GLIPIZIDE IMPROVES PLASMA C-PEPTIDE LEVELS OVER A THREE YEAR PERIOD AFTER DIAGNOSIS OF TYPE 2 DIABETES

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ABSTRACT

Twenty type 2 diabetic patients treated with glipizide monotherapy were followed for a period of three years. Fasting and postprandial plasma glucose values, glycosylated haemoglobin and fasting and stimulated C-peptide levels were measured annually. At the end of three years, there was a significant reduction in fasting plasma glucose ($p = 0.002$), post prandial plasma glucose ($p = 0.001$) and glycosylated hemoglobin levels ($p < 0.001$). The fasting and stimulated C-peptide levels increased from 0.4 pmol/l to 0.8 ± 0.4 pmol/l ($p = 0.045$) and 0.9 pmol/l to 1.4 pmol/l ($p = 0.028$) respectively. The study shows that after glipizide monotherapy for first three years after diagnosis of type 2 diabetes, the pancreatic beta cell reserve is not only preserved but also marginally improved.

KEY WORDS: Glipizide; Type 2 diabetes; C-peptide.

INTRODUCTION

Diabetes is one of the top causes of mortality worldwide (1). The World Health Organization (WHO) has projected that by 2025 India would contribute 20% of the total diabetic patients worldwide (2). Fortunately, if diabetes is controlled properly, we could prevent complications and decrease the associated loss of man-hours and economy (3,4). Diet and exercise are the first line therapy for type 2 diabetes. However, majority of patients would require pharmacological intervention to control hyperglycemia.

The first choice of drugs for non-obese type 2 diabetic patients is sulphonylurea group of agents that have been in use for more than 40 years (5). The second-generation sulphonylurea like glipizide, glibenclamide and gliclazide are more popular than the first generation drugs. The second-generation sulphonylureas, particularly glipizide lower the blood glucose actually by stimulating the release of insulin from the pancreas. Earlier studies using experimental models have shown an increase in serum insulin levels within 15 minutes after a dose of glipizide (6). Further, this drug has been shown to prevent autoimmune events and diabetes in the BB rat (7). These beneficial effects of glipizide on islet cell secretion encouraged us to perform the present study that is aimed at determining the effect of glipizide on plasma C-peptide levels, a measure of pancreatic beta cell reserve. To our knowledge this is one of the first studies to show long-term effects of glipizide on pancreatic beta cell function in Indian type 2 diabetic subjects.

METHODS

Type 2 diabetic patients attending the outpatient division of M.V. Diabetes Specialities Centre, Chennai and satisfying the inclusion criteria were recruited for the study. The inclusion criteria for the study was newly detected type 2 patients within the age range of 12 – 40 years. Known diabetic patients and type 1 diabetic patients were excluded from the study. Patients with ketosis, diabetes related complications, hepatic or renal disease, pancreatic calculi, cardiac problems, uncontrolled hypertension and malnutrition were also excluded from the study. The ethical committee of the hospital approved the study and informed consent was obtained from all the study subjects.

Protocol and Study Design: 22 type 2 diabetic patients who satisfied the inclusion and exclusion criteria were taken up for the study. They were initiated on glipizide therapy (2.5 mg, 5 mg, 10mg) depending upon the severity of the disease (glycemic level). Patients received a standard diabetic diet of High Carbohydrate High Fibre (HCHF) as described earlier (8). A dietitian checked the adherence to the diet at each visit to ensure that it was kept constant throughout the study. Subjects were requested to make frequent visits to ensure the adequacy of the anti diabetic treatment. If the response was not sufficient, i.e. did not produce adequate

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glycemic control, the dose of glipizide was increased. All study subjects were requested to undertake a battery of tests during their yearly checkup for a three-year period after diagnosis.

Investigations: Patient's clinical history was recorded at baseline. During the yearly visits, blood pressure was recorded. The fasting and postprandial plasma glucose, glycosylated haemoglobin, fasting and stimulated C-peptide estimation was performed. For obtaining stimulated C-peptide measurements, 1 mg of glucagon was injected and a second sample was drawn after 6 minutes (9).

Fasting and postprandial plasma glucose (glucose-oxidase method) were estimated using kits supplied by Boehringher Mannheim, Germany. Glycosylated haemoglobin (HbA1c) was estimated by HPLC method using the variant machine (Bio-Rad, U.S.A). C-peptide assays were done by ELISA technique using DAKO kits (Dako Diagnositics Ltd., UK). The intra-assay and the inter-assay co-efficient of variation for C-peptide assay were 4.0% and 8.3% respectively and the lower detection limit was 0.02 pmol/ml.

Statistical Analysis: Paired 't' test was used to compare the data among different visits.

RESULTS

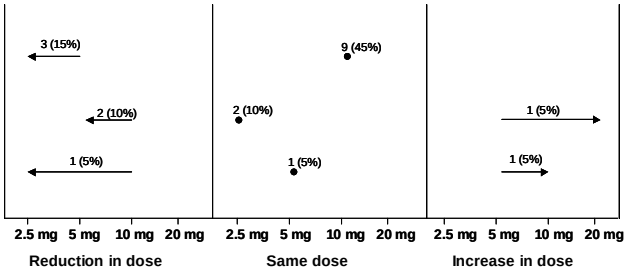
Of the 22 patients, 2 patients were excluded from the study, as they required metformin therapy to control the diabetes. Table 1 presents the clinical features of the 20 study subjects who completed the study. 55% (n = 11) of the study subjects were males, the mean age of the study group was 34 ± 5 years and the mean BMI was 24.4 ± 2.8 kg/m^2.

Table 1: Clinical Features of the Study Subjects

Male, n (%)	11 (55%)
Age (yrs)	34 ± 5
Body mass index (kg/m^2)	24.4 ± 2.8
Systolic blood pressure (mm Hg)	133 ± 8
Diastolic blood pressure (mm Hg)	81 ± 4
Smoking, n (%)	3 (15%)
Alcohol, n (%)	3 (15%)

Initially 5% (n = 1) of patients were prescribed 2.5 mg (1/2 OD) of glipizide, 30% (n = 6) of patients were prescribed 5 mg (1/2 BD) of glipizide and 20% (n = 4) of patients were prescribed 10 mg (1 BD) of glipizide.

Fig 1 shows the dosage pattern of glipizide prescribed for the patients during their visits. 60% of the patient continued the same dose throughout the study. 30% had a reduction in dose of glipizide at the end of three years and 10% of the patients had to increase their dose to achieve adequate glycemic control.



Dosage comparison between baseline and 3 years after glipizide treatment

Values above the arrows and dots indicate n(%)

Figure 1: Glipizide Dosage Pattern in Study Subjects – Dosage Comparison Between Baseline and Three Years after Glipizide Treatment

Table 2 presents the biochemical features of the study subjects. Fasting plasma glucose (p = 0.002) and postprandial glucose (p = 0.001) showed a significant reduction at the end of 3 years compared to the base line levels. Similarly HbA_{1c} level also showed a significant reduction compared to the baseline values (p < 0.001).

Table 2: Glucose, Glycosylated Haemoglobin Levels at Baseline and Three Years after Glipizide Treatment

Variables	At Baseline	At end of study (3 yrs)	p value
Fasting plasma glucose (mg/dl)	207 ± 60	135 ± 33	0.002
Postprandial plasma glucose (mg/dl)	324 ± 87	206 ± 66	0.001
HbA_{1c} (%)	10.0 ± 1.9	7.5 ± 1.3	< 0.001

The plasma C-peptide levels in the study subjects during the follow up visits showed the following results.

The fasting C-peptide levels increased from 0.4 þmol/ml to 0.8 þmol/ml (p = 0.045), and the mean stimulated C-peptide levels increased from 0.9 þmol/ml to 1.4 þmol/ml (p = 0.028) (Fig. 2).

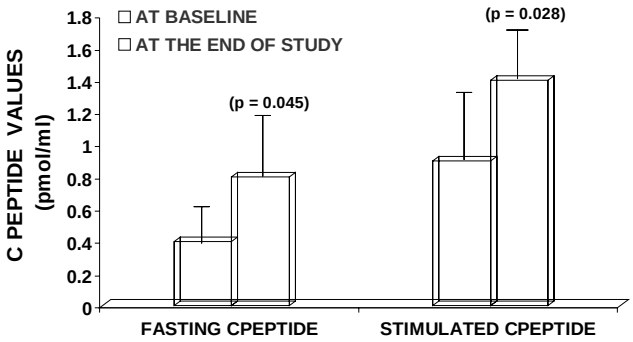


Figure 2: C-Peptide Levels at Baseline and Three Years after Glipizide Treatment

DISCUSSION

Oral sulphonylurea therapy is effective only in diabetic subjects who are capable of producing endogenous insulin (10). The primary mechanism of action is to stimulate the release of insulin from pancreas. Its effect on first phase of insulin secretion in the case of first generation sulphonylurea is minimal, while it has an appreciable effect on the second phase. However, the second generation drug glipizide and glimepiride have been shown to improve the first phase insulin secretion also (11). Also, in contrast to the first generation sulphonylureas, the second generation drugs stimulate insulin secretion in response to a glucose load, which nearly mimics the physiological nature of insulin secretion. In addition, glipizide stimulates insulin action through extra pancreatic effects that affect insulin receptor binding and enhance tissue responsiveness to insulin (12). Yet another beneficial effect of the glipizide is that the fasting hypoglycemia is less prevalent among glipizide users (13).

In the present study, glipizide offered a very satisfactory control of blood sugar levels in the study patients. Nearly 70% of the type 2 diabetic patients in their initial stages have been shown to achieve adequate blood sugar control using oral sulphonylurea drug. Moreover, studies have shown that the mean dose required to maintain good glycemic control reduced after four years of glipizide treatment (14). In the present study nearly 90% of the study subjects achieved good glycemic control with either lower doses of glipizide (30%) or by continuing the same dose of glipizide (60%).

Even a single dose of glipizide is capable of maintaining the blood sugar for 24 hours. Glipizide has been proven to be more effective when administered about 30 minutes before food rather than after the meal (15). Combination therapy with metformin has been suggested to have additional therapeutic effects in type 2 diabetic patients (16). Studies on induction of remission have shown that chronic dose of glipizide prolongs near normoglycemia in diabetic subjects (17,18). This remission could probably be due to increased stimulation of pancreatic beta cell to secrete insulin.

In this study we looked at the C-peptide levels of study patients before and after glipizide therapy. There was an increase on the C-peptide value following glipizide treatment for three years, which suggests that glipizide preserves the beta cell function at least up to three years after diagnosis. Our results are in agreement with an experimental study done at California (6). A study on 79 type 2 diabetic patients reported that the effect of glipizide was equivalent to low dose insulin in type 2 diabetic subjects (19). This could probably be due to the augmentation of insulin release and availability as shown by Sartor et al (9) and others (20 – 24).

One of the limitations of the study is the small study numbers. However, there are very few studies in the literature that have prospectively followed type 2 diabetic patients using C-peptide estimation and virtually none using glipizide monotherapy. Another limitation is that it is an open study with no control group.

To conclude, our data suggests that glipizide protects and preserves beta cells at least over a three-year period. The observations are in accordance with the data from other studies. In order to confirm the beta cell preservation effects of glipizide, it is necessary to conduct a well-controlled long term trial comparing glipizide with other sulphonylureas or other modes of therapy.

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