PIOGLITAZONE VS GLIMEPIRIDE
TO EVALUATE THE EFFECT OF ON RENAL FUNCTION TESTS IN TYPE 2 DIABETES IN PATIENTS

ORIGINAL
PROF-1725

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ABSTRACT... Objectives: To compare the improvement in renal function tests (RFTs) of type 2 diabetic patients who were taking glimeperide alone and this drug in combination with piogliatzone and pioglitazone alone. **Data source:** Data was analyzed using ANOVA. P < 0.05 was taken as significant. **Study Design:** Randomized prospective study. **Setting:** This study was conducted in the diabetic clinic of Fauji Foundation hospital Rawalpindi and the tests were analyzed in the Biochemistry Lab of Islamic International Medical College Rawalpindi. **Duration of study:** 12 weeks. **Materials & Methods:** Blood glucose levels were determined by glucose oxidase method (globe marketing GD Italy), HbA1c by Microlab 200, urea/creatinine /uric acid by Selectra E & micro albumin by Spin colour. **Results:** No significant differences were observed for the variables of hemoglobin A1c, uric acid and urinary albumin P >0.05. Significant decreases were observed in the levels of fasting plasma glucose, urea and creatinine P< 0.05. **Conclusions:** In patients with type 2 diabetes pioglitazone and the combinations of glimepiride with pioglitazone produced significant improvements in measures of glycemic control and RFTs.

Key words: Peroxisome proliferator activated receptor gamma receptor (PPAR), glycated hemoglobin (HbA1c), renal function tests (RFTs).

INTRODUCTION

Diabetes is estimated to have affected 171 million people worldwide in 2006 and is projected to affect 366 million by 2030[1]. Diabetic nephropathy is the single most common disorder leading to renal failure. Its incidence has increased in the last ten years to reach 44% of all end stage renal disease. Structural changes may be advanced before any clinical findings manifest[2].

Glycemic control has long been the mainstay for preventing progression of diabetic complications; however such control is not easily achieved. Long- term prospective trials relating to treatment and control of hyperglycemia in type 1 and 2 diabetics have shown that microvascular related morbidity can be significantly reduced but not entirely prevented through long-term glycemic and blood pressure control[3].

A variety of strategies and techniques are used to manage diabetes. Thiazolidinediones are oral antidiabetics. They work mainly by decreasing insulin resistance at peripheral sites and secondarily by decreasing hepatic glucose output Thiazolidinediones function through peroxisome proliferator activated receptor (PPAR) gamma receptor, which is expressed mainly in the adipose tissue and is also found in the muscle, liver, pancreas, and vasculature[4]. PPAR gamma receptor agonists regulate transcription of genes by controlling glucose and lipid metabolism[5]. Sulphonylureas mainly act by stimulating insulin secretion. They increase the number of insulin receptors and insulin sensitivity. The most commonly used sulphonylurea is glimepride in our setting[6].We conducted this study to compare the improvement in renal function tests (RFTs) of type 2 diabetic patients who were taking glimeperide alone and this drug in combination with piogliatzone and pioglitazone alone.

Settings

Islamic International Medical College, Rawalpindi in collaboration with Fauji Foundation hospital, Rawalpindi.

Design

Randomized prospective study.

METHODS

This study was conducted in the diabetic clinic of Fauji Foundation hospital Rawalpindi and the tests were analyzed in the Biochemistry Lab of Islamic International Medical College Rawalpindi. Duration of study was 12 weeks. It was carried out in 90 diabetic patients between the ages of 30-70 years, all diagnosed to have type 2 diabetes mellitus recently and were not on any treatment. The study consisted of an initial induction day followed by

follow-up visits after every fortnight. Dosage regime:Glimeperide 5mg1OD, Pioglitazone 15mg 1OD, Glimeperide/Pioglitazone 5mg +15mg OD. Fasting blood glucose levels were recorded at every visit during the study.We evaluated the metabolic changes that occurred in patients with type 2 diabetes who were treated with glimeperide and pioglitazone with no other medication regimens for diabetes or dyslipidemia.

90 patients were included in the analysis. Urea, creatinine, uric acid and urinary albumin were checked, along with fasting glucose, glycated hemoglobin (HbA1c).They were randomly categorized into three groups, one group on pioglitazone only and second on glimeperide only and third one on both pioglitazone and glimeperide. Blood glucose levels were determined by glucose oxidase method (globe marketing GD Italy), HbA1c by Microlab 200, urea/creatinine /uric acid Selectra E & micro albumin by Spin colour.

The following data were collected: age, gender, duration of diabetes, weight, body mass, hemoglobin A1c, fasting plasma glucose, urea, creatinine, uric acid and urinary albumin after the patient had received medication for at least 12 weeks.

INCLUSION CRITERIA

1. Diagnosis of type 2 diabetes mellitus,
2. Treatment with a stable dose of glimeperide and pioglitazone for at least 12 weeks.

EXCLUSION CRITERIA

1. A change in diabetes, thyroid, estrogen-containing, or lipid-lowering medication.
2. Patients using psychotropic medications, systemic glucocorticoids, or protease inhibitors during the study period.
3. Patients with liver or end stage renal diseases.

STATISTICAL ANALYSIS

The analyses were carried out with SPSS 17 statistical software and the data expressed as means ± standard deviations. Data was analyzed using ANOVA. $P < 0.05$ was taken as significant.

RESULTS

The comparisons of Hb A1c, fasting plasma glucose, urea, creatinine, uric acid and urinary albumin are given in tables. No significant differences were observed for the variables of hemoglobin A1c uric acid and urinary albumin $P > 0.05$. Significant decreases were observed in the levels of fasting plasma glucose, urea and creatinine $P < 0.05$. Fasting glucose and glycated Hb profile are shown in Table 1.Significant decreases were observed in the levels of fasting blood sugar $P < 0.05$, which shows a mean of 13.0± 3.2 mmol/l before starting the drugs, and a mean of 5.7± 1.4mmol/l after the treatment was started. No significant difference was observed in the values of HbA1c $P > 0.05$ with a mean value of 3.45±.18 % before and 3.46±.16% after the start of the treatment.

Table-II. Shows the levels of urea and creatinine, which showed significant decrease $P < 0.05$ after the treatment was started with mean values of 14.5± 2.2mmol/l before and 10.5± 1.5mmol/l after the treatment for urea, and 357±91umol/l before and 285±34 umol/l after the treatment was started for creatinine.

Table-III shows the levels of uric acid and microalbumin. For both uric acid and microalbumin the levels were not significantly altered $P > 0.05$, with values of 290±70 umol/l before and 233±53 after the treatment for uric acid. Microalbumin was normal before the treatment.

DISCUSSION

Patients with Type 2 diabetes almost always develop mild to moderate renal impairment as a complication of inadequate glycemic control. Patients with diabetes are 17 times more prone to kidney disease than non diabetics, with diabetic nephropathy being the most common complication[7]. Renal impairment has to be managed promptly in diabetic patients as most oral hypoglycaemic agents are eliminated primarily by renal mechanisms. Impaired renal function may result in greatly reduced excretion and this leads to the accumulation of drug and active metabolites which increases the risk of hypoglycaemia . The results suggest that glimeperide and pioglitazone both were effective in lowering fasting glucose level, if used regularly for 12 weeks. By increasing â-cell output, glimepiride lowers

Table-I. Blood glucose Profile

	N	Minimum	Maximum	Mean	Std. Deviation	Sig.
FBSmmol/lbefore	90	8.30	19.90	13.0267	3.21775	.000
FBSmmol/lafter 12 weeks	90	3.70	9.00	5.7722	1.40896	.896
HbA1c%before	90	4.20	6.50	5.2933	.77486	.042
HbA1c%12weeks	90	4.20	6.50	5.3067	.76552	.378

Table-II. Urea/ Creatinine profile

	N	Minimum	Maximum	Mean	Std. Deviation	Sig.
Ureammol/lbefore	90	10.60	19.90	14.5150	2.22654	1.000
Ureammol/lafter 12 weeks	90	8.34	14.00	10.5674	1.58502	.000
Creatinineumol/before	90	207.00	581.00	357.7333	91.83740	1.000
Creatinineumol/lafter 12weeks	90	200.00	356.00	285.0778	34.56576	.050

Table-III. Uric acid/microalbumin

	N	Minimum	Maximum	Mean	Std. Deviation	Sig.
Uricacidumol/lbefore	90	173.00	445.00	290.0333	70.80920	1.000
Uricacidumol/lafter 12 weeks	90	156.00	395.00	233.1222	53.49301	.767
Microalbuminamg/lbefore	90	16.00	29.00	20.8000	3.70302	1.000
Microalbuminmg/lafter 12 weeks	90	16.00	29.00	21.1000	3.57598	.931

blood glucose levels. We have observed that pioglitazone significantly reduces FBG during this duration as compared to glimeperide, and same was the case with combined therapy and glimeperide i.e. p < 0 .05. On the other hand reduction in FBG with combined therapy and pioglitazone was not statistically significant p> 0.05. Fuken et al describes that glimeperide has additional peroxisome proliferator-activated receptor gamma agonistic (PPARã)-stimulating effect and found it more effective in combination with TZDs[8] which is in accordance with our study.

According to the study by Yamanouchi T pioglitazone monotherapy reduces HbA1c levels by around 1.0%, but it is less likely to be successful in patients with an HbA1c > 8.0%[9]. Patients in our study had HbA1c around 4- 6.50%. Significant decrease in the levels of HbA1c are seen in patients receiving pioglitazone treatment of 15 mg at the end of 16 weeks duration[10].In contrast our study duration was of 12 weeks only. Similarly reduction of 2.1% in the levels of HbA1c was observed but the duration was for 36 weeks[11].

It was seen in our study that urea and creatinine were improved by the pioglitazone and combined therapy as compared to glimeperide and as the elimination of pioglitazone and its metabolites is mainly by hepatic oxidation, pioglitazone may have potential value in patients with Type 2 diabetes who have renal impairment[12].

There was no statistically significant difference in the values of uric acid levels between glimeperide, pioglitazone and combined therapy. In one of the study

conducted by cook et al they showed relationship between glucose levels and uric acid levels. Uric acid levels according to their study decreased with higher glucose levels i.e. more than 10 mmol/l[13]. This is not in accordance to our study in which uric acid levels were decreased with low glucose levels, but were statistically not significant.

CONCLUSIONS

In patients with type 2 diabetes pioglitazone and the combinations of glimepiride with pioglitazone produced significant improvements in measures of glycemic control and RFTs. Pioglitazone can be considered as the simplest and most convenient and cost effective choice for the patient. The effects of this drug need to be studied in patients with high levels of glycated hemoglobin.

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Article received on: 11/12/2010 Accepted for Publication: 00/00/0000 Received after proof reading: 12/08/2011

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Article Citation:
Rahim A, Shahzad A. To evaluate the effect of pioglitazone vs glimepiride on renal function tests in type 2 diabetes in patients of Fauji Foundation Hospital, Rawalpindi. Professional Med J Sep 2011;18(3): 450-453.