Role of Glimepiride “A Novel Sulfonylurea” in the Management of Type 2 Diabetes Mellitus

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ABSTRACT
Background: Diabetes mellitus (DM) is probably one of the oldest diseases known to man. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. Type 2 Diabetes mellitus is the most common form of diabetes mellitus characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. There are many effective treatment options available for the type 2 diabetes mellitus. But sulfonylureas still play a primary role in pharmacologic management of type 2 diabetes. Therefore we evaluated the effect of Glimepiride on fasting blood sugar level in patients of type 2 diabetes mellitus.

Objective: To find out the effect of Glimepiride on fasting blood sugar level in type 2 diabetes mellitus patients.

Material & Methods: This study was conducted by the Department of Pharmacology in association with Department of Medicine at Maharishi Markandeshwar Institute of Medical Sciences & Research (MMIMSR), Mullana Ambala. Total 25 patients were selected for the study and these patients were administered Glimepiride in dose range of 1-6 mg/day, for 24 weeks.

Statistical Analysis: statistical analysis was done by Student's “t”- test.

Result: During the study it was found that there was a significant reduction in fasting blood sugar score (p<0.05) after 24 weeks.

Conclusion: Glimepiride play an important role in type 2 diabetes patients because glimepiride effectively reduced fasting blood sugar.

Keywords: Fasting blood sugar, glimepiride, sulfonylurea, type 2 diabetes mellitus

INTRODUCTION
Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago [1]. In 1936, the distinction between type 1 and type 2 diabetes mellitus was clearly made [2]. Type 2 diabetes mellitus was first described as a component of metabolic syndrome in 1988 [3]. Type 2 diabetes mellitus (formerly known as non-insulin dependent diabetes mellitus) is the most common form of diabetes characterized by hyperglycemia, insulin resistance, and relative insulin deficiency [4]. Type 2 diabetes mellitus results from interaction between genetic, environmental and behavioral risk factors [5]. People with type 2 diabetes mellitus are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. It is estimated that 366 million people had diabetes mellitus in 2011; by 2030 this ratio raised to 552 million [6]. The number of people with type 2 diabetes is increasing in every country. Diabetes mellitus caused 4.6 million deaths in 2011[6]. It is estimated that 439 million people would have type 2 diabetes by the year 2030 [7]. The incidence of type 2 diabetes varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors [8]. It is predicted that the prevalence of type 2 diabetes mellitus will increase in the next two decades and much increase will occur in developing countries.
where the majority of patients are aged between 45 and 64 years [9].

Type 2 diabetes presents as a spectrum of metabolic abnormalities with prominent insulin resistance and relative insulin deficiency [10]. Effect of diabetes is not limited to carbohydrate metabolism but lipid and protein metabolism play an important role in the progression of the disease [11].

Major risk factors for type 2 diabetes mellitus
1. Family history of diabetes (parents or siblings with diabetes)
2. Obesity (≥120% over desired body weight or BMI ≥27 kg per m²)
3. Ethnicity (e.g., black, Hispanic, native American, Asian American, Pacific Islander)
4. Age ≥45 years
5. Previously identified IFG or IGT
6. Hypertension (≥140/90 mm Hg)
7. HDL cholesterol level ≤35 mg per dl (0.90 mmol per L) and/or a triglyceride level ≥250 mg per dl (2.83 mmol per L)
8. History of gestational diabetes mellitus or delivery of babies over 4,032 g (9 lb)
   IFG = impaired fasting glucose; IGT = impaired glucose tolerance; HDL = high-density lipoprotein.


There are many effective treatment options available for the type 2 diabetes mellitus. But sulfonylureas still play a primary role in pharmacologic management of type 2 diabetes. Patients who respond best to treatment with sulfonylureas include those with a diagnosis of type 2 diabetes mellitus before 40 years of age, duration of disease less than five years before initiation of drug therapy and a fasting blood glucose level of less than 300 mg per dl [12]. The sulfonylureas are divided into two groups or generations. All members of this class of drugs are substituted arylsulfonylureas. They differ by substitutions at the para position on the benzene ring and at one nitrogen residue of the urea moiety. The sulfonylurea drug class has evolved as different generations of agents. The first-generation sulfonylureas are the oldest and include tolbutamide, tolamazide, chlorpropamide and acetohexamide. The second-generation sulfonylureas include glyburide (also known as glibenclamide), glipizide, gliclazide and glimepiride. Glimepiride is a once-daily oral antidiabetic drug indicated for type 2 diabetes when diet, physical activity, and weight reduction alone do not control the disease and is available in many countries [13].

Pharmacology of Glimepiride: Glimepiride is comparatively a newer second generation oral hypoglycemic agent belonging to sulfonylurea group. The systematic name of glimepiride is trans-1-{4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1carboxamide)ethyl]-phenylsulfonyl}-3-(4-methyl cyclohexyl) urea [14]. The main effect of sulfonylurea (including glimepiride) is increase in the beta cells insulin release as a response to the serum glucose level. These drugs bound to the surface receptors of the beta cell membrane, inhibiting ATP sensitive potassium channels and causing depolarization of the cell membrane. Depolarization leads to potassium channel opening which enables extracellular calcium to enter the cells. Increased intracellular calcium concentration enhances the binding of calcium to the transport protein calmodulin. This leads to microfilament contraction and release of insulin containing granules. Increased insulin secretion causes reduction of serum glucose, which improves beta cells sensitivity to glucose and potentiates insulin secretion. After oral administration, glimepiride is rapidly and completely absorbed from the gut. Maximum plasma concentrations are achieved after approximately 2.5 hours. Unchanged drug is ~ 99 % bound to serum proteins especially albumin. The volume of distribution is about 0.2 L/kg. Glimepiride is metabolized by the liver and the metabolites are excreted in the urine.

MATERIAL & METHODS
This randomized, open study was conducted in the patients suffering from type 2 diabetes mellitus by the Department of Pharmacology in association with Department of Medicine at Maharishi Markandeshwar Institute of Medical Sciences & Research (MMIMSR), Mullana.
Ambala. 25 patients of both the sexes suffering from type 2 diabetes mellitus were selected for the study. Eligible patients diagnosed with type 2 diabetes mellitus were administered Glimepiride in dose range of 1-6 mg/day, for 24 weeks. Patients with history of drug allergy, alcohol intake, congestive cardiac failure, female patients who were pregnant, lactating were excluded. Clinical evaluation of all the patients was done by measuring blood sugar before administration of drug. Efficacy of the glimepiride evaluated by measuring the fasting blood sugar level at start of pharmacotherapy, 2 weeks, 4 weeks and then every 4 weeks upto 24 weeks. Data were collected and the analysis of each variable was performed on the change from baseline values using Student’s “t”-test. A ‘p’ value less than or equal to 0.05 was considered statistically significant and p>0.05-non significant.

RESULTS
Patients (n=25) were given Tab. Glimepiride (1-6 mg/day) orally for 24 weeks.

Table 1: Characteristics of the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Range (years)</td>
<td>30-75</td>
</tr>
<tr>
<td>Mean Age</td>
<td>53.08±11.69</td>
</tr>
<tr>
<td>Sex(Male/Female)</td>
<td>13/12</td>
</tr>
<tr>
<td>Fasting blood sugar(mg/dl)</td>
<td>172.17±30.25</td>
</tr>
</tbody>
</table>

The parameters were normally distributed

Table 2: Mean Scores of Fasting Blood Sugar in Patients of Type 2 Diabetes Mellitus with Treatment Over 24 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>172.17±30.25</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>168.73±30.37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 4</td>
<td>166.57±31.25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 8</td>
<td>163.65±31.27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 12</td>
<td>161.25±31.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 16</td>
<td>159.08±31.94</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 18</td>
<td>158.20±32.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 22</td>
<td>156.20±32.10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Week 24</td>
<td>153.92±32.18</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

p<0.05-significant

Table 2 shows that the mean scores of fasting blood sugar reduced significantly (p<0.05).

DISCUSSION
Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is an epidemic in some countries of the world with the number of people affected and expected to double in the next decade due to increase in ageing population, thereby adding burden for healthcare providers, especially in poorly developed countries. The progression of diabetes is caused by numerous metabolic events that occur over a period of years. By controlling these metabolic events, the progression of the disease may be slowed or stopped. Despite its high prevalence, diabetes is largely under diagnosed [15]. There is evidence that retinopathy begins to develop at least seven years before the clinical diagnosis of type 2 diabetes is made [16]. Patients with undiagnosed diabetes mellitus are at serious risk for coronary heart disease, stroke and peripheral vascular disease, and have a greater risk of dyslipidemia, hypertension and obesity. The risk of cardiovascular disease increases with diabetes and is greater in patients with coexisting dyslipidemia. Thus this disease is associated with significant rates of morbidity and mortality due to cardiovascular events. Near-normal or improved glycemic control has been shown to significantly diminish the risk of long-
term complications in patients with type 2 diabetes [17]. Type 2 diabetes mellitus is due to lifestyle and genetic factors. A number of lifestyle factors are known to be important to the development of type 2 diabetes mellitus. These are physical inactivity, sedentary lifestyle, cigarette smoking and consumption of alcohol [18]. Obesity has been found to contribute to approximately 55% of cases of type 2 diabetes mellitus [19]. The treatment of non-pregnant patients with "impaired fasting glucose" should begin with lifestyle modification, including meal planning and exercise.

The parameter used to assess the efficacy of glimepiride was the fasting blood sugar. The results showed that the mean score of fasting blood sugar at baseline was 172.17±30.25, at 4 weeks 166.57±31.25 and at 24 weeks, it dropped to 153.92 ± 32.18 shows that the patients started improving significantly with treatment by the end of 2nd week as the mean scores of fasting blood sugar reduced significantly (p<0.05) (Table 2). The improvement continued over time and mean scores were reduced significantly at the end of 24 weeks. The result of the study was in consistence with the study done by Korytkowski M et al. [20] in 11 obese subjects suffering from type 2 diabetes mellitus underwent euglycemic and hyperglycemic episodes before and during glimepiride therapy. During this study it was concluded that glimepiride reduced the fasting blood sugar level by reducing the post absorptive endogenous glucose production.

**CONCLUSION**

Type 2 diabetes mellitus is a disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity but when not controlled by diet and exercise alone Glimepiride play an important role in type 2 diabetes patients because glimepiride effectively reduced fasting blood sugar.

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