



## SULFONYL UREAS FOR ANTIDIABETIC THERAPY, AN OVERVIEW FOR GLIPIZIDE

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### ABSTRACT

Glipizide is a "second generation" sulfonylurea, an oral hypoglycemic agent for the management of non-insulin dependent diabetes mellitus. Oral delivery of glipizide shows bioavailability problems and causes hypoglycemia with gastric disturbances. To overcome these problems, controlled release formulations as sustained release and controlled release tablets are available. Solubility of glipizide increases with increase in pH. Like any other sulfonylurea, glipizide appears to act principally by stimulating the insulin secretion from pancreatic beta-cells. Glipizide overdose symptoms include low blood sugar.

**Keywords:** Antidiabetic, Sulfonyl urea, Glipizide

### INTRODUCTION

Glipizide is one of the most commonly prescribed drugs for treatment of type II diabetes. It is an oral hypoglycemic drug from sulfonylurea group. It is active at very low doses, a characteristic feature of second generation sulfonylureas. Oral therapy with glipizide comprises problems of bioavailability fluctuations and may be associated with severe hypoglycemia and gastric disturbances. The physicochemical characteristics of glipizide has been given in Table 1. Although it is closely related to other sulfonylureas of the same therapeutic class such as glibenclamide, blood insulin and glucose time courses differ. It also carries much lower risk of hypoglycemia.

### DIABETES

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentrations (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance<sup>3</sup>. Non Insulin Dependent Diabetes Mellitus (NIDDM) represents a heterogeneous group comprising milder form of diabetes that occur predominately in adults and a vast majority of diabetic patients possess NIDDM<sup>4</sup>. The analytical parameters of glipizide which will prove beneficial to researchers are shown in Table 2. Glipizide has been in extensive use to treat NIDDM and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness<sup>4</sup>; but it has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy in normal doses.

### MECHANISM OF ACTION AND PHARMACOLOGY

1) Glipizide is a "second generation" sulfonylureas, an oral hypoglycemic agent for the management of non-insulin dependent diabetes mellitus (type II diabetes; maturity-onset diabetes). On a weight basis, glipizide is 100 times more potent than tolbutamide in animal studies<sup>5</sup>. Glipizide has a more rapid onset of hypoglycemic effect than glyburide (glibenclamide) and a shorter duration of action<sup>5</sup>.

2) Glipizide reduces blood glucose by stimulating insulin secretion and altering insulin sensitivity; the drug causes a sustained increase in glucose-stimulated insulin secretion in most patients during prolonged therapy.

3) Like other drugs belonging to the class of sulfonylureas, glipizide appears to act principally by stimulating the insulin secretion from pancreatic beta-cells<sup>6</sup>. Glipizide is also reported to exert a major portion of its antidiabetic effect by altering the responsiveness of insulin-sensitive tissues, such that the action of insulin is potentiated<sup>5,7</sup>, an effect also postulated for chlorpropamide<sup>7</sup>. It is

presumed that this effect is related to an alteration of the tissue plasma membrane, resulting in an increased number of insulin receptors<sup>7</sup>. Data also suggest that glipizide improves glucose utilization not only by promoting pancreatic insulin release but also by enhancing extra-pancreatic availability of insulin and/or the number of insulin receptors<sup>8</sup>.

4) Studies have demonstrated that during long-term treatment with sulfonylureas agents, plasma insulin levels either returned to pretreatment values or actually decrease<sup>9</sup>. However, glipizide (unlike other sulfonylureas agents which result in decreased insulin levels following long term treatment) maintains an elevated insulin secretory response (increased from 100% to 1500% above untreated values) for periods of 2 to 6 years or longer<sup>7,10</sup>. These data indicate that glipizide causes a long-term increase in glucose-stimulated insulin secretion.

5) Glipizide has shown to potentiate chronic effects on insulin secretion<sup>7</sup>. At the same time, other studies utilizing glipizide for periods of over 6 months have not reported tolerance to hypoglycemic effects<sup>10</sup>. Stabilization of blood glucose levels were reported for at least 4 years with glipizide therapy<sup>10</sup>. One study reported that glipizide maintained control for up to 6 years in 70% of patients<sup>7</sup> (cumulative secondary failure rate of approximately 30%).

6) Studies by Brogden et al and other researchers has shown that glipizide improved control of hyperglycemia in patients with poor results from other sulfonylureas<sup>5,10</sup>. However, improvement with glipizide has been greater in patients who were well-controlled on previous sulfonylureas therapy, compared to patients who responded poorly.

7) At the cellular level, sulfonylureas is known to bind to a sulfonylureas receptor on the pancreatic beta-cell inhibiting the adenosine triphosphate-dependent potassium channel (K-ATP). Stabilization of potassium efflux causes depolarization and activation of the L-type calcium channel. Influx of calcium stimulates insulin secretion. The effect of sulfonylureas is similar to that of glucose at the cellular level; however, sulfonylureas only stimulates phase I (initial rapid peak) release of insulin and shows no effect on phase II (prolonged insulin release). When sulfonylureas treatment is initiated, insulin levels increase and plasma glucose levels gradually decrease. As the glucose levels decrease, insulin levels also decrease but still remain higher than pretreatment levels.

### ADVANCES IN DELIVERY SYSTEMS

Some of the recent advancements incorporated for improved delivery of glipizide but yet to be released into the market is given briefly below:

- Ashok V. Bhosale et al. has reported a formulation of glipizide with beta cyclodextrin as a controlled release matrix tablet. The invitro evaluation shows promising results for the drug where the release is for an extended period of time with constant levels (Ashok V. Bhosale et al.,2009).
- Mutalik, S. et al. has prepared and evaluated glipizide matrix transdermal systems for diabetes mellitus. Preclinical studies are also completed for this formulation where the results are adaptable for comfortable long term therapy<sup>13</sup>.
- Mutalik, S. et al. has also performed pharmacological evaluation of membrane moderated transdermal system of glipizide with results which are acceptable for controlling diabetes<sup>13</sup>.
- Jain, S, et al, have prepared and studied glipizide loaded biodegradable nanoparticles and the influence of variables on the formulation to show that it can be the future for diabetic therapy<sup>14</sup>.

**Table 1: Physico characteristics of Glipizide<sup>2</sup>**

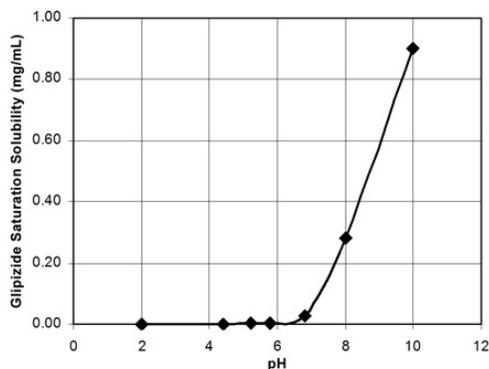
Sr. no.	Description	
1	Molecular formula	C <sub>21</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub> S
2	Molecular weight	445.5
3	Physical state	Powder (white)
4	Melting point	205 °C
5	Solubility	Soluble Insoluble Sparingly soluble
		Chloroform, dimethylformamide, Water, ethanol Acetone
6	Dissociation constant	pK <sub>a</sub> 5.9
7	Partition coefficient	Log P(octanol/water), 1.9
8	Colour test	Mercurous Nitrate—black

**Table 2 Analytical parameters of Glipizide<sup>2</sup>**

Particulars		
<b>Thin layer chromatography</b>	<b>System</b>	<b>Rf value</b>
	TA	Rf 87
	TB	Rf 00
	TC	Rf 41
	TE	Rf 07
	TL	Rf 05
<b>High performance liquid chromatography</b>	<b>System</b>	<b>RI value</b>
	HX	478
	HY	423
	HZ	Retention time 4.5 min.
	HAA	Retention time 17.6 min.
Ultraviolet spectrum	λ <sub>max</sub>	276 nm
Infra-red spectrum	Principal peaks	1528,1690,1650,1159, 1032,900 cm <sup>-1</sup> (KBr disk).
Mass spectrum	Principal ion at	m/z 150,121,56,93,39,151,66,94.

**Table 3: Saturation Solubility of Glipizide at Different pH**

Sr. no.	Medium Ph	Saturation solubility(µg/mL)
1	2	1.1
2	4.4	1.3
3	5.22(DI water)	3.9
4	5.8	4.9
5	6.8	26.6
6	8	280.7
7	10	898.9



**Fig. 1: pH solubility profile of Glipizide**

The solubility is expected to increase by rise in pH. As given, glipizide shows increased solubility immediately above the pKa values which is shown in Figure 1 and Table 3. It is recommended to study the dissolution of glipizide at pH 6.8 buffer for experimental purposes.

#### CONVENTIONAL AND NOBLE FORMULATIONS OF GLIPIZIDE

Glipizide is available in market mainly in tablet form (2.5mg, 5 mg, 10mg). Some of different marketed brands available are shown in Table 4.

#### PHARMACODYNAMICS/KINETICS

##### Bioavailability

- 1) Oral, immediate release, complete<sup>16</sup>.
- 2) Oral, extended release, 100% release

##### Effects of Food

Clinically insignificant

Food does NOT affect total absorption but absorption may be delayed when glipizide is given with food.

##### Distribution

Protein Binding is 97% to 99%.

Volume of Distribution is 11 to 25 L<sup>5</sup>. The apparent volume of distribution at steady state was 0.089 liters/kilogram (L/kg) (central compartment) and 0.112 L/kg (peripheral compartment) adjusted for ideal body weight, respectively. This study differed from other researchers due to use of a 2-compartment open model.

##### Metabolism

A) **Metabolism Sites** is liver extensively<sup>5</sup>. First pass metabolism is minimal<sup>5</sup>.

##### B) Metabolites

- 1) 4-trans-hydroxycyclohexyl derivative, inactive.
- 2) 3-cis-hydroxycyclohexyl derivative, inactive.
- 3) N-(2-acetylamino-ethyl-phenyl-sulfonyl)- N-cyclohexyl urea, inactive.

#### Excretion

A) Through Kidney - Renal Excretion is 63% to 89%. Only 3% to 9% of a dose is eliminated as unchanged drug; the majority of a dose is recovered as metabolites<sup>5</sup>.

B) Other excretion is via feces, 11% .

#### Elimination half-life

Elimination half-life is 2 to 5 hours<sup>5,17</sup>. The half-life did NOT differ between middle-aged (8.4 hours; mean=46.1 years) and elderly patients (10.3 hours; mean=64.8 years). This study differs from earlier ones by using a 2- compartment model. The half-life in obese versus nonobese patients was 5.4 hours and 6.7 hours, respectively, at steady state. This study differs from earlier ones by using a 2-compartment model.

#### DOSAGE

Oral (allow several days between dose titrations): Adults: Initial: 5 mg/day; adjust dosage at 2.5-5 mg daily increments as determined by blood glucose response at intervals of several days.

**Immediate release tablet:** Maximum recommendation of immediate release tablet is once-daily dose: 15 mg; maximum recommended total daily dose: 40 mg

**Extended release tablet (Glucotrol® XL):** Maximum recommended dose: 20 mg

#### When converting dosage from insulin to glipizide:

Current insulin requirement 20 units: Discontinue insulin and initiate glipizide at usual dose

Current insulin requirement >20 units: Decrease insulin by 50% and initiate glipizide at usual dose; gradually decrease insulin dose based on patient response. Several days should elapse between dosage changes.

**Elderly:** Initial: 2.5 mg/day; increase by 2.5-5 mg/day at 1- to 2-week intervals

**Dosing adjustment/comments in renal impairment:** Clcr<10 mL/minute: Some investigators recommend not using glipizide<sup>5</sup>.

**Dosing adjustment in hepatic impairment:** Initial dosage should be 2.5 mg/day

#### ADVERSE REACTION

Frequency of the adverse reaction is not defined. However, the possible adverse effects have been shown in Table 5.

**Table 4: Some marketed formulations of Glipizide**

Sr. no.	Brand name	Company	Delivery system
1	Glide	Franco Indian	Tablet (5 mg)
2	Glucolip	Wallace	Tablet (5 mg)
3	Glynase	USV	Tablet (5 mg)
4	Glyzip	Stadmed	Tablet (2.5mg,5mg)
5	Glynase-XL	USV	SR Tablet (5mg,10mg)
6	Glzip-5 CR	Stadmed	CR Tablet(5mg)

**Table 5: Possible adverse effects of Glipizide**

Sr. no.	Body system	Reaction
1	Cardiovascular	Edema, syncope
2	Central nervous system	Anxiety, depression, dizziness, headache, insomnia, nervousness
3	Dermatologic	Rash, urticaria, photosensitivity, pruritus
4	Endocrine & metabolic	Hypoglycemia, hyponatremia, SIADH (rare)
5	Gastrointestinal	Anorexia, nausea, vomiting, diarrhea, epigastric fullness, constipation, heartburn, flatulence
6	Hematologic	Blood dyscrasias, aplastic anemia, hemolytic anemia, bone marrow suppression, thrombocytopenia, agranulocytosis
7	Hepatic	Cholestatic jaundice, hepatic porphyria
8	Neuromuscular & skeletal	Arthralgia, leg cramps, myalgia, tremor
9	Ocular	Blurred vision
10	Renal	Diuretic effect (minor)
11	Miscellaneous	Diaphoresis, disulfiram-like reaction

There are several postmarketing and case reports with abdominal pain reported after administering glipizide.

#### OVERDOSE/TOXICITY

Glipizide overdose symptoms include low blood sugar, tingling of lips and tongue, nausea, yawning, confusion, agitation, tachycardia, sweating, convulsions, stupor and coma. Intoxication with sulfonylureas can cause hypoglycemia and patients are best managed with glucose administration (oral for milder hypoglycemia or by injection in more severe forms<sup>13</sup>).

#### WARNING/PRECAUTIONS

- Use of glipizide in patients suffering from severe hepatic disorders must be with utmost care and caution.
- Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds and it is advised to avoid use of glipizide when previous reaction has been severe.
- The extended release formulation generally has a matrix / coat / polymer and the drug is enclosed within a nondeformable matrix. Following drug release/absorption, the matrix/shell is expelled in the stool. The use of non deformable products in patients with known stricture / narrowing of the GI tract has been associated with symptoms of obstruction. Avoid use of extended release tablets (Eg. Glucotrol® XL) in patients with severe gastrointestinal narrowing or esophageal dysmotility.
- Product labeling states oral hypoglycemic drugs may be associated with increased cardiovascular mortality compared to treatment with diet alone or diet plus insulin. However, data to support this claim is limited.
- Pregnancy Implications – glipizide is known to cross placenta. Abnormal blood glucose levels are associated with a higher incidence of congenital abnormalities. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. If glipizide is used during pregnancy, discontinue and change to insulin at least 1 month prior to delivery to decrease prolonged hypoglycemia in the neonate.

#### DIETARY CONSIDERATIONS

It is advised to administer immediate release tablets 30 minutes before meals; extended release tablets with breakfast. Dietary modification based on ADA recommendation is a part of therapy. Decreased blood glucose concentration and Hypoglycemia may occur in selected patients. Patients must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

#### CARDIOVASCULAR CONSIDERATIONS

The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, presently there is only limited data to support this promise, particularly with newer generation agents. An earlier study suggested poor cardiovascular outcomes in diabetic patients treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in diabetic patients receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylureas therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

#### DENTAL HEALTH: EFFECTS ON DENTAL TREATMENT

Glipizide-dependent diabetics (noninsulin dependent, type II) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

#### MENTAL HEALTH: EFFECTS ON PSYCHIATRIC TREATMENT

Glipizide may rarely cause agranulocytosis; it is advised to take caution with clozapine and carbamazepine administration;

phenothiazines and TCAs may antagonize glipizide hypoglycemic effects. MAO inhibitors and TCAs may enhance hypoglycemic effects.

#### Comparative Efficacy and Evaluation With Other Therapies

##### A) Chlorpropamide

For treatment of Diabetes mellitus Glipizide is comparable to chlorpropamide in lowering blood glucose in type II diabetes<sup>18,19,20,21</sup>. In a review of controlled studies in type II diabetes, glipizide is reported to be as effective as or possibly more effective than chlorpropamide and tolbutamide in controlling blood glucose<sup>22</sup>.

##### B) Gliquidone

Gliquidone in a mean daily dose of 70 milligrams (mg) produced significantly lower plasma glycosylated hemoglobin levels (HbA1) than glipizide (mean daily dose 9 mg) in a long-term (one year) study involving 39 patients with non-insulin-dependent diabetes mellitus<sup>23</sup> (p < 0.01). The dose of gliquidone is comparatively high.

##### C) Gliclazide

The different comparative studies revealed the results that gliclazide is effective in controlling blood glucose levels and in reduction of glycosylated hemoglobin levels in non-insulin-dependent (type II) diabetic patients as first-generation and other second-generation sulfonylureas<sup>23,24,25,26,27</sup>.

Short term comparative studies with a small sample (n = 47) was performed and the results showed better control of blood glucose as compared to glyburide<sup>28</sup> though it was not confirmed in controlled studies<sup>23</sup>. In another study, gliclazide showed better control of hemoglobin levels than glipizide<sup>25</sup>.

In long term studies, a randomized study was performed where n = 247. A significant lower secondary failure rate after 5 years of treatment was 7 % with gliclazide but 26 % with glipizide for NIDDM patients. However, the 18% secondary failure rate shown by glyburide (18%) was not significantly different from that of gliclazide. In this study, secondary failure was considered to be lack of achievement of postprandial blood glucose levels below 10 mmol/L or glycosylated hemoglobin levels<sup>25</sup> of less than 10%. It is recommended for further studies to confirm long term efficacy of gliclazide.

##### D) Glipizide / Metformin Hydrochloride in Diabetes mellitus type II

Looking into the combination therapy and taking into consideration, the fixed combination of glipizide / metformin, it is seen that this combination is more effective than glipizide monotherapy in type II diabetic patients.

Fixed glipizide / metformin tablets (1.25/250 milligrams (mg), 2.5/250 mg, and 2.5/500 mg) were investigated as initial therapy in type II diabetic patients poorly controlled on diet / exercise alone (glycosylated hemoglobin 7.5 to 12.5%, fasting plasma glucose less than 300 milligrams / deciliter (mg/dL)) in a 24-week, unpublished, active-controlled study<sup>29</sup> (n=868). Patients were initially randomized to receive one tablet daily of the glipizide/metformin formulations, or metformin alone (500 mg) or glipizide alone (5 mg), with dose adjustments after two weeks to achieve a mean daily glucose level of 130 mg/dL or lower (maximum dose, 10/2000 mg for glipizide/metformin). Data for the 1.25/250-mg fixed formulation were not provided. After 24 weeks, reductions in glycosylated hemoglobin in the 2.5/250- and 2.5/500-mg groups (each by about 2.1%) were significantly greater compared to glipizide monotherapy (-1.8%) or metformin monotherapy (-1.5%). A final glycosylated hemoglobin level of less than 7% was achieved by more patients receiving either 2.5/250 or 2.5/500 mg glipizide/metformin (about 58%) than those assigned to metformin alone (35%) or glipizide alone (43%) (statistical analysis was not applied). Fasting plasma glucose was significantly and similarly reduced in both fixed-combination dose groups (by approximately 55 mg/dL); although falls were greater compared to metformin or glipizide alone, statistical comparison was not provided. Compared

to baseline, a significantly greater reduction in the 3-hour postprandial glucose AUC was observed with fixed glipizide/metformin relative to metformin or glipizide alone, although specific data were not presented. Fixed glipizide/metformin was reported to enhance the postprandial insulin response, with no effect on fasting insulin levels.

Second-line therapy with fixed glipizide/metformin was effective in treating type II diabetic patients who were poorly controlled (glycosylated hemoglobin 7.5% or greater) on at least a half-maximal labeled dose of a sulfonylureas in an 18-week randomized comparison with metformin alone and glipizide alone (n=247). A fixed-combination dose of 5/500 mg daily was given initially, with dose adjustment during the first 8 weeks to achieve a mean daily glucose level of 130 mg/dL or lower (maximum dose, 20/2000 mg). Patients randomized to glipizide alone and metformin alone received 30 mg and 500 mg, respectively; metformin (but not glipizide) doses were titrated similarly. At 18 weeks, significantly lower mean final glycosylated hemoglobin and fasting plasma glucose levels were observed in patients assigned to glipizide/metformin compared to the monotherapy. More patients receiving the fixed combination (36%) achieved a final hemoglobin level of less than 7% than those treated with metformin alone (10%) or glipizide alone (9%), although statistical analysis of these differences was not provided. Compared to baseline, a significantly greater reduction in the 3-hour postprandial glucose AUC was observed with fixed glipizide/metformin relative to metformin or glipizide alone, although specific data were not presented. Fixed glipizide/metformin had no significant effect on fasting insulin<sup>30</sup>.

#### E) Tolbutamide

Glipizide appears to be as effective, but probably not superior to, tolbutamide in the treatment of type II diabetes<sup>11,31</sup>.

Similar efficacy was reported with glipizide (up to 40 milligrams daily) and tolbutamide (up to 3 grams daily) in type II diabetes; however, glipizide had more chronic effects on insulin secretion during 6 months of treatment<sup>11</sup>. Glipizide has effectively treated hyperglycemia in patients not controlled with tolbutamide<sup>21,31</sup>.

#### F) Glyburide

Glyburide is a more potent drug as compared to glipizide. The maximal hypoglycemic effects of glyburide are similar to those of other sulfonylureas, including glipizide<sup>21,32</sup>. Several controlled studies have reported the comparable efficacy of glyburide and glipizide in type II diabetics who were unresponsive to diet alone, as well as in patients whose blood glucose was controlled (adequately or inadequately) with previous therapy<sup>21,33,34</sup>. Additionally, glipizide undergoes more rapid elimination thus possibly reducing the risk of hypoglycemia<sup>5</sup>. Glipizide and glibenclamide were compared in a double-blind, crossover study, utilizing similar doses of each drug (5 mg initially, to a maximum maintenance of 20 mg daily), for a period of 4 months. Increases in post-prandial blood glucose levels were significantly lower with glipizide as compared to glibenclamide; fasting blood glucose and glucose concentrations in the urine were significantly lower during glibenclamide treatment<sup>34</sup>.

Glyburide was effective in lower doses than glipizide for the treatment of non-insulin dependent diabetes mellitus in a randomized open study<sup>35</sup>. Although both drugs were effective, substantial increases in the dose of glipizide were required throughout the study (2 to 6-week dose-adjustment phase and a 3-month maintenance phase). Mean initial doses were 8.2 and 9.6 mg daily for glyburide and glipizide, respectively. After the 3-month maintenance phase, mean doses were 10.3 and 18.3 mg daily, respectively. Significantly lower doses of glyburide were required to maintain glucose levels below 140 mg/dL throughout the study; lower doses of glyburide were also required to maintain glycosylated hemoglobin at 9% of hemoglobin or less. During a 15-month study, glipizide and glyburide resulted in comparable decreases in glycosylated hemoglobin and fasting plasma glucose. The fasting plasma glucose decreased to 9.1 and 9.3 at 3 and 15 months, respectively, in patients receiving glipizide compared to 7.7 and 8.4 at 3 and 15 months, respectively, in patients receiving

glyburide. This study included only 46 patients with diabetes mellitus and no previous pharmacologic treatment, who were randomly assigned to glyburide, glipizide, or placebo. The maximum allowable dose was 15 milligrams of each agent. Results of this study should be interpreted with caution due to the small sample size and number of drop-outs (placebo - 4, glyburide - 2).

#### G) Insulin

Treatment with sulfonylureas or exogenous insulin results in equivalent improvement in insulin action in patients with non-insulin-dependent diabetes mellitus<sup>36</sup>. Eight patients were studied before and after three months treatment with each agent, using a randomized crossover design. Decreases in mean glycosylated hemoglobin were similar as well as lowering of postabsorptive glucose production rates. Glucose utilization at supraphysiologic insulin concentrations was increased, while neither agent altered erythrocyte insulin binding at physiologic insulin concentrations. The authors suggest that both agents operate by modifying a postbinding defect.

In a placebo-controlled, double-blinded, randomized, crossover study, the use of glipizide was evaluated in combination with insulin. Ten patients with type II diabetes mellitus, but requiring insulin, were studied. After 8 weeks on combined glipizide and insulin therapy, no significant difference was found in fasting blood glucose, glycosylated hemoglobin and plasma lipoproteins when compared to insulin alone<sup>37</sup>.

Pre-treatment with insulin before instituting therapy with glipizide was evaluated in patients with type II diabetes mellitus. The study group consisted of 69 Mexican American type II diabetics who were obese, had poor glycemic control, and had previously failed therapeutically on a first-generation sulfonylurea. The study subjects were randomized to receive either glipizide or a short course (10 weeks) of insulin prior to switching to glipizide. After 10 weeks, insulin was found to provide a more rapid decrease in fasting blood glucose, two-hour postprandial glucose and glycosylated hemoglobin than glipizide. However, by the end of the study (10 months) no significant differences were found between the group receiving the insulin pretreatment and the group that had been simply started on glipizide<sup>38</sup>.

The combination of insulin and glipizide was compared to insulin and placebo in 20 type II diabetics who previously failed on oral hypoglycemic agents<sup>39</sup>. Overall, there was no significant change in diabetic control in either group; however, the median fasting plasma glucose fell in the glipizide group, but not in the placebo group. There was no significant change in fasting C-peptide and no increase in C-peptide response to glucagon. However, an increase in fasting insulin concentration was noted in the glipizide group as compared to the placebo group.

#### H) Nateglinide

Glipizide immediate release (IR), glipizide gastrointestinal therapeutic system (GITS), and nateglinide provided control of postprandial glucose levels in patients with type II diabetes mellitus (DM). In a small, randomized, placebo-controlled, cross-over study, 15 adult patients with type II DM (body mass index less than 40 kilogram/squared meter (kg/m<sup>2</sup>)) and glycosylated hemoglobin (HbA1c) less than 8%), received glipizide IR twice daily, nateglinide 120 mg four times daily, and glipizide GITS once daily for 7 to 10 days. A cross-over design was used with a 48 hour washout period. Glipizide dosage was titrated to a fasting capillary glucose level below 6 millimoles/liter (mmol/L). Glipizide IR was given 30 minutes before breakfast and dinner, glipizide GITS 30 minutes before breakfast, and nateglinide 10 minutes before meals and bedtime snack. At day 7 to 10 of each study period patients returned for laboratory testing at which time, study medication was administered before test meals in a placebo-controlled, double-blind fashion. Overall postprandial hyperglycemia, the primary endpoint, was determined by the glucose area-under-the-curve (AUC) at 11 hours post breakfast and peak postprandial glucose. Significantly lower plasma glucose levels compared to placebo (p less than 0.05) occurred with all drug regimens. However, between group

comparisons are difficult to access because the authors choose to report standard error of the mean rather than the mean, itself<sup>40</sup>.

## CONCLUSION

It can thus be concluded that taking into consideration all the above presented facts, glipizide, a drug belonging to sulfonylurea class, can be effectively used for controlling type II diabetes with little or no adverse effects and improves patient condition even after chronic therapy.

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