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PRIMARY PIOGLITAZONE FAILURE IN ASIAN INDIAN DIABETICS IS NOT RELATED TO COMMON Pro12Ala POLYMORPH OF PPAR-γ GENE

SANDEEP K. MATHUR*, RAJKUMAR RATHORE**, SHIVANI CHANDRA****, B. B. SHARMA***, LOKENDER SHARMA**, PRASHANT MATHUR** AND MUKUL MATHUR

**Clinical Endocrinology Unit,*
*Departments of **Pharmacology and ***Medicine,*
S. M. S. Medical College,
J. L. N. Marg, Jaipur – 302 004

and

*****Birla Institute of Scientific Research,*
Statue Circle, Jaipur

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Abstract : To determine the various factors influencing glycemic response to pioglitazone mono therapy in newly diagnosed Asian Indian T2DM patients.

Thirty T2DM patients (age 53.23±8.067 yrs, M : F ratio 14:16) were treated with pioglitazone for at least 14 weeks. Relationship between its glucose lowering effect and following patient parameters was studied: BMI, W:H ratio, HOMA-R, HOMA-β and Pro12Ala polymorph of PPAR-γ gene.

Glycemic targets could be achieved in 20 (66.67%) subjects. All the parameters were comparable among responders and non-responders at the start of therapy. All the participants were homozygous for Pro allele of Pro12Ala polymorph of PPAR-γ gene. There was a significant positive association between glycemic response to pioglitazone and W: H ratio (beta = 0.426, P = 0.034) and HOMA-R (beta = 0.563, P = 0.008).

Primary pioglitazone failure cannot be explained on the basis of body fat and its distribution, insulin resistance and secretory function and Pro12Ala polymorph of PPAR-γ gene. Among responders central obesity and high insulin resistance were associated with better glycemic response.

Key words : pioglitazone, Pro12Ala, PPAR-γ, insulin resistance, insulin secretion, visceral obesity

Abbreviations : BMI : body mass index, W:H ratio: waist to hip ratio, HOMA-R: homeostasis model assessment of insulin resistance, HOMA-β: homeostasis model assessment of beta cell function, PPAR-γ: peroxisome proliferator activated receptor gamma, T2DM: type-2 diabetes mellitus.

*[1]Corresponding Author : Dr. Sandeep K. Mathur, Professor & Head, Endocrinology Unit, S.M.S. Medical College, J.L.N. Marg, Jaipur – 302 004; E-mail : drsandeepmathur@rediffmail.com

INTRODUCTION

Asian Indians are known for a tendency towards central obesity and high insulin resistance (1–3). Furthermore, diabetic patients belonging to this population not only have higher W.H. ratio, plasma FFA levels and HOMA-R, but also show a significant positive association between FFA level and HOMA-R(4). These findings suggest significant role of FFA mediated insulin resistance in the pathogenesis of T2DM in this population. Pioglitazone, a PPAR-γ agonist selectively decreases insulin resistance by decrease in FFA levels and seems to be the most appropriate anti-diabetic drug for this population (5–7). However, there are only a few studies on efficacy of this drug in this population (8). Moreover, it is also not certain that what patient characteristics could predict better glycemic response to pioglitazone in this population. Therefore, we studied relationship between important patient characteristics and response to pioglitaone monotherapy in Asian Indian T2DM patients.

MATERIALS AND METHODS

The study was conducted on 30 T2DM subjects diagnosed as per American Diabetes Association criteria and already on standard diet and exercise and in whom glycemic targets were not achieved (i.e. fasting plasma glucose < 126 mg/dl, HbA1c < 7%). Exclusion criteria included (1) history of liver disease or SGOT/PT > 2.5 time upper limit of normal, (2) congestive heart failure NYHA grade 3 or above, (3) obesity (BMI > 30), (4) active infection, (5) history of allergy to pioglitazone (9).

Initial evaluation included detailed history, physical examination, and laboratory investigations: fasting plasma glucose, insulin, lipid profile, SGOT/PT, HbA1c. All biochemical investigations were done using Merck Spectra 2 auto analyzer and HbA1c was done with Biorad DiaSTAT machine. Insulin was estimated using DPC Immulyte 2000 chemiluminescence analyzer. Following parameters were estimated from initial evaluation (1) BMI, (2) W: H ratio, (3) HOMA-R, (4) HOMA-β Genotyping for Pro12Ala polymorph of PPAR-γ gene was done by PCR-RFLP method (10).

All patients were treated with pioglitazone, 30 mg once a day. Plasma glucose was checked at least once a week in those doing self home glucose monitoring. It was also checked every month in hospital laboratory during their office visit. SGOT/PT were measured at 2 weeks and then at two monthly interval. HbA1c was measured after 3 months. All the patients were followed for at least 14 weeks. Those subjects achieving glycemic targets (either lab fasting glucose < 126 mg/dl or HbA1c < 7%) were labeled as responders. HbA1c 7% is the American Diabetes Association recommended target of glycemic control. Those with less than 10% fall in lab fasting glucose value were labeled primary non responders. Those with more than 10% fall in fasting glucose but not achieving glycemic targets were labeled as partial responders. Approval of institutional ethics committee was obtained and written consent was obtained from the participants.

Statistical analysis

The data is presented as mean and

standard deviation. Student's t-test was used for comparison of data between two groups. ANOVA was done studying relationship between patient characteristics and glycemic response to pioglitazone.

RESULTS

Table I shows baseline information. All the participants were homozygous for Pro12 variant of PPAR-γ gene (Fig. 1). All the

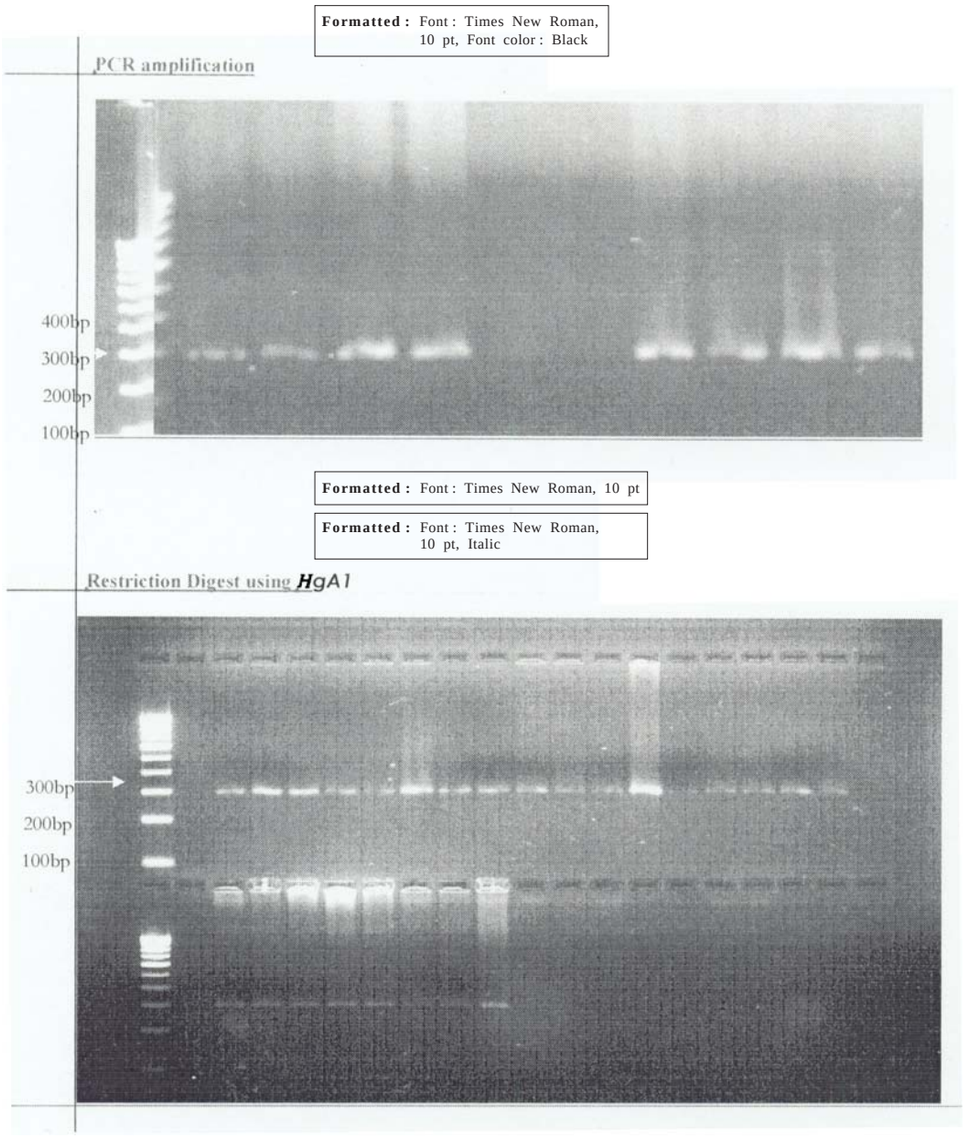

Fig. 1: PCR-RFLP analysis for Pro12Ala polymorphism of PPAR-γ gene: Digestion of exon-2 amplification products by HgA1 restriction enzyme.

TABLE I: Baseline information of the participants.

	Mean	*SD*
Age (yr)	53.23	8.067
M: F ratio	14:16	
BMI (kg/M^2)	25.207	5.0158
W:H ratio	0.927	0.0933
Fasting plasma glucose (mg/dl)	178.233	38.4839
HbA1c (%)	8.70	00.5292
Fasting plasma insulin (μIU/ml)	13.33	4.3623
HOMA-R	6.06767	2.18928
HOMA-β	46.494	21.1378

subjects completed at least 14 weeks follow-up. The mean duration of follow up was 15.4 weeks. Glycemic targets (fasting plasma glucose < 126 mg/dl or HbA1c < 7.0) could be achieved in 20 (66.67%) subjects. In three subjects, though they could not reach glycemic targets, but there was at least 10% fall in fasting plasma glucose. Seven (23.34%) subjects were primary non-responders, and 3 subjects were partial responders (On average, fasting plasma glucose decreased by 41.2 mg/dl and HbA1c by 0.617%). Average weight gain was 3.2 kg. None of the patients had significant change in SGOT/PT or any other major side effect. Mild edema developed in 2 subjects. No major cardiovascular event was observed during the study.

Table II shows comparison of characteristics of treatment responders and non-responders. It was observed that responders and non-responders did not differ in terms of age, sex, fasting plasma glucose and HbA1c, BMI, W: H ratio, HOMA-R and HOMA-β.

Table III shows relationship between patient characteristics and glycemic response to pioglitazone. It should be noted that there was a significant positive association between W: H ratio and HOMA-R and the glycemic response to pioglitazone.

TABLE II: Comparison of patient characteristics among responders and non-responders.

Characteristic	*Responders*	*Non-responders*	*t**	*P***
Age (yr)	52.7±8.98	55.0±3.79	-0.65	NS
W:H ratio	0.92±0.08	0.96±0.11	-1.01	NS
BMI (kg/M^2)	24.74±5.59	26.75±1.76	-0.92	NS
Fasting plasma glucose (starting) mg/dl	178.04±41.72	183.14±27.45	-0.30	NS
Fasting plasma glucose (after 14 weeks) mg/dl	120.35±28.43	196.14±34.33	-5.89	<.0001
HbA1c (starting)	8.06±0.51	8.10±0.61	-0.16	NS
HbA1c (after 14 weeks)	7.20±0.45	8.27±0.51	5.23	<.0001
HOMA-R	6.08±2.27	6.04±2.06	0.04	NS
HOMA-β	47.50±21.80	43.20±20	0.46	NS

*t value on student's t-test; **P value <0.05 was taken as significant.

TABLE III: ANOVA table depicting relationship between patient characteristic and glucose lowering effect of pioglitazone.

Patient characteristic	*Un-standardized coefficient*		*Standardized coefficient (B)*	*T*	*Sign*
	B	*Std error*			
Constant	247.112	90.151		2.741	.011
BMI	–2.825	1.640	–.325	–1.723	.097
W:H ratio	–199.145	88.669	–.426	–2.246	.034
HOMA-R	11.214	3.862	–.563	2.904	.008
HOMA-β	–0.389	–0.188	–.188	–1.031	.312

DISCUSSION

The present study is a pilot study to determine factors influencing glucose

lowering efficacy of pioglitazone in Asian Indian diabetics. The results show that glycemic targets could be achieved in two third of the participants (treatment responders). Among the responders the glucose lowering effect was better in those having central obesity and higher insulin resistance. In 23.34% of patients there was no significant glucose lowering response to this drug (primary failure). This failure could not be explained because of age, sex, fasting plasma glucose or HbA1c at start of treatment, body fat distribution or insulin resistance/ secretion functions and Pro12Ala polymorph of PPAR-γ gene.

Pioglitazone has several advantages over sulfonylurea. It does not cause hypoglycemia, preserves pancreatic beta cell function, there is no secondary failure, no significant drug interactions, it is safe and can be administered once a day irrespective of food intake (11–14). Moreover, this drug also has favorable effect on progression of atherosclerosis (15–16). Our finding that glycemic targets could be achieved in as many as two third of subjects, suggests that this could be the first line anti diabetic drug for Asian Indians, particularly those who have central obesity or high insulin resistance. However, it is worth mentioning here that study subjects in the present study had relatively milder degree of hyperglycemia (HbA1c 7–9%). Also the glucose lowering efficacy of pioglitazone observed in the present study is almost similar to that observed in western population (decrease in fasting plasma glucose by about 50 mg/dl and HbA1c by 0.8–1.1%) (11–13, 17). An important limitation of this study is that cardiovascular endpoints were not studied and only glycemic parameters were mainly studied. Therefore, drawing any conclusion about its superiority from cardio protection point of view is not possible in this short term study. However, there is no data on the role of pioglitazone in progression of atherosclerosis in high risk Asian Indian population and needs further investigations.

An interesting finding in the present study was that almost a quarter of participants were primary non-responders to pioglitazone and they could not be identified on the basis of age, sex, body weight, fat distribution, insulin resistance or secretion. The cause of primary pioglitazone failure is not known and is an interesting field of investigation. Though the primary failure could be because of several reasons like, defects in drug absorption or metabolism, polymorphs of PPAR-γ or its co-activator gene, altered expression of PPAR-γ gene in adipose tissue or even polymorphs of genes transcription of which is controlled by activated PPAR-γ. A large number of PPAR-γ gene polymorphs have been identified with a spectrum of phenotypic manifestations and varying frequency in different races (18). Pro12Ala polymorph of PPAR-γ has been found to be associated with better glycemic response with rosiglitazone, but not with pioglitazone (19–20). All the participants in the present study were homozygous for Pro polymorph and primary pioglitazone failure could not be explained on its basis. Therefore, detailed study of PPAR-γ gene, its co activator and response elements is suggested for the purpose of identifying markers of primary pioglitazone failure.

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