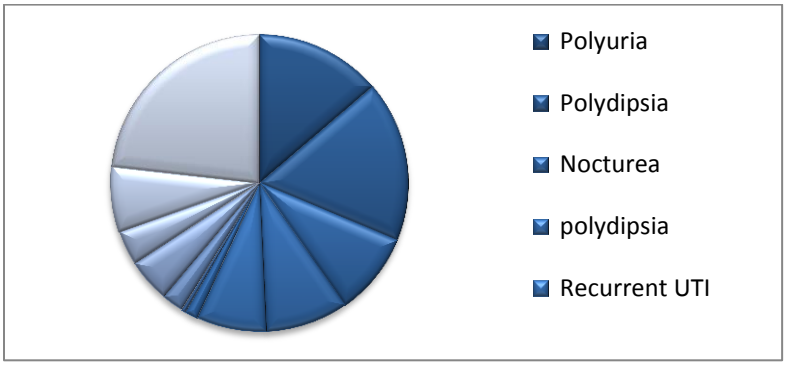

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TABLE 2: DOSING SCHEDULE OF DIFFERENT HYPOGLYCEMIC DRUGS IN MILLIGRAM PER DAY

Group - 1						
Drug	Glimepiride					
Time Interval in months	0	3	6			
Mean Dailly dose ±	1.27 ± 0.118	1.53 ± 1.33	1.53 ± 1.33			
Dosage Range	1-2 mg	1-2 mg	1-2 mg			
Reference Range	1 mg - 8 mg					
Group - 2						
Drug	Pioglitazone					
Time Interval in months	0	3	6			
Mean Dailly dose ±	21.00 ± 1.96	25.00 ± 1.88	27.00 ± 2.17			
Dosage Range	15-30 mg	15 -30 mg	15-45 mg			
Reference Range	15 mg - 45 mg					
Group - 3						
Drug	glimepiride			Metformin		
Time Interval in months	0	3	6	0	3	6
Mean Dailly dose ±	1.4 ± 0.131	1.6 ±0.131	1.67 ± 0.126	833.33 ± 93.43	733.43 ± 66.67	700.00 ± 65.47
Dosage Range	1-2 mg	1 - 2 mg	1-2 mg	500 - 1500 mg	500 - 1000 mg	500- 1000 mg
Reference Range	1 mg - 8 mg			500 mgs- 2.5 gms		
Group - 4						
Drug	Pioglitazone			Metformin		
Time Interval in months	0	3	6	0	3	6
Mean Dailly dose ±	24 ± 1.96	25 ± 2.39	22 ± 2.00	833.33 ±79.68	733.33 ±82.61	766.67 ± 66.67
Dosage Range	15 - 30 mg	15- 45 mg	15 - 30 mg	500 - 1500 mg	500-1500 mg	500- 1000 mg
Reference range	15 mg - 45 mg			500 mgs - 2.5 gms		

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Table 3: EFFECT OF GLIMEPIRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMINON GLYCOSYLATED HAEMOGLOBIN (MEAN±S.E)

GLYCOSYLATED HAEMOGLOBIN				
Time Interval in Months	**Glimepiride**	**Pioglitazone**	**Glimepiride± Metformin**	**Pioglitazone± Metformin**
0	**9.6±.2**	**9.0±.15**	**9.19±.25**	**9.26±.32**
6	**8.02±.14**	**7.97±.18**	**7.31±.0.24**	**7.69±.0.25**
Change in Gly. Hb.	**1.58±.0.13**	**1.03±.0.09**	**1.88±.0.16**	**1.57±.0.12**

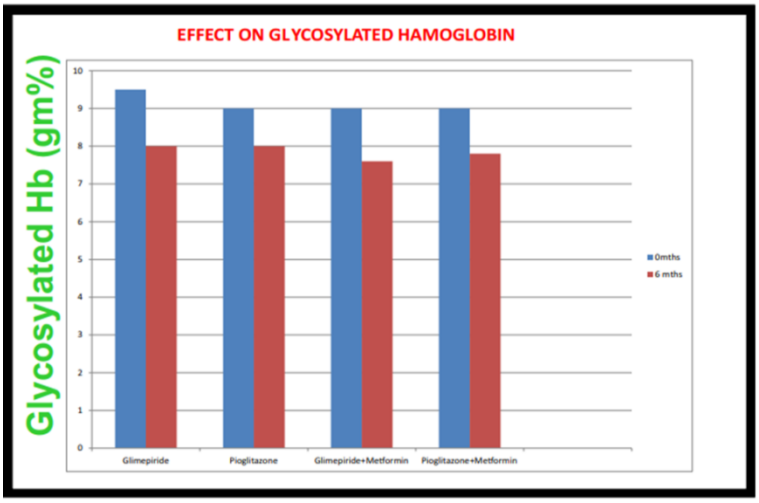

Table 4: EFFECT OF GLIMEPRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMIN ON FASTING AND POST PRANDIAT BLOOD SUGAR (MEAN ± S.E.)

Time	**BLOOD SUGER (mg/dl)**							
Intervals	**Glimepiride**		**Pioglitazone**		**Gimepiride+Metformin**		**Pioglitazone+Metformine**	
in months								
	FBS	**PP**	**FBS**	**PP**	**FBS**	**PP**	**FBS**	**PP**
0	166.73 ± 6.74	263.93 ± 10.58	147.07 ± 4.09	236.27 ± 7.88	166.06 ± 6.9	252.8 ± 9.76	177.6 ± 4.2	264.93 ± 9.49
3	143.8 ± 5.77	244.27 ± 9.48	125.07 ± 5.1	219.2 ± 7.42	128.8 ± 4.5	230.33 ± 7.64	134.4 ± 1.94	230 ± 9.8
6	124.13 ± 4.57	213 ± 8.29	115.00 ± 4.81	196.33 ± 6.19	101.2 ± 3.06	182.13 ± 7.68	117.0 ± 2.87	199.07 ± 7.77
Change								
0 – 3	22.93 ± 2.04	23.66 ± 2.8	22 ± 1.9	17.07 ± 2.0	37.8 ± 3.4	39.47 ± 3.4	43.2 ± 3.5	34.73 ± 4.5
3 - 6	90.67 ± 2.6	30.87 ± 7.0	9.8 ± 2.1	22.87 ± 2.6	27.6 ± 3.4	31.2 ± 4.37	16.47 ± 2.8	31.13 ± 5.0
0 – 6	42.6 ± 3.03	54.53 ± 6.9	31.8 ± 2.7	39.93 ± 3.5	65.4 ± 5.2	70.67 ± 6.4	59.67 ± 6.9	65.86 ± 6.9

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Table 5: EFFECT OF GLIMEPIRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMINON BODY MASS INDEX, WAIST HIP RATIO, BODY WEIGHT (MEAN ± S.E.)

	Glimepiride			Pioglitazone			Glimepiride+ Metformine			Pioglitazone+ Metformin		
Time interval in months	**BMI (kg/m2)**	**WHR**	**WEIGHT (kg)**	**BMI (kg/m2)**	**WHR**	**WEIGHT (kg)**	**BMI (kg/m2)**	**WHR**	**WEIGHT (kg)**	**BMI (kg/m2)**	**WHR**	**WEIGHT (kg)**
0	22.74 ± 1.12	0.904 ± 0.03	57.87 ± 2.89	23.71 ± 2.89	0.95 ± 0.027	65.2 ± 4.83	22.62 ± .89	0.867 ± 0.021	58.93 ± 2.57	26.32 ± 1.19	0.96 ± 0.03	69.67 ± 3.59
3	22.6 ± 1.11	0.905 ± 0.29	57.53 ± 2.92	23.92 ± 1.67	0.95 ± 0.028	65.8 ± 4.76	22.39 ± .87	0.861 ± 0.021	58.33 ± 2.53	26.15 ± 1.19	0.94 ± 0.0314	69.2 ± 3.60
6	22.55 ± 1.1	0.902 ± .028	57.4 ± 2.87	24.11 ± 1.66	0.94 ± 0.027	66.33 ± 4.74	22.02 ± .85	0.85 ± 0.02	57.4 ± 2.54	26.00 ± 1.22	0.94 ± 0.032	68.8 ± 3.67
Change	0.19 ± 0.06	0.001 ± 0.008	-0.47 ± 2.1	-0.4 ± 0.1	0.004 ± 0.01	-1.13 ± 0.3	0.6 ± 0.17	0.01 ± 0.006	-1.53 ± 1.53	0.32 ± 0.1	0.02 ± 0.04	-0.87 ± 0.29

Table 6: EFFECT OF GLIMEPIRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMIN ON LIPID PROFILE (mg/dl)(MEAN ± S.E.)

Drugs	**Glimepiride**			**Pioglitazone**			**Glimepiride + Metformin**			**Pioglitazone+ Metformin**		
Time interval in months	**0**	**6**	**Change**	**0**	**6**	**Change**	**0**	**6**	**Change**	**0**	**6**	**Change**
Tests												
TC	207.76 ± 7.3	205.12 ± 7.55	2.64 ± 1.7	203.79 ± 3.8	211.03 ± 3.1	-7.24 ± 3.1#	207.64 ± 7.78	206.51 ± 7.34	-1.13 ± 1.14	205.03 ± 3.56	207.99 ± 3.62	-2.96 ± 2.16
HDL	42 ± 0.92	42.8 ± 1.03	-0.8 ± 0.44	41.47 ± 0.64	43.4 ± 1.05	-1.93 ± 0.7#	40.67 ± 1.38	42.4 ± 1.38	-1.7 ± 0.7#	40.4 ± 1.61	42.93 ± 1.51	-2.53 ± 0.6$
LDL	127.13 ± 7.55	124.87 ± 7.68	2.27 ± 0.46	127.2 ± 3.45	131.4 ± 2.4	-4.2 ± 2.07	128.33 ± 7.74	126.33 ± 7.1	2 ± 0.9#	128.6 ± 3.11	132.27 ± 3.29	-3.67 ± 1.8
VLDL	38.49 ± 1.0	37.45 ± 0.97	1.04 ± 0.5	35.12 ± 0.81	33.83 ± 0.8	1.3 ± 0.48#	38.64 ± 0.50	37.76 ± 0.58	0.88 ± 0.39#	35.09 ± 1.57	32.79 ± 1.43	2.31 ± 0.4$
TG	192.47 ± 5	187.27 ± 2.86	175.6 ± 4.03	175.8 ± 4.03	169 ± 4.06	6.6 ± 2.42#	193.2 ± 2.49	188.8 ± 2.89	4.4 ± 1.9#	175.47 ± 7.86	163.93 ± 7.19	11.5 ± 1.98$

#p<0.05 – significant; $p≤0.001 highly significant

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Table 7: EFFECT OF GLIMEPIRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMIN ON LIVER FUNTION TEESTS (MEAN ± S.E.)

	Glimepiride		Pioglitazone		Glimepride + Metformin		Pioglitazone + Metformin	
Time interval in (months)	**0**	**6**	**0**	**6**	**0**	**6**	**0**	**6**
Tests								
TB (mg.)	0.65 ± 0.03	0.65 ± 0.02	0.6 ± 0.04	0.59 ± 0.04*	0.59 ± 0.05	0.58 ± 0.05	0.62 ± 0.04	0.62 ± 0.04
DB (mg.)	0.18 ± 0.03	0.19 ± 0.02	0.19 ± 0.02	0.18 ± 0.02*	0.43 ± 0.05	0.43 ± 0.05	0.16 ± 0.02	0.17 ± 0.02
IB (mg.)	0.47 ± 0.02	0.46 ± 0.02	0.18 ± 0.19	0.41 ± 0.04	0.16 ± 0.01	0.15 ± 0.02	0.46 ± 0.04	0.45 ± 3.9
ALT (IU)	25.3 ± 1.6	25.0 ± 1.6	22.9 ± 1.6	22.4 ± 1.4*	23.04 ± 2.2	23.1 ± 2.2	21.07 ± 1.5	21.27 ± 1.7
AST (IU)	21 ± 1.8	20.8 ± 1.8	22.3 ± 1.8	22.0 ± 1.8	20.1 ± 1.08	19.7 ± 1.1	23.73 ± 1.4	23.5 ± 1.4

Table 8: EFFECT OF GLIMEPIRIDE AND PIOGLITAZONE ALONE OR IN COMBINATION WITH METFORMIN ON RENAL FUNTION TEESTS (MEAN ± S.E.)

	Glimepiride		Pioglitazone		Glimepride + Metformin		Pioglitazone + Metformin	
Time interval in (months)	**0**	**6**	**0**	**6**	**0**	**6**	**0**	**6**
Tests								
Serum creatinine(mg/dl)	0.97 ± 0.03	0.93 ± 0.2	1.05 ± 2.15	1.02 ± 0.02	1.0 ± 0.02	0.95 ± 0.02	0.97 ± 0.02	0.91 ± 0.02
Blood urea nitrogen (mg/dl)	18.6 ± 0.21	18.2 ± 0.28	18.7 ± 0.23	18.1 ± 0.19	17.4 ± 2.9	16.9 ± 2.9	18.1 ± 0.3	17.5 ± 0.3

DISCUSSION:

The most common complaint which the patients had was weakness or fatigue. Polydipsia, polyphagia and polyuria and weight loss were also present in most of the patients at the time of enrollment (Table 1.).

For each of the four treatment groups oral hypoglycemia drugs were administered in different dosage range (table 2) after 2 weeks of more of titration phase.

It was observed that effect on HbA1c was maximum with combination of glimepiride + metformin. (Table 3.)

It was seen that the fall was more significant in 0-6 months than 0-3 months in all the groups. Intergroup comparison showed that the decrease with combination therapy was more than the monotherapy that to in glimepiride +metformin group that was 64.86 mg/dl and 70.67mg/dl in fasting and PPBS which was slightly more than pioglitazone +metformin group which was 60.6 and 65.86mg/dl.

In Table 5. A small decrease in waste hip ratio was noticed (WHR) was noticed in all the four groups. The change was slightly more in combination therapy group and was significant (p value <0.05).

BMI- there is small increase in BMI in the pioglitazone group and a decrease was noticed in all other three groups and was more significant in glimepiride +metformin group.

There was a gain in pioglitazone group whereas in other groups weight loss was seen. Maximum weight loss is seen in glimepiride +metformin group.

Table 6. In glimepiride group and glimepiride +metformin a fall in total cholesterol was seen whereas in pioglitazone and pioglitazone +metformin group a rise was noticed and was significant for 'P' group (p value <0.05).

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There was an increase in the levels of HDL seen in all the three groups except 'G'group where there was fall and was insignificant ($p>0.05$). Change was significant in 'G+M'group ($p <0.05$).
There was decrease in the levels of VLDL in all the groups, it was insignificant in 'G' group and significant in 'P' and 'G+M' group ($p<0.05$) whereas it was highly significant in 'P+M' group ($p<0.001$).
There was a decrease in the levels of TG (triglyceride) in all the four groups which was highly significant in 'P+M' group ($p<0.001$) and significant in 'P'and 'G+M' group ($p<0.05$) but insignificant in 'G' group ($p>0.05$).
During the study no significant change was seen in LFT ($p>0.05$).
No significant change was seen in KFT like BUN and serum creatinine ($p>0.05$).
Adverse drug reactions: adverse drug events were monitored according to patients self complaints. All the three drugs were very well tolerated. Only 1 patient encountered metformin related diarrhea whereas 3 patients encountered hypoglycemia seen in 'G' group.

Conclusion:

In type 2 patients percentage of males was slightly more than females. Most of the patients were literate reflecting a better compliance. It is a disease of third or fourth decade, but now younger generation is also affected. Considering the glycemic control all the therapies, mono as well as combination was effective. Favorable lipid profile was best seen with a combination of 'P+M' though 'P' alone also had a positive response but increase in LDL value was also seen, which was insignificant in 'P' and 'M' group. Weight reduction was observed in 'G+M' group while in 'P' group weight gain was noticed.
Adverse events encountered were mild without affecting compliance and none of the patients required hospitalization. Almost all the patients achieved normoglycemic by the end of study. The overall results of this study shows that the combination therapy with pioglitazone and metformin was better than the other groups in all the parameters like glycemic control, effect on lipid profile and weight gain and safety profile also.

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