



# An Open Labelled, Prospective, Non-comparative, Multicentric Post Marketing Experience for Evaluation of Efficacy and Safety of Glizid-M In Type 2 Diabetes.

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## ABSTRACT

Glizid-M is the fixed dose combination of Gliclazide (80mg) and Metformin (500mg). The efficacy and safety of this combination therapy in type 2 diabetes has been evaluated in an open-label, prospective, non-comparative multicentric, phase IV study conducted in India over a period of 6 weeks in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The superiority of the combination therapy and its effects on glycaemic parameters and lipid profile has been observed. A discussion of the same with brief review of literature has been presented here. (*The Ind. Pract.* 2005; 58(6): )

## KEY WORDS

Glizid-M, Gliclazide, Metformin, type 2 diabetes and diabetes mellitus.

## INTRODUCTION

Type 2 or non insulin dependent diabetes mellitus (NIDDM) is a disabling metabolic disorder that affects more than 150 million people world-wide.<sup>1</sup> Three major pathophysiologic abnormalities are associated with NIDDM: *impaired insulin secretion, excessive hepatic glucose output, and insulin resistance* in skeletal muscle, liver, and adipose tissue.<sup>2</sup>

## Treatment

### **The treatment goals in NIDDM are:**

- The alleviation of symptoms through normalization of blood glucose levels and,
- The prevention of acute and long - term complications.<sup>3</sup>

Although diet and exercise remain the cornerstones of treatment, in the vast majority of patients with NIDDM, pharmacologic agents are frequently needed to achieve optimal glycaemic control and reduce the incidence of microvascular and possibly macrovascular complications, as

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shown in the *United Kingdom Prospective Diabetes Study (UKPDS)*.<sup>2</sup>

The therapeutic objectives recommended by the *American Diabetes Association (ADA)* include fasting plasma glucose (FPG) 80 - 120 mg/dL, post prandial plasma glucose < 180 mg/dL, and glycosylated hemoglobin (HbA<sub>1c</sub>) < 7%.<sup>2</sup> For patients with NIDDM, oral monotherapy may be initially effective for controlling blood glucose, but it is associated with a high secondary failure rate (primary failure is frequent only with patients with high baseline blood glucose at the time of beginning monotherapy, whereas secondary failure is to be expected in the course of the disease). The different classes of oral hypoglycaemic agents used to treat NIDDM have complementary mechanisms of action, and their use in combination often results in blood glucose reduction that are significantly greater than those that can be obtained with maximal doses of any single drug and this was clearly demonstrated in the UKPDS.<sup>2, 4</sup> Wide ranges of combinations have been used effectively to achieve glycaemic control in patients in whom oral monotherapy has failed<sup>4</sup>. The best-studied combination is that of sulfonylurea plus metformin, a therapeutic approach that addresses both underlying defects in the disorder: insulin deficiency and insulin resistance.<sup>5</sup>

### **Sulfonylureas**

Sulfonylureas continue to be used as the initial pharmacologic therapy, particularly when hyperglycemia is pronounced and evidence of impaired insulin secretion is present. Furthermore, they are often the foundation of combination therapy because of their ability to increase or maintain insulin secretion. They have a long history of use and few serious side effects (including hypoglycemia). Placebo - controlled studies have shown that sulfonylureas reduce FPG levels by about 54-72 mg/dL and HbA<sub>1c</sub> levels by 1.5 - 2% in patients with long-standing NIDDM.<sup>6-8</sup> Sulfonylureas can increase insulin secretion at sub stimulatory concentrations of glucose, suggesting an enhancement of beta-cell response, and when beta cells are exposed to maximally effective glucose concentrations,

demonstrating an additive effect independent of glucose concentrations.<sup>9</sup> Prolonged administration of sulfonylureas may also produce extrapancreatic effects that contribute to its hypoglycaemic activity. These effects include reduction of basal hepatic glucose production and an enhanced peripheral sensitivity to insulin secondary to intracellular signaling events that follow insulin receptor binding. Although the main effect of sulfonylureas appears to be stimulation of basal insulin secretion, these antidiabetic agents also stimulate the secretion of insulin throughout the duration of a meal.<sup>9</sup>

### **Biguanides**

Oral biguanide agents (phenformin and metformin) were introduced for the treatment of NIDDM in the late 1950s. Their use is encouraged for the treatment of NIDDM either as monotherapy or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin. Although their mechanism of action has not been clearly determined, decreased hepatic gluconeogenesis is thought to be the primary therapeutic effect of metformin in NIDDM. In addition, metformin appears to improve utilization of glucose in skeletal muscle and adipose tissue by increasing cell membrane glucose transport. This effect may be due to improved binding of insulin-to-insulin receptors since metformin is not effective in diabetics without some residual functioning pancreatic islet cells. Another effect of metformin that may contribute to its glucose-lowering properties is its ability to decrease fatty acid oxidation.<sup>10</sup> Other mechanisms may include decreased intestinal glucose absorption; however, this has only been observed in animals. Thus, in insulin-resistant patients with NIDDM, metformin increases insulin sensitivity by both decreasing hepatic glucose output and enhancing peripheral glucose uptake. In a recent study, 3 months of metformin treatment reversed the increased activity of lymphocyte plasma cell differentiation antigen (PC-I) found in NIDDM.<sup>11</sup> Metformin also decreases plasma very low density lipoprotein (VLDL) and triglycerides,

resulting in modest decreases in plasma total cholesterol.

### **Rationale of the combination (Gliclazide - Metformin)**

The goal of combination therapy is to take advantage of the differing mechanisms of action of the various pharmacologic agents and create an individualized treatment plan for achieving effective glycaemic control.

If monotherapy with a sulfonylurea or metformin fails to achieve the desired level of glycaemic control, the other second oral agent (if not contraindicated) should be added, with dose escalation over 4 - 8 weeks to the maximum. The use of a sulfonylurea with metformin is the most widely and extensively studied combination of oral hypoglycaemic agents and lowers HbA<sub>1c</sub> by an additional 1.7%<sup>12</sup>. Setter S. M et al reviewed the role of metformin hydrochloride in the treatment of type 2 diabetes mellitus with a focus on dual therapy. At the end of the study they concluded that metformin has multiple benefits in patients with type 2 diabetes. It can effectively lower HbA<sub>1c</sub> values, positively affect lipid profiles, and improve vascular and hemodynamic indices. Adverse effects are generally tolerable and self-limiting. The availability of products combining metformin with a sulfonylurea has expanded the array of therapies for the management of type 2 diabetes.<sup>13</sup> There is large number of literature evidence which reemphasizes that the high secondary failure rates with oral monotherapy and, moreover, the high primary failure rate in patients with very high blood glucose at diagnosis, coupled with the effectiveness of combination treatment, supports the suggestion that multiple-drug regimens be considered for initial pharmacologic treatment in patients with symptomatic type 2 diabetes whose blood glucose is not controlled by diet alone.<sup>14</sup> With this premise that treatment a sulfonylurea-metformin this combination provides a fair to good glycaemic control, it was also required to compare this combination with other existing choices. A multicentric, double blind study conducted by Hanefeld M et al observed one-year glycaemic control with a

sulfonylurea plus pioglitazone versus sulfonylurea plus metformin in patients with type 2 diabetes, with primary efficacy end point of HbA<sub>1c</sub> at week 52 and also measured fasting plasma glucose, insulin, and lipid profiles. The results demonstrated that HbA<sub>1c</sub> was reduced by 1.2% in the sulfonylurea plus pioglitazone group and 1.36% in the sulfonylurea plus metformin group; moreover fasting plasma glucose was reduced by 2.2 and 2.3 mmol/l in the respective groups. Clinically equivalent improvements in glycaemic control were observed for both combinations.<sup>15</sup>

The current study was planned to further establish the efficacy and safety of Gliclazide - Metformin in Indian patients with non insulin dependent diabetes mellitus.

### **PATIENTS AND METHODS**

#### **Study Objectives and Design**

Evaluation of efficacy, safety and tolerability of fixed dose combination of Glizid-M type 2 diabetes. An open labeled, non-comparative, and multicentric study.

#### **Study Centers**

The study was conducted at 6 centers all over India.

#### **Study Duration**

Duration of protocol therapy was 6 weeks. While the duration of study was 8 months

#### **Study Population and Sample Size**

The study was carried out in patients suffering from Type 2 diabetes mellitus inadequately controlled by diet, exercise or metformin or gliclazide alone or any combination therapy except study medication. A total of 126 patients were enrolled in the study and 121 patients were evaluated at the end of therapy.

#### **Selection of Subjects**

##### **Inclusion Criteria**

Male and female patients with Type 2 diabetes, aged 30 to 65 years, body mass index between 20-35 kg/m<sup>2</sup>, having fasting blood glucose  $\geq$  126 mg/dL and post prandial blood glucose  $\geq$  200 mg/dL, having no serious physical or biochemical abnormalities other than those generally

associated with type 2 diabetes and who were willing to give written informed consent were included in the study.

### **Exclusion criteria**

Following patients have been excluded from the study:

Patients having diabetes other than non insulin dependent diabetes mellitus, having a history of documented oral sulfonylurea treatment failure (primary or secondary), having insulin therapy within the 12 months prior the enrolment, having history of hypersensitivity to sulfonylureas or biguanides, liver or kidney damage or gastrointestinal disorders, acute infections, diseases of blood or haematopoietic organs, pregnant or lactating women and patients receiving any concomitant medication, which may have interacted with hypoglycaemic action of study drug.

### **Ethical Aspects**

The study was conducted in accordance with the Declaration of Helsinki and ICH-GCP guidelines. Regular monitoring was done to ensure compliance with the protocol and ICH-GCP guidelines.

### **Study Procedure**

After taking voluntary written informed consent, subjects were screened for inclusion/exclusion criteria. The pertinent demographic information and medical history was taken and subject's health status was checked. Subjects who passed the screening were included in the study and given Gliclazide (80mg) and Metformin (500mg) combination 1-2 tablets once or twice daily with meals up to a maximum of 4 tablets per day for 6 weeks. Patients were assessed on baseline (day 0), week 2, week 4 and week 6 of the treatment period. Fasting plasma glucose and 2-hour post prandial plasma glucose was measured on day 0, week 2, week 4 and week 6. Glycosylated hemoglobin and lipid profile were assessed on day 0 and week 6. Fasting insulin level was an optional investigation at baseline (day 0) and week 6.

### **Subject Compliance**

Subjects taking  $\geq 70\%$  of test medication over the duration of therapy were said to be

compliant with the protocol therapy. Subjects taking  $< 70\%$  of the test medication over the duration of therapy were said to be non-compliant with protocol therapy.

### **Concomitant Medication**

The subjects were not allowed to take any other oral hypoglycaemic agent during the study. If any other concomitant drug therapy was administered during the period of treatment, decision to continue or discontinue the subject was based on the pharmacology and pharmacokinetics of the non-study medications and likelihood of drug-drug interactions thereby affecting the pharmacodynamic profile of study medication.

### **Criteria For Evaluation Of Study Efficacy And Safety**

#### **Efficacy Criteria:**

- Primary Endpoints
  - Reduction in plasma glucose levels (fasting and post prandial glucose)
  - Reduction in HbA<sub>1c</sub> level
- Secondary Endpoints
  - Improvement in lipid profile (triglycerides, HDL, LDL & total cholesterol levels)

#### **Safety Criteria**

- Drug related adverse effects
- Vital signs and physical examinations (pulse rate, blood pressure, weight)
- Selected biochemistry and haematology parameters at baseline and after treatment

#### **Serious Adverse Events**

It was mentioned in the protocol that in case of a serious ADR, investigator would notify to the sponsor (within 48 hours) and take appropriate measures to safeguard the subject. Separate serious adverse event forms were also provided with each case report form.

#### **Statistics**

Descriptive statistics (minimum, maximum, mean, median, standard deviation/ standard error) for continuous

variables and numbers along with percentage (%) for categorical variables are presented. Depending upon the distributional assumptions paired t-test, Wilcoxon signed rank test and paired sign test was employed to compare pre treatment and post treatment assessment parameters. McNemar's test was applied for the paired design to detect the differences in percentages of subjects reporting an adverse effect symptom.

## RESULTS

A total of 126 subjects were enrolled in the study and 121 subjects were evaluable at the end of therapy. For statistical analysis, all patients who complied with  $\geq 70\%$  of test medication consumed over duration of protocol therapy were eligible for "intent to treat" (ITT) analysis.

### Demographics

The study group comprised of both males and females with the age ranging from 30 to 65 years having non-insulin dependent diabetes (Table 1 & Table 2). The total number of subjects enrolled in the study was 126, of which 75 were males and 51 were females.

Of these 126 subjects enrolled, 5 subjects dropped out (because of lost to follow up) which included 2 males and 3 females. All subjects were evaluable for body weight &

BMI at baseline and 121 were evaluable at the end of the study (Week 6). Mean body weight & BMI remained almost same at all visits with negligible variability.

### Blood Pressure Monitoring

Mean systolic blood pressure decreased continuously from baseline through week 6 and mean diastolic blood decreased marginally between baseline and week 6. The decrease in blood pressure (both systolic & diastolic) was not significant (Table 3).

### Efficacy Parameters

#### Fasting Blood Glucose Levels

Data for 121 subjects was analyzed for fasting plasma glucose levels at baseline, week 2, week 4 and week 6 of protocol therapy and the results indicated a statistically significant decrease in fasting plasma glucose levels of 68.2 mg/dL from baseline to week 6 (Table 4).

#### Post Prandial Glucose Levels

Data for post prandial glucose levels was analyzed for 121 subjects at baseline and week 6 and for 120 subjects at week 2 and week 4 (as one subject did not come for follow up at week 2 and week 4). The results indicated a statistically significant decrease in post prandial plasma glucose levels of 98.4 mg/dL from baseline to the end of the therapy, i.e., week 6 (Table 4).

**Table 1**  
**Sex distribution of study population**

Sex	Completed subjects	Drop Outs	Total
Male	73 (60.3 %)	2	75 (59.5 %)
Female	48 (39.7 %)	3	51 (40.5 %)
Total	121 (100 %)	5	126 (100 %)

**Table 2**  
**Demographic data (Age, Weight, Height & BMI) category of study population**

Parameters (N = 126)	Min	Max	Mean	Median	Std. Deviation
Age	30	65	49.6	50.0	8.4
Weight	46.0	90.0	66.4	65.0	8.7
BMI	20.1	34.2	25.0	24.9	3.4

**Table 3**  
**Descriptive Statistics for Systolic and Diastolic Blood Pressure**

Parameters	Mean ± SD	Mean ± SD (p value)			
		Baseline (N = 126)	Week 2 (N = 126)	Week 4 (N = 123)	Week 6 (N = 121)
B.P. (Systolic)	133.7 ± 12.7	133.2 ± 12.9 (0.295)	132.2 ± 10.3 (0.153)	131.3 ± 10.0 (0.198)	
B.P. (Diastolic)	84.3 ± 8.7	84.5 ± 6.8 (1.000)	83.8 ± 6.4 (0.166)	83.4 ± 5.5 (0.143)	

**Table 4**  
**Efficacy Parameters**

Parameters	Baseline		Week 2		Week 4		Week 6	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Fasting glucose mg/dL	121	179.6 ± 41.8	121	145.5 ± 28.3 <sup>†</sup>	121	128.4 ± 22.1 <sup>†</sup>	121	111.4 ± 19.2 <sup>†</sup>
PP glucose mg/dL	121	256.1 ± 52.3	120	200.5 ± 42.1 <sup>***</sup>	120	178.8 ± 33.5 <sup>***</sup>	121	157.7 ± 32.2 <sup>**</sup>
Glycosylated Hb (%)	121	8.26 ± 1.31	-	-	-	-	121	7.98 ± 1.27 <sup>#</sup>
Fasting Insulin level mIU/ml)	68	96.3 ± 29.3	-	-	-	-	68	98.19 ± 27.99 <sup>***</sup>
Total cholesterol (mg/dL)	121	202.8 ± 34.1	-	-	-	-	121	189.25 ± 28.78 <sup>†</sup>
Triglycerides (mg/dL)	121	365.0 ± 54.9	-	-	-	-	121	148.91 ± 42.86 <sup>†</sup>
HDL-C (mg/dL)	121	46.3 ± 8.3	-	-	-	-	121	48.14 ± 8.41 <sup>**</sup>
LDL-C (mg/dL)	121	112.5 ± 31.3	-	-	-	-	121	102.56 ± 26.95 <sup>†</sup>

\*p < 0.05 vs. baseline (Paired t test) - Significant; \*\*p < 0.01 vs. baseline (Paired t test) - Highly Significant; \*\*\*p > 0.05 vs baseline (Paired t test)- Non Significant  
<sup>†</sup>p < 0.05 vs. baseline (Paired sign test)- Significant; <sup>††</sup>p > 0.05 vs. baseline (Paired sign test)- Non Significant  
<sup>#</sup>p < 0.05 vs. baseline (Wilcoxon signed rank test)- Significant  
<sup>\*\*</sup>p > 0.05 vs. baseline (Wilcoxon signed rank test)- Non Significant

### **Glycosylated Hemoglobin (HBA<sub>1c</sub>)**

Data for HBA<sub>1c</sub> levels was analyzed for 121 subjects at baseline and week 6 and the results showed a statistically significant decrease of 0.28% in the mean value (Table 4).

### **Fasting Insulin level Levels**

Fasting insulin level being an optional investigation, data for 68 subjects was

available for analysis at baseline and week 6. Although there was a marginal increase 1.89 mIU/ml in the mean value from baseline to week 6, this change was not statistically significant (Table 4).

### **Lipid Profile**

121 subjects were evaluated for lipid profile at baseline and at week 6. All the parameters of lipid profile demonstrated a

**Table 5**  
**Frequency (%) of Hypoglycemic Episodes (N= 121)**

<b>No. Of Hypoglycemic Episodes</b>	<b>Total in Week 1</b>	<b>Total in Week 2</b>	<b>Total in Week 3</b>	<b>Total in Week 4</b>	<b>Total in Week 5</b>	<b>Total in Week 6</b>
0	112 (92.6%)	112 (92.6%)	114 (94.2%)	117 (96.7%)	111 (91.7%)	111 (91.7%)
1	5 (4.1%)	8 (6.6%)	4 (3.3%)	2 (1.7%)	7 (5.8%)	9 (7.4%)
2	4 (3.3%)	1 (0.8%)	3 (2.5%)	1 (0.8%)	2 (1.7%)	1 (0.8%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)
Total no. of observed Hypoglycemic Episodes	13(10.7%)	10 (8.3%)	10 (8.3%)	7 (5.8%)	14 (11.6%)	11 (9.1%)

significant change. Decrease of 13.55 mg/dL in mean values of total cholesterol was observed, from baseline to week 6. Similar finding was observed for LDL- cholesterol, which decreased by 9.94 mg/dL from baseline to week 6. Moreover, triglyceride levels showed a decrease of 216.09 mg/dL in the mean values. HDL- cholesterol levels showed an increase of 1.84 mg/dL from baseline to week 6 (Table 4).

**Safety Parameters**

**Hypoglycaemic Episodes**

121 subjects were observed for hypoglycaemic episodes at every visit from week 1 to week 6.

More than 90% of the subjects did not have any hypoglycaemic episodes. Occurrence of a single hypoglycaemic episode was observed on 35 occasions out of a total of 726 data points (4.8%). Occurrence of two hypoglycaemic episodes was observed in 12 (1.7%) occasions and that of three episodes only on 2 (0.3%) occasions.

None of the hypoglycaemic episode led to hospitalization or hypoglycaemic coma. (Table 5)

**Adverse Drug Reactions**

Safety evaluation was done for all the subjects enrolled in the study.

Heartburn, nausea and abdominal discomfort were the most common

gastrointestinal adverse effects of these, the first two showed a statistically significant reduction by the end of therapy. Other adverse reactions were mild, transient and not of clinical significance (Table 6).

**DISCUSSION**

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or peripheral insulin uptake<sup>16</sup>. An estimated 30 million people worldwide had diabetes in 1985. By 1995, this number had shot up to 135 million. The latest WHO estimate (for the number of people with diabetes world-wide in 2000) is 177 million. This will increase to at least 300 million by 2025. The number of deaths attributed to diabetes was previously estimated at just over 800,000. However, it has long been known that the number of deaths related to diabetes is considerably underestimated. A more plausible figure is likely to be around 4 million deaths per year related to the presence of the disorder. This is about 9% of the global total. Many of these diabetes related deaths are from cardiovascular complications. For WHO and the International Diabetes Federation (IDF), sponsors of World Diabetes Day, this increase can and must be prevented with the right measures.<sup>17</sup>

**Table 6**  
**Frequency (%) of Adverse Drug Reactions**

ADR		Specific Component Number of subjects (%)				
		Week 2	Week 4	Week 6	p value*	p value**
<b>Gastrointestinal</b>	Heartburn	20(16.1%)	9 (7.3%)	3 (2.4%)	0.003 <sup>†</sup>	0.000 <sup>†</sup>
	Nausea	18(14.5%)	6 (4.8%)	2 (1.6%)	0.008 <sup>†</sup>	0.000 <sup>†</sup>
	Abdominal discomfort	18(14.5%)	17(13.7%)	9 (7.3%)	1	0.096
	Constipation	13(10.5%)	11 (8.9%)	9 (7.3%)	0.774	0.424
	Loss of appetite	12 (9.8%)	17(13.7%)	14(11.4%)	0.267	0.804
	Diarrhea	10 (8.1%)	5 (4%)	6 (4.9%)	0.180	0.289
	Metallic taste	9 (7.3%)	14(11.3%)	4 (3.3%)	0.267	0.804
	Vomiting	6 (4.8%)	5 (4.0%)	4 (3.3%)	1	0.727
	Jaundice	1 (0.8%)	2 (1.6%)	0 (0.0%)	1	1
	<b>CNS</b>	Headache	12 (9.7%)	8 (6.5%)	3 (2.4%)	0.344
Dizziness		2 (1.6%)	5 (4.0%)	2 (1.6%)	0.375	1
Blurred vision		2 (1.6%)	1 (0.8%)	1 (0.8%)	1	1
<b>Dermatological</b>	Rash	6 (4.8%)	2 (1.6%)	2 (1.6%)	0.289	0.289
	Flushing	5 (4.0%)	1 (0.8%)	5 (4.0%)	0.219	1
	Pruritis	3 (2.4%)	2 (1.6%)	0 (0.0%)	1	0.250
	Erythema	2 (1.6%)	2 (1.6%)	2 (1.6%)	1	1
	Urticaria	2 (1.6%)	2 (1.6%)	2 (1.6%)	1	1
	Allergic vasculitis	1 (0.8%)	1 (0.8%)	1 (0.8%)	1	1
	Photosensitivity reactions	0 (0.0%)	2 (1.6%)	2 (1.6%)	0.5	0.5
<b>Musculoskeletal</b>	Joint pain	11 (8.8%)	10 (8.0%)	7 (5.7%)	1	0.219
	Back pain	12 (9.6%)	7 (5.6%)	6 (4.9%)	0.125	0.109
	Hyperglycemia	6 (4.8%)	3 (2.4%)	1 (0.8%)	0.453	0.063
	Muscle pain	0 (0.0%)	2 (1.6%)	0 (0.0%)	0.5	-
	Sinusitis	1 (0.8%)	0 (0.0%)	0 (0.0%)	1	1
	<b>Others</b>	Oedema	2 (1.6%)	4 (3.2%)	1 (0.8%)	0.625
Sinusitis		1 (0.8%)	0 (0.0%)	0 (0.0%)	1	1

\*Week 2 vs. Week 4, \*\*Week 2 vs. Week 6; <sup>†</sup>Statistically Significant ( $p < 0.05$ )

Four major classes of oral hypoglycaemic agents are available for treatment. They act as follows at major sites of defects in type 2 diabetes mellitus: by increasing insulin availability (secretagogues, i.e., sulfonylureas and meglitinides), by suppressing excessive hepatic glucose output (biguanides, viz metformin), by improving insulin sensitivity (thiazolidinediones viz, rosiglitazone and pioglitazone) and finally by delaying gastrointestinal glucose absorption ( $\alpha$ -glucosidase inhibitors viz acarbose and miglitol). As non insulin dependent diabetes mellitus is a progressive disorder, and although oral monotherapy is often initially successful, it is associated with a high secondary failure rate, which contributes to the development of long-term diabetic complications resulting from persistent hyperglycemia. For patients not taking insulin, accumulating evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective in achieving and maintaining target blood glucose levels. Low-dose combination therapy may be associated with fewer side effects than higher-dose monotherapy and may achieve similar or better glycaemic control. A therapeutic approach that addresses both underlying defects in diabetes viz insulin deficiency and insulin resistance, is gliclazide plus metformin.<sup>5</sup> Where gliclazide belongs to the sulfonylurea group of oral hypoglycaemic agents. It is rapidly absorbed from the GIT, and is metabolised in the liver. It appears in the blood within 1-2 hrs and peak level is achieved in 4-6 hrs. The plasma  $t_{1/2}$  is 8-12 hrs and its duration of action is 12 hrs. It is indicated for non insulin dependent diabetes mellitus. It stimulates insulin secretion by pancreatic beta cells. In the long-term it reduces hepatic gluconeogenesis, and increases insulin effects by acting at receptor or post-receptor sites. Metformin is the only currently available oral hypoglycaemic agent that acts predominantly by inhibiting hepatic glucose release. As patients with non-insulin dependent diabetes often have excess

hepatic glucose output, use of metformin is effective in lowering glycosylated hemoglobin ( $HbA_{1c}$ ) by 1-2 % when used as monotherapy or in combination with other blood-glucose lowering agents<sup>18</sup>. It is extensively plasma protein bound (more than 90%).

Addition of gliclazide to metformin therapy gives an additive glucose-lowering effect.<sup>19,20,21</sup> Similarly, addition of metformin to sulfonylurea therapy gives an additive response, both with respect to glucose-lowering<sup>20,21,22</sup> and lipid-lowering<sup>20, 24</sup> effects. Hermann et al<sup>20</sup> showed that in most patients with newly diagnosed type 2 diabetes (FPG level, 12.2 to 13.3 mmol /L [220 to 240 mg/dL]), blood glucose levels could be controlled with combined sulfonylurea-metformin therapy. Similar findings were reported in the UKPDS.<sup>25,26</sup>

In the current study, patients were administered a FDC of Gliclazide (80mg) and Metformin (500mg) i.e. Glizid-M, 1-2 tablets, once or twice daily with meals to a maximum of 4 tablets/day as per the patients glycaemic control. Assessment of fasting plasma glucose (FPG) and 2-hour post prandial glucose was performed at the baseline, at week 2, week 4 and at the end of the therapy (i.e. at week 6). Other critical parameters like glycosylated haemoglobin ( $HbA_{1c}$ ); lipid profile and fasting insulin levels were also assessed at baseline and at end of the therapy.

The results of the study showed a statistically significant decrease in fasting plasma glucose levels at every visit from a mean of 179.6 mg/dL at baseline to 145.5 mg/dL at week 2, 128.45 mg/dL at week 4 and 111.4 mg/dL at week 6. 98 subjects (86.7%) could achieve the current goals for treatment of type 2 diabetes mellitus in non pregnant adults laid by American Diabetes Association (ADA 2004) of fasting plasma glucose of  $\leq 130$  mg/dL at the end of the therapy. The efficacy of Glizid-M was further demonstrated by analyzing the mean values for post prandial plasma glucose levels. None of the subjects at baseline met the ADA criteria for optimal glycaemic control, whereas at the end of the therapy, 96 subjects (79.3%) achieved the goal of optimal

post prandial plasma glucose  $\leq$  180 mg/dL (ADA 2004).

Glycosylated Hb (HbA<sub>1c</sub>) levels significantly decreased by 3.4% in just 6 weeks of therapy indicating a definite trend towards better glycaemic control. Results showed a decrease in the mean value of HbA<sub>1c</sub> from 8.26 % at baseline to 7.98% at week 6.

Lipid profile was also analyzed in all the subjects at baseline and week 6 considering the fact that Metformin is additionally useful in treatment of diabetic dyslipidemia (characterized by low HDL, normal/marginally raised LDL & high triglycerides). Results of this study demonstrated a significant improvement in lipid profile after treatment with Glizid-M. Statistically significant increase in HDL (from mean values of 46.3 mg/dL to 48.14 mg/dL), decrease in total cholesterol (from mean values of 202.8 mg/dL to 189.25 mg/dL), LDL (from mean values of 112.5 mg/dL to 102.56 mg/dL) and significant decrease in triglycerides (from mean values of 365 mg/dL to 148.9 mg/dL) were observed.

Considering the fact that optimal lipid levels for adults with diabetes as per the American Diabetic Association (ADA 2004) include HDL cholesterol levels  $>$  45 mg/dL, LDL Cholesterol  $<$  100 mg/dL and triglycerides  $<$  200 mg/dL, the results of the current study demonstrated a highly significant improvement in HDL - cholesterol (4.7%) and significant decrease in triglycerides (59.2%). This implies that ADA target w.r.t HDL-cholesterol was achieved in 12 out of 58 subjects (20.7%) and ADA target w.r.t triglycerides was achieved in 10 out of 24 subjects (41.7%). This fact is particularly important in Indian context where low HDL and high triglycerides are especially common and increased levels of triglycerides is an independent risk factor for atherosclerotic cardiovascular disease.

As an optional investigation, at baseline and week 6, 68 subjects were also analyzed for fasting insulin levels and the changes observed were statistically not significant at the end of therapy.

Glizid-M was well tolerated by all the subjects except few suspected episodes of hypoglycemia but none of these episodes led to hospitalization. Few subjects also complained of mild gastrointestinal and dermatological adverse effects although these were not statistically significant.

## CONCLUSION

The study demonstrates that the fixed dose combination of Gliclazide and Metformin: Glizid-M is an effective and safe agent in treatment of type 2 diabetes mellitus. It not only helps patient to achieve optimal glycaemic control but also improves diabetic dyslipidemia.

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