Comparative efficacy between glimepiride and metformin in preventing progression of prediabetes to type 2 diabetes

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ABSTRACT

Background: Several recent studies have shown that treatment with therapeutic lifestyle changes, and/or several drugs retard progression of prediabetes to type 2 diabetes. However, none of these studies used a Sulfonylurea (SU), although in UKPDS, SUs delayed the progression of hyperglycemia and several subjects would have been categorized as having prediabetes by present diagnostic criteria. Thus, SUs may have delayed the progression in this group as well.

Objective: Therefore, we examined comparative efficacy of glimepiride and metformin in progression to diabetes in subjects with prediabetes.

Methods: Twenty men and 18 women ages 28 - 81 years with prediabetes were followed for 5 - 9 years. Prediabetes was diagnosed by impaired fasting glucose and HbA1C between 5.7% - 6.4% with two consecutive determinations as recommended by American Diabetes Association. Twenty obese subjects were administered metformin 500 mg/day and 18 non obese subjects received glimepiride 0.5 mg/day, in addition to dietary and exercise counseling. Results: Mean duration of follow up was 5.8 ± 0.2 years. Fasting Plasma Glucose (FPG) and HbA1C levels promptly decreased to <100 mg/dl and <5.7% in all subjects by 6 months. During the follow up period, 9 of 20 (45%) subjects receiving metformin and 5 of 18 (27%) in glimepiride group progressed to diabetes (p < 0.01) as determined by FPG ≥ 126 mg/dl and HbA1C ≥ 6.5% (RR, 1.61 with Confidence Interval, 1.43 - 1.74 for metformin vs glimepiride; p < 0.01). The mean duration to progression was 32 ± 4 months in metformin group and 47 ± 5 months in subjects receiving glimepiride. FPG and HbA1C levels promptly returned to <100 mg/dl and <5.7% on increasing daily dose of both metformin (1000 - 1500 mg) and glimepiride (2 - 4 mg). The glycemic control was maintained till the end of observation period. None of the subjects in either group manifested a cardiovascular event nor any of the subjects died during the period of observation.

Conclusion: Glimepiride may be more effective in delaying the progression of prediabetes to diabetes in non-obese subjects in comparison to metformin in obese subjects with no significant difference in cardiovascular morbidity or overall mortality.

Keywords: Type 2 Diabetes Pharmacotherapy; CVD/Lipids/Insulin Resistance; Prediabetes

1. INTRODUCTION

Several studies using therapeutic lifestyle interventions [1-8] have delayed the progression of prediabetes (impaired fasting glucose and impaired glucose tolerance) to type 2 diabetes as defined by diagnostic criteria established by American Diabetes Association [9]. Similarly, several recent reports described delaying progression of prediabetes to type 2 diabetes with use of drugs approved for treatment of hyperglycemia in subjects with type 2 diabetes including metformin, acarbose, voglibose, rosiglitazone and pioglitazone [2,10-16]. Finally, in UKPDS, sulfonylureas, e.g. glibenclamide and chlorpropamide delayed the worsening of hyperglycemia in subjects with type 2 diabetes as well [17,18]. However, several subjects in this study were in the stage of “prediabetes” by the present criteria established by American Diabetes association [1] for diagnosis of diabetes (fasting plasma glucose ≥ 126 mg/dl) since subjects were categorized as
having diabetes based on fasting plasma glucose level of
>110 mg/dl [19,20]. Moreover, tolbutamide, 1st generation
SU was reported to be effective in prevention of
progression of impaired glucose tolerance to type 2 dia-
betes in short term study over the duration of 1 year and
over a 10 year period in another long term study [21,22].
None of the newer sulfonylurea agents have been well
tested for prevention or delay of progression from pre-
diabetes to diabetes although glimepiride appeared to
delay progression in a recent study with results barely
missing attaining a statistical significance [23]. The lack
of significant improvement may be attributed probably to
subjects in the study being obese in whom presence of
insulin resistance is a major contributing factor [24]. In
contrast occurrence of prediabetes and diabetes in non
obese subjects is mainly attributed to the decline in insu-
lin secretion [24]. Therefore, we addressed the efficacy
of glimepiride, a long acting sulfonylurea for delaying
progression to diabetes in non obese subjects with pre-
diabetes and compared it with well proven efficacy of
metformin in obese subjects with prediabetes.

2. SUBJECTS AND METHODS

Body weight, glycemic control (fasting plasma glu-
cose and HbA1C levels) and comprehensive metabolic
panels were recorded at intervals of 3 - 6 months for 5 - 9
years in 20 men and 18 women, ages 28 - 81 years with
prediabetes. The diagnosis of prediabetes was based on
fasting plasma glucose between 100 - 125 mg/dl and
HbA1C between 5.7% - 6.4% on two consecutive deter-
minations. Obese subjects with BMI over 30 kg/m² were
administered metformin in a daily dose of 500 mg be-
cause the major contributing factor to prediabetes and
diabetes in obese subjects is insulin resistance whereas
glimepiride, 0.5 mg was chosen in the remaining non
obese subjects with the BMI ≤ 27 kg/m² because the de-
cline in insulin secretion has been documented to play a
major role in inducing prediabetes and diabetes in this
group [24]. Nutritional and exercise counseling was
conducted at yearly intervals. Progression to type 2 DM
was defined as increase in fasting plasma glucose > 125
mg/dl and/or a rise in HbA1c above 6.4% requiring in-
creased dosage of metformin or glimepiride to regain
normal glycemic control (fasting plasma glucose < 100
mg/dl and HbA1c < 5.7%).

3. RESULTS

Fasting plasma glucose and HbA1C concentrations
declined within 6 months individually as well as a group
following treatment with either metformin or glimepiride
(Table 1). Hypoglycemic symptoms or FPG ≤ 70 mg/dl
were not reported in either of the groups. In metformin
group, 9 of 20 subjects progressed to type 2 DM between
24 - 35 months whereas the progression was noted in 5
of 18 glimepiride treated subjects between 37 - 48
months. In all these subjects, normal glycemic control
was restored by increasing the daily dose of metformin
and glimepiride respectively (Table 2). In subjects not
progressing to type 2 DM, eleven (55%) in metformin
group and 13 [73%] in glimepiride group, both fasting
plasma glucose and HbA1C remained within normal
range, <100 mg/dl and <5.7% respectively by the end of
period of observation. None of the subjects in either
treatment group manifested a cardiovascular events nor
any subject died during the period of observation.

4. DISCUSSION

This study demonstrates that glimepiride delays pro-
gression of prediabetes to diabetes as defined by criteria,
the fasting plasma glucose and HbA1C concentrations in
a significantly higher number of subjects as compared to
subjects treated with metformin (P < 0.01). Moreover,
the time to progression in glimepiride group was also
significantly longer compared to subjects treated with
metformin. [P < 0.01] Similar observations have been
documented with use of tolbutamide, a 1st generation
sulfonylurea [21,22]. A similar efficacy of chlorpropa-
mide and glibenclamide in delaying the progression to
type 2 DM was also probably evident in UKPDS since
several subjects in this study belonged to the present
“prediabetes” state since the criteria used for diagnosis of
diabetes was fasting plasma glucose concentration of

Table 1. Fasting plasma glucose (FPG) and HbA1c in subjects
prior to (Pre) and at the end of 6 months following (Post) ther-
apy (Rx).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>FPG mg/dl</th>
<th>HbA1c %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin PreRx</td>
<td>118 ± 3</td>
<td>6.1 ± 0.2</td>
</tr>
<tr>
<td>Metformin Post Rx</td>
<td>94 ± 2</td>
<td>5.4 ± 0.1*</td>
</tr>
<tr>
<td>Glimepiride Pre Rx</td>
<td>116 ± 4</td>
<td>6.2 ± 0.2</td>
</tr>
<tr>
<td>Glimepiride Post Rx</td>
<td>95 ± 3</td>
<td>5.5 ± 0.1*</td>
</tr>
</tbody>
</table>

*p < 0.01 vs Pre Rx.

Table 2. Efficacy of metformin (obese) and glimepiride (non-
obese) in delaying progression from pre-diabetes to type 2 DM.

<table>
<thead>
<tr>
<th>Metformin 500 mg</th>
<th>Glimepiride 0.5 mg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>9/20</td>
<td>5/18</td>
</tr>
<tr>
<td>Duration at Progression (Months)</td>
<td>30 ± 3</td>
<td>47 ± 4</td>
</tr>
</tbody>
</table>

*Confidence interval.
Therefore, we believe that glimepiride may be useful as yet another therapeutic option in delaying the progression of prediabetes towards diabetes especially in non-obese subjects, in whom the decline in beta cell function is a more prominent physiologic aberration in contrast to obese subjects, characterized by major contribution by rising insulin resistance to glucose dysregulation. Finally, it is apparent that it is as effective as metformin in terms of ensuing cardiovascular outcomes as well as overall mortality. However, in both obese and non-obese subjects with prediabetes, both the declines in insulin secretion and insulin sensitivity are contributory factors. Therefore, although glimepiride may improve both these abnormalities, its combination with metformin, a distinctly more effective agent to ameliorate insulin resistance may be more effective in delaying progression of prediabetes to diabetes for even a longer duration than that observed with individual agent in all subjects irrespective of the body weight. Moreover, the daily dosage of these agents required to achieve the objective may be smaller than when used as a monotherapy resulting in lesser side effects as well.

The major limitation of the study is the small number of subjects as well as the lack of observation on the effect of discontinuation of drugs on progression from prediabetes to diabetes. Therefore, a similar study as well as a study using both drugs in combination recruiting a large population of obese and non-obese subjects with prediabetes may be useful in further examination of our observation.

REFERENCES


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