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Original Research Article

Study of glycemic response of oral anti-diabetic drugs in type 2 diabetic patients

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is one of the most common non-communicable diseases associated with short term and long term avoidable complications. The treatment of T2DM often is initiated with monotherapy of oral antidiabetic drugs, which often do not decrease the plasma sugar levels effectively and consistently that will reduce the complications associated with T2DM. Hence the current study is aimed to determine the effectiveness of commonly available and affordable oral anti-diabetic drugs (OADs) in type 2 diabetic patients.
Methods: This study consisted of 210 T2 Diabetic patients, 120 males and 90 females with a mean age of 50.93yrs were divided equally into six groups with equal number of males and females in each group depending upon the OADs they received in solo or in combination for 24weeks. After the written consent, a detail Clinical history, Clinical examination, Biochemical investigations including, Fasting plasma sugar (FPS), Post prandial sugar (PPS), Glycosylated heamoglobin (HBA1c), serum Creatinine, serum Electrolytes, Chest X-ray PA view and standard ECG were done. Repeat FPS, PPS and HBA1c were done after 4, 12 and 24weeks of study.
Results: After 4 weeks, FPS, PPS decreased significantly in combination therapy ($p < 0.05$), while after 12weeks and 24weeks of study, FPS, PPS and HBA1c decreased significantly ($p < 0.01$ to $p < 0.001$ in both monotherapy and in combination therapy. Non-diabetic levels of plasma sugars were obtained in 25-45% with monotherapy and 37-57% in combination therapy. Metformin was an effective monotherapy to initiate treatment of T2DM, but eventually combination therapy was required in most of the patients. The combinations of metformin-teneligliptin and metformin-glimepiride were found to be most effective because of their favourable pharmacokinetic characters and complementary pharmcodynamic effects.
Conclusions: OADs are affordable, effective hypoglycemic agents to initiate treatment as monotherapy and for subsequent treatment as combination therapy for T2DM.

Keywords: Affordable, Combination therapy, Monotherapy, Non-diabetic plasma sugar levels, Oral anti-diabetic drugs, Type 2 diabetes mellitus

INTRODUCTION

Diabetes Mellitus(DM) is the most common non-communicable disease in the present millennium. The World Health Organization(WHO) predicts and estimates that the number of people with DM in the world will be 300million by 2025, and India will be the diabetic capital of the world by 2020 which imparts a huge burden on the public health system.[1-4] DM is not only a global public health problem but a leading cause of death worldwide accounting for 1 death every 6secs.[5] It is a chronic and a progressive disorder associated with metabolic syndrome, cardiovascular disease, nephropathy, stroke, neuropathy

and retinopathy responsible for disability, reduced quality of life and premature death. Dyslipidemia with its associated complications are usual in T2 Diabetic patients with poorly controlled glycemia.[6] Hence the current study is focused to determine which common oral anti-diabetic drugs in solo or in combination are most effective and consistent in lowering plasma sugars that may reduce short term and long term complications, with good safety profile and tolerability; thereby enhancing our approach to drug selection for the best management of T2DM which is affordable and available to all.

METHODS

This is a Prospective comparative study of T2DM patients conducted in the Departments of Pharmacology and Medicine, Mallareddy Institute of Medical Sciences and Hospital, Suraram, Hyderabad, TS, after the Institutional Ethical Committee approval. DM was diagnosed as per 2016 American Diabetic Association (ADA) guide lines.[7] Patients who were smokers, alcoholic, with Coronary artery disease (CAD), Chronic kidney disease were excluded from the study.

After a written consent from each patient, a detailed Clinical history, Clinical examination, Biochemical investigations: Fasting plasma sugar (FPS), Post prandial plasma sugar (PPS), Glycosylated heamoglobin (HBA1c), serum Creatinine, serum Electrolytes, Chest X-ray PA view and standard Electrocardiogram (ECG)were done. Patients were categorized into six groups, each comprising 35 patients (25males,15females):

- Group (Gr) 1: patients received Metformin (1000-2000mg/day) only,
- Group (Gr) 2: patients received Glimepiride (1-3mg/day) only,
- Group (Gr) 3: patients received Teneligliptin (20 mg/day) only,
- Group (Gr) 4: patients received Metformin (1000-2000mg/day) and Glimepiride (1-3mg/day),
- Group (Gr) 5: patients received Metformin (1000-2000mg/day) and Teneligliptin (20mg/day),
- Group (Gr) 6: patients received Glimepiride(1-3mg/day) and Teneligliptin (20mg/day). Repeat FPS, PPS and HBA1c were done after 4, 12 and 24weeks of treatment with OADs.

Statistical analysis

The data obtained from the study are presented as mean with standard deviation and percentage and results are assessed by using Student's t test; P <0.05 values are considered as statistical significance.

RESULTS

Clinical profile

This study consisted of 210 T2 DM patients with 120(57.14%) males and 90(42.86%) females with age ranging from 33 to 65yrs with a mean of 50.93yrs±7.6. Each group consisted of 35 patients with 20 males (57.14%) and 15 females (42.86%) (Table 1 and Figure 1). The duration of DM in this study ranged from 2-10yrs with a mean of 4.6yrs±.2.3 (Table 1).

Table 1: Age and duration of DM in type 2 diabetic patients.

Parameter		Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (glimepiride & teneligliptin)
Age (yr)	Range	35-63	38-65	35-65	35-64	37-61	38-62
	Mean	49.75 ±7.7	50.68±8.5	51.85±8.3	50.60±8.1	52.15±6.1	50.55±6.1
DM (yr) duration	Range	2-9	2-9	2-8	2-9	2-7	2-10
	Mean	4.7±1.3	4.4±1.7	4.5±1.5	4.8±1.8	4.7±1.4	4.5±1.6

Routine investigations

The routine biochemical investigations: serum creatinine, and serum electrolytes were within Normal limits. However, 15 patients (7.14%) of the study had cardiomegaly on chest X-ray PA view and left ventricular hypertrophy in standard ECG who had concomitant hypertension

Plasma sugars

The plasma sugars analyzed included, FPS, PPS and HBA1c

Initial

- FPS: In this study the initial FPS ranged between 131-210 mg/dl with a mean of 180.5mg/dl±23.2 (Table 2). The mean FPS is slightly higher in females as compared to males in all groups except Gr 1-179.3 vs 178.2mg/dl in Gr 2; 180.2 vs 179.3mg in Gr 3/dl; 192 vs 181mg/dl in Gr 4; 190 vs 186mg/dl in Gr 5 and 178 vs 171mg/dl in Gr 6.
- PPS: Similarly, the initial PPS ranged between 204-313mg/dl with a mean of 269.4mg/dl±33.6 in this study (Table 3). So also, the mean PPS is slightly

higher in females as compared to males in all groups except Gr 1-269.9 vs 267.3mg/dl in Gr 2; 270 vs 269mg/dl in Gr 3; 288 vs 271.5mg/dl in Gr 4; 285 vs 279mg/dl in Gr 5 and 267 vs 256mg/dl in Gr 6.

- HBA1c: The initial HBA1c ranged between 7.3-9.7% with a mean of 8.5%±0.7 in this study (Table 4). The mean HBA1c is slightly higher in females as compared to males in Gr 3 (8.8 vs 8.3%), Gr 5 (8.8 vs 8.7%) and in Gr 6 (8.8 vs 8.7%).

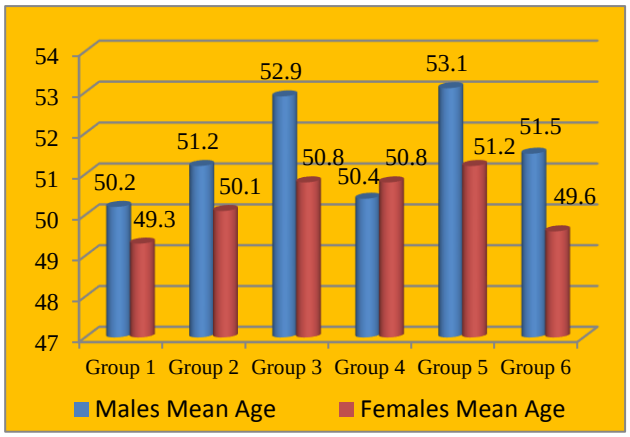

Figure 1: Mean age of the patients in yrs.

After 4 weeks of OADs therapy

- FPS: The mean FPS decreased by 7.2 mg/dl (4%) in Gr1; by 5.4mg/dl (3%) in Gr 2; by 7.4mg/dl (4.13%) in Gr 3; by 11.3mg/dl (6.06%) in Gr 4; by 12mg/dl (6.61%; p<0.05) in Gr 5 and by 9mg/dl (5.15%) in Gr 6 (see Table 5). The decrease of mean FPS was statistically significance in combination therapy of metformin and teneligliptin, but did not decrease to <126mg/dl in any of the groups.
- PPS: The mean PPS decreased by 10.7mg/dl (4%) in Gr 1; by 8mg/dl (3%) in Gr 2; by17mg/dl (6.3%; p<0.05) in Gr 3; by 14.5mg/dl (5.36%,) in Gr 4; by 22mg/dl (8.11%, p <0.05) in Gr 5 and by 16.3mg/dl (6.09%; p<0.05) in Gr 6. (Table 6). The decrease of mean PPS was statistically significance with teneligliptin and its combination with metfromin or glimepiride. PPS reached 200mg/dl in 5 (14.29%) patients in Gr 3. It was <200mg/dl in 9 (25.71%) patients in Gr 5 and in 7 (20%) patients of Gr 6.
- HBA1c: The mean HBA1c decreased in all groups, but was not statistically significant. It decreased by 0.3 % (3.57%)in Gr 1; by 0.3% (3.53%) in Gr 2, by 0.3% (3.53%) in Gr 3; by 0.4% (4.71%;) in Gr 4; by 0.5% (5.81%) in Gr 5 and by 0.4% (4.65%;) in Gr 6 (Table 7); It did not decrease to <6.5% in any group.

Table 2: Fasting plasma sugar and oral anti-diabetic drugs.

Blood sugar: FPS (mg/dl)		Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (glimepiride & teneligliptin)
Initial	Range	140-200	138-200	142-200	146-210	142-199	131-190
	Mean	179.6±20.1	178.8±22.2	179.8±21.2	186.5±22.3	181.5±19.3	174.5±18.1
After 4weeks	Range	134-193	134-194	136-192	138-199	133-167	129-180
	Mean	172.5±21.2	173.4±21.3	172.4±20.1	169.2±22.2	169.5±19.2	165.5±17.3
After 12weeks	Range	128-184	128-186	130-184	125-189	124-175	122-171
	Mean	164.5±22.2	165.5±20.1	164.5±22.2	161.3±21.2	160.2±18.4	156.5±19.2
After 24weeks	Range	125-180	125-182	124-178	124-184	119-167	120-168
	Mean	161.5±23.4	161.4±25.3	159.5±23.4	157.5±20.1	152.1±22.2	153.2±18.2

Table 3: Post prandial plasma sugar and oral anti-diabetic drugs.

Blood sugar: PPS (mg/dl)		Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (glimepiride & teneligliptin)
Initial	Range	210-300	207-300	213-300	219-313	213-295	204-285
	Mean	269.3±33.4	268.6±32.3	269.5±31.5	270.4±34.3	271.2±30.5	267.5±25.3
After 4weeks	Range	201-294	200-291	200-282	208-299	195-274	191-267
	Mean	258.6±32.3	260.6±30.5	252.5±32.3	255.9±33.2	249.2±29.6	251.2±25.4
After 12weeks	Range	193-281	192-279	193-273	197-286	185-259	181-253
	Mean	247.2±31.5	249.3±31.5	244.5±30.5	241.4±32.5	235.7±25.3	237.5±21.2
After 24weeks	Range	189-275	188-273	187-264	192-277	174-244	177-247
	Mean	242.1±32.2	243.2±33.4	236.5±29.6	237.4±31.5	227.2±23.4	232.3±20.1

Table 4: Glycosylated heamoglobin and oral anti-diabetic drugs.

Blood sugar: HBA1C (%)		Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (glimepiride & teneligliptin)
Initial	Range	7.4-9.6	7.5-9.5	7.6-9.6	7.7-9.6	7.6-9.6	7.3-9.7
	Mean	8.4±0.7	8.5±0.8	8.5±0.9	8.5±0.9	8.6±1.0	8.6±0.9
After 4weeks	Range	7.1-9.2	7.3-9.2	7.3-9.0	7.3-8.9	7.1-9.0	6.9-9.2
	Mean	8.1±0.8	8.2±0.7	8.2±0.8	8.1±0.8	8.1±0.9	8.2±0.8
After 12weeks	Range	6.8-8.8	7.0-8.8	7.0-8.7	6.9-8.5	6.8.4	6.6-8.7
	Mean	7.7±0.9	7.9±0.9	7.9±0.8	7.7±0.7	7.7±0.7	7.8±0.7
After 24weeks	Range	6.4-8.0	6.9-8.6	6.8-8.4	6.4-7.9	6.3-7.6	6.4-8.5
	Mean	7.2±0.6	7.7±0.8	7.6±0.6	7.1±0.6	7.1±0.6	7.6±0.8

Table 5: Effects of oral anti-diabetic drugs on fasting plasma sugar.

Blood sugar Parameter: mean FPS (mg/dl)	Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (metformin & teneligliptin)
Initial	179.6	178.8	179.8	180.5	181.5	174.5
After 4wks	172.5	173.4	172.4	169.2	169.5	165.5
% of ↓	-7.2; 4%	-5.4;3%	-7.4;4.13%	-11.3; 6.06%	-12; 6.61% (p<0.05)	-9; 5.15%
After 12wks	164.5	165.5	164.5	161.3	160.2	156.5
% of ↓	-13.2; 7.3% (p<0.05)	-13.3;7.4% (p<0.05)	-15.3;8.5% (p<0.05)	-19.2; 10.64% (p<0.001)	-21.3; 11.74% (p<0.001)	-18; 10.32% (p<0.001)
After 24wks	161.5	161.4	159.5	157.5	152.1	153.2
% of ↓	-18.2;10.12% (p<0.01)	-17.4;9.7% (p<0.01)	-20.3; 12.74% (p<0.001)	-23; 12.33% (p<0.001)	-29.4; 16.20% (p<0.001)	-21.3; 12.20% (p<0.001)

Table 6: Effects of oral anti-diabetic drugs on postprandial plasma sugar.

Blood sugar Parameter: mean PPS (mg/dl)	Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (metformin & teneligliptin)
Initial	269.3	268.6	269.5	270.4	271.2	267.5
After 4wks	258.6	260.6	252.5	255.9	249.2	251.2
% of ↓	-10.7; 4%	-8; 3%	-17; 6.3% (p<0.05)	-14.5; 5.36%	-22; 8.11% (p<0.05)	-16.3; 6.09% (p<0.05)
After 12wks	247.2	249.3	244.5	241.4	235.7	237.5
% of ↓	-22.1; 8.21% (p<0.05)	-19.3; 7.18% (p<0.01)	-25; 9.3% (p<0.01)	-29; 10.72% (p<0.01)	-35.5; 13.09% (p<0.001)	-30; 11.21% (p<0.001)
After 24wks	242.1	243.2	236.5	237.4	227.2	232.3
% of ↓	-27.2; 10.10% (p<0.01)	-25.4; 9.46% (p<0.01)	-33; 12.24% (p<0.001)	-33;12.20% (p<0.001)	-44.1;16.22% (p<0.001)	-35.2; 13.16% (p<0.001)

After 12 weeks of OADs therapy

- FPS: The mean FPS decreased by 13.2 mg/dl (7.3%; p<0.05) in Gr 1; by 13.3mg/dl (7.4%; p<0.05) in Gr 2; by 15.3mg/dl (8.5%; p<0.05) in Gr 3; by 19.5mg/dl (10.5%; p<0.01) in Gr 4; by 23mg/dl (12.23%; p<0.001) in Gr 5 and by 18mg/dl (10.32%; p<0.001) in Gr 6. (Table 5). The decrease of mean FPS was statistically significance both with monotherapy and in combination therapy. FPS <126mg/dl occurred in 9 (25.71%) patients of Gr 4; in 8 (22.86) patients of Gr 5 and in 7 (20%) patients of Gr 6.

- PPS: The mean PPS decreased by 22.1mg/dl (8.21%; p<0.01) in Gr 1; by 19.3mg/dl (7.19%; p<0.05) in Gr 2; by 25mg/dl (9.3%; p<0.01) in Gr 3; by 29mg/dl (10.72%; p<0.01) in Gr 4; by 35.5mg/dl (13.09%, p<0.001) in Gr 5 and by 30mg/dl (11.21%; p<0.001) in Gr 6 (Table 6). So also, the decrease of mean PPS was statistically significant with monotherapy and highly significant in combination therapy. PPS <200mg/dl was achieved in 6 (17.14%) patients of Gr 1; in 5 (14.29%) patients of Gr 2; in 11 (31.43%) patients of Gr 3; in 7 (20%) patients of Gr 4; in 14 (40%) patients of Gr 5 and in 12 (34.29%) patients of Gr 6.
- HBA1c: The mean HBA1c decreased by 0.7% (8.33%; p<0.05) in Gr 1; by 0.6% (7.06%; p<0.05) in Gr 2; by 0.6% (7.06%; p<0.01) in Gr 3; by 0.8% (9.41%; p<0.001) in Gr 4; by 0.9% (10.47%; p<0.001) in Gr 5 and by 0.8% (9.30%; p<0.001) in Gr 6. (Table 7). The decrease of mean HBA1c was statistically significant in all groups of patients. However, <6.5% of HBA1c was not achieved in any patients.

Table 7: Effects of oral anti-diabetic drugs on HBA1c.

Blood sugar Parameter: mean HBA1c (%)	Group 1 (metformin)	Group 2 (glimepiride)	Group 3 (teneligliptin)	Group 4 (metformin & glimepiride)	Group 5 (metformin & teneligliptin)	Group 6 (metformin & teneligliptin)
Initial	8.4	8.5	8.5	8.5	8.6	8.6
After 4wks	8.1	8.2	8.2	8.1	8.1	8.2
% of ↓	-0.3; 3.57%	-0.3; 3.53%	-0.3; 3.53%	-0.4; 4.71% (p<0.01)	-0.5; 5.81% (p<0.001)	-0.4; 4.65% (p<0.05)
After 12wks	7.7	7.9	7.9	7.7	7.7	7.8
% of ↓	-0.7;8.33% (p<0.05)	-0.6; 7.06% (p<0.05)	-0.6;7.06% (p<0.01)	-09; 9.41% (p<0.001)	-0.9; 10.47% (p<0.001)	-0.8;9.2% (p<0.001)
After 24wks	7.2	7.7	7.6	7.1	7.1	7.6
% of ↓	-1.2; 14.28% (p<0.001)	-0.8; 9.41% (p<0.001)	-0.9; 10.59% (p<0.001)	-1.4; 16.47% (p<0.001)	-1.5; 17.44% (p<0.001)	-1.0; 11.63% (p<0.001)

After 24 weeks of OADs therapy

- FPS: The decrease of mean FPS was statistically highly significant in all groups of patients. It decreased by 18.2mg/dl (10.1%; p<0.01) in Gr1; by 17.3mg/dl (9.7%; p<0.01) in Gr 2; by 20.3mg/dl (11.3%; p<0.001) in Gr 3; by 23mg/dl (12.74%; p<0.001) in Gr 4; by 29.4mg/dl (16.20%; p<0.001) in Gr 5 and by 21.3mg/dl (12.20%; p<0.001) in Gr 6. (Table 5). FPS <126mg/dl occurred in 11 (31.43%) patients of Gr1; in 10 (28.57%) patients of Gr 2; in 11 (31.43%) patients of Gr 3;16 (45.71%) patients of Gr 4 and Gr 5; and 15 (42.85%) patients of Gr 6.
- PPS: Similarly, the decrease of mean PPS was statistically highly significant in all groups of patients. It decreased by 27.2mg/dl (10.10%; p<0.01) in Gr 1; by 25.4mg/dl (9.46%; p<0.01) in Gr 2; by 33mg/dl (12.24%; p<0.001) in Gr 3; by 33mg/dl (12.20%; p<0.001) in Gr 4; by 44mg/dl (16.22%, p<0.001) in Gr 5 and by 35.2mg/dl (13.16%; p<0.001) in Gr 6. (Table 6). PPS <200mg/dl occurred in 9 (25.71%) patients of Gr 1 and Gr 2; in 16 (45.71%) patients of Gr 3; in 14 (40%) patients of Gr 4; in 20 (57.14%) patients of Gr 5; and in 18 (51.41%) patients of Gr 6.
- HBA1c: So also, the decrease of mean HBA1c was statistically highly significance in all groups of patients. It decreased by 1.2% (14.28%; p<0.001) in Gr 1 it; by 0.8% (9.41%; p<0.001) in Gr 2; by 0.9% (10.59%; p<0.001) in Gr 3; by 1.4% (16.47%; p<0.001) in Gr 4; by 1.5% (17.44%; p<0.001) in Gr 5 and by 1.0% (11.63%; p<0.001) in Gr 6. (Table 7). HBA1c <6.5% occurred in 11 (31.43%) patients of Gr 1; in 14 (40%) patients of Gr 4 and in 13 (37.14%) patients of Gr 5 and Gr 6. HBA1c was >6.5% but <7% in 14 (40%) patients of Gr 2 and in 16 (45.71%) patients of Gr3.

DISCUSSION

Monotherapy: The monotherapy for T2DM in this study included: metformin, glimepiride or teneligliptin.

Metformin is a biguanide oral anti diabetic drug which inhibits hepatic gluconeogenesis, increases peripheral insulin sensitivity and decreases intestinal glucose absorption. Glimepiride is a second-generation sulfonylurea oral anti diabetic drug which stimulates pancreatic β cell activity inducing insulin secretion.

Teneligliptin is a third-generation class 3 dipeptidyl peptidase (DPP)-4 inhibitor oral anti diabetic drug which increases serum insulin levels and decreases serum glucagon levels by increasing the levels of active glucagon like peptide-1 and glucose dependent

insulotropic polypeptide through inhibition of DPP-4 enzymatic activity.

In this study after 4weeks of monotherapy with metformin, glimepiride or teneligliptin resulted in decrease of mean FPS, mean PPS and mean HBA1c in all patients. But non-diabetic levels of plasma sugars could not be achieved.

After 12weeks of monotherapy significant decrease of FPS, PPS and HBA1c ($p<0.05$ to <0.01) occurred and <200mg/dl of PPS attained in 31.43% with teneligliptin, 17.14% with metformin and 14.29% with glimepiride. Similarly, non-diabetic levels of FPS (<126mg/dl) and HBA1c (<6.5%) could not be achieved. Eto T et al found significant decrease in FPS and PPS after 4weeks of teneligliptin monotherapy.[8] Robinson AC et al also found significant decrease of HBA1c besides improvement in the lipid profile with metformin monotherapy as compared to placebo.[9] Weitgassr R et al reported significant decrease of HBA1c and FPS levels with glimepiride.[10] Kadowaki et al similarly reported significant decrease of FPS and HBA1c with teneligliptin.[11]

There was very significant decrease ($p<0.01$ to <0.001) of FPS, PPS and HBA1c after 24weeks of monotherapy in this study; and non-diabetic levels of FPS were achieved in 31.43% with metformin and teneligliptin and in 28.57% with glimepiride; while PPS <200mg/dl occurred in 45.71% with teneligliptin and 25.71% each with metformin and glimepiride montherapy; and non-diabetic levels of HBA1c was achieved in 31.43% with metformin therapy. However, HBA1c <6.5% but <7% occurred in 45.71% with teneligliptin and 40% with glimepiride monotherapy.

Similarly, metformin and glimepiride were reported to be effective hypoglycemic agents and found no difference between them in their antihyperglycemic action by Yamanouchi T et al and Yoon KH et al and in a meta-analysis by Zhu H et al.[12-14] So also a review by Kishimoto M reported significant decrease in HBA1c levels after a long term (52weeks) teneligliptin montherapy.[15]

Combination therapy: The combination therapy for T2DM in this study included: metformin-glimepiride, metformin-teneligliptin and glimepiride-teneligliptin. After 4weeks of combination therapy; mean FPS, mean PPS decreased significantly ($p<0.05$), and nondiabetic levels of PPS was achieved in 25.71% with metformin-teneligliptin and in 20% with glimepiride-teneligliptin combination. But non-diabetic levels of FPS and HBA1c were not achieved.

After 12weeks of combination therapy, there was very significant decrease of FPS, PPS and HBA1c ($p<0.001$); and non-diabetic levels of FPS were obtained in 25.71%, 22.86% and 20% with metformin-glimepiride, metformin-teneligliptin and glimepiride-teneligliptin combinations respectively. Similarly, PPS <200mg/dl was achieved in 40%, 34.29% and 20% with metformin-teneligliptin, glimepiride-teneligliptin and metformin-glimepiride combinations respectively. But <6.5% of HBA1c was not achieved in any patients.

Similarly, previous studies of combination therapy with metformin and glimepiride reported effective glycemic control, reducing the levels of FPS and HBA1c after 8-12weeks of therapy.[16-19] A 16weeks of combination therapy of metformin and teneligliptin by Kim MK et al reported similar significant decrease of FPS and HBA1c in their study.[20] So also a 12weeks study by Kadowaki T et al of glimepiride and teneligliptin combination found effective reduction in FPS, PPS and HBA1c and reduction in HBA1c was maintained even at 52weeks.[21]

Similarly, in this study there was very significant decrease ($p<0.001$) of FPS, PPS and HBA1c after 24weeks of all combination therapy and non-diabetic levels of FPS were found in 45.71% each with metformin-glimepiride and metformin-teneligliptin and in 42.85% with glimepiride-teneligliptin combinations.

In our study PPS <200mg/dl achieved in 57.14% with metformin-teneligliptin; in 51.41% with glimepiride-teneligliptin and in 40% with metformin-glimepiride combinations. Achieving non-diabetic levels of PPS should also be the therapeutic goal in T2DM patients as post prandial hyperglycemia is associated with increased production of free radicals leading to oxidative stress and endothelial dysfunction which increases CV disease risk, as well as long term macrovascular complications.[22,23]

Similarly, non-diabetic levels of HBA1c (<6.5%) occurred in 40% with metformin-glimepiride and in 37.14% each with metformin-teneligliptin and glimepiride-teneligliptin combinations in our study.

Principles in selecting antihyperglycemic agents and rationale for selecting specific combination therapy; considering the huge epidemic of T2DM and its substantial economic impact on the society and individuals, choosing specific anti-hyperglycemic agents (OADs) depends not only on the effective glycemic control, extra-glycemic effects, safety profile and tolerability to prevent short and long-term complications associated with DM, but also on their compliance and affordability. So, the present study high lights on the metformin monotherapy as initial treatment of T2DM. However, non-diabetic levels of FPS, PPS and HBA1c were achieved better and in most of the patients with combination therapy as compared to monotherapy. So also in UKPDS study, glycemic control was reached in only 25% of patients treated with monotherapy and 75% of patients required combination therapy.[24]

Hence in T2DM optimal transition from monotherapy to combination therapy is a must if desired non-daibetic

glycemic levels are not attained even after 12weeks of monotherapy together with life style modifications.[25] This is essential to maintain not only effective glycemic control, but also to minimize disease progression, complications and improved compliance and thereby to get economic benefits. Present study concludes metformin-teneligliptin and metformin-glimepiride are best suited for combination therapy of OADs in T2DM patients because of their favourable pharmacokinetic characters and complementary pharmcodynamic effects which aid in effective glycemic control and thereby reducing/preventing complications/risks associated with T2DM economically.

CONCLUSION

Present study showed that all commonly available OADs require minimum of 12 weeks of therapy for effective glycemic control. Achieving non-diabetic levels of plasma sugars (<126mg/dl of FPS, <200mg/dl of PPS, <6.5% of HBA1c) should be the goal of treatment of T2DM to minimize disease progression and complications. Achieving non-diabetic levels of PPS is also essential as Post prandial hyperglycemia is associated with increase CV disease risk and long term macrovascular complications. Non-diabetic levels of plasma sugars were achieved better and in most of the patients with combination therapy as compared to monotherapy. Metfromin monotherapy is best for initiation of T2DM treatment.

However, for effective glycemic control, most of the patients require combination therapy at a later stage. Metformin-teneligliptin and metformin-glimepiride combination therapy for T2DM are better for their effectiveness and economics.

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