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Inter-patient Variability in Clinical Efficacy of Metformin in Type 2 Diabetes Mellitus Patients in West Bengal, India

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Abstract

Background and objective: Metformin is often used as a first-line therapy for Type 2 diabetes mellitus (T2DM), but the glycemic response to metformin is variable in patients. Here, we aimed to assess the inter-patient variability in terms of glycemic response to metformin in the state of West Bengal, India.

Material and methods: We enrolled newly diagnosed treatment naïve 113 patients with T2DM. Patients were subjected to assay of glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PP) and measurement of body mass index (BMI), waist circumstances (WC) before and after the end of 3 months of immediate release metformin (2000mg/day) therapy.

Results: Out of 113 patients, 111 (58 male and 53 female; average age 43.13 years) were provided with 3 months of metformin therapy. 102 individuals responded to metformin, but HbA1c levels of 9 patients did not improve after 3 months of drug therapy.

Conclusions: In the present study, metformin lead to improvements in glycemic control in 92% of newly diagnosed T2DM patients but in 8% does not which is much less in this part of India.

Keywords: Type 2 diabetes mellitus; Metformin; Glycemic response; Glycated hemoglobin; Non-responder

Introduction

Type 2 diabetes mellitus (T2DM) is a major health problem in worldwide [1]. T2DM is a multifactorial, heterogeneous group of disorder with varying prevalence among different ethnic groups [2]. The disease is affecting at an alarming rate to both rural and urban populations in India [3-6]. Recent epidemiologic studies have shown more than 62 million diabetic individuals currently diagnosed with the disease in India [7]. The prevalence of diabetes in West Bengal state, India, is in between 2.7% - 13.2% [6].

The pathophysiology of T2DM is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining beta cell function. It can now be treated with several classes of approved drugs, in addition to diet and exercise regimens [8]. Among them, metformin, a biguanide is one of the most widely prescribed oral anti-hyperglycemic drugs. It ameliorates hyperglycemia by decreasing hepatic glucose output, gastrointestinal glucose absorption, improving insulin sensitivity and improvement of peripheral glucose uptake in skeletal muscle and fat [9-11]. Metformin is slowly absorbed in the Gastrointestinal (GI) tract and not bound with any protein and also remained intact during the process of metabolism. The drug is mainly eliminated by renal excretion with renal clearance 4-5 times greater than glomerular filtration rate [12]. It is effective as monotherapy or in combination with other agents, such as insulin secretagogues, other insulin-sensitizing drugs, or inhibitors of glucose absorption. The anti-diabetic drug metformin has attracted much attention for several reasons. Metformin does not cause weight gain, may lead to weight loss. Metformin also has beneficial effects on several cardiovascular risk factors such as dyslipidemia elevated plasma plasminogen activator inhibitor, other fibrinolytic abnormalities and insulin resistance [13].

The antidiabetic response to metformin differs significantly from patients to patients. Based on clinical trial experience, patients using metformin monotherapy as their first-ever anti hyperglycemic drug, less than two-thirds of patients achieve a desired fasting glucose level or the HbA1c goal of <7% [14]. The non-response rate to metformin may be upwards to 50% [15]. This incomplete response rate of metformin coupled with waning effectiveness over time, highlights the need for personalized medications to maintain tight glycemic control [16]. To date, no such studies in patients with T2DM have shown that glycemic response to metformin is variable in subpopulation of West Bengal, India. Thus, we have conducted an open-label study for 12 months with a course of metformin in 111 patients with well characterized T2DM.

Materials and Methods

Study sample

The 113 subjects were recruited from the diabetes out-patient department of Seth Sukhlal Karnani Memorial Hospital (SSKM) & Institute of Post Graduate Medical Education & Research (IPGME&R), Kolkata, West Bengal, India in the period of November, 2013-September, 2014. Patients were diagnosed based on the American diabetes association criteria [17].

We excluded those patients from our study who had i) glomerular filtration rates (GFRs) less than 60 ml. $min^{-1}.1.73\ m^{-2}$ ii) Severe cardiovascular, malignant or chronic inflammatory diseases iii) active infection iv) metabolic decompensation or HbA1c>12% and

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v) pregnant patients or women hoping to conceive. We also excluded patients who were co-prescribed acarbose, glitazone, sulfonylurea, or insulin at the time of one of the two Hb_{A1C}, FBS and PPBS measurements. There are no generally accepted criteria in the clinical cut-off point to divide patients into metformin responder and non-responder. Thus we selected the criteria, based on clinical experience and previous reports [10, 18]. 1) Responder: Where HbA1c levels had decreased more than 1% from the baseline within 3 months of metformin therapy. 2) Non-responder: decrease in HbA1c levels less than 1% from the baseline or another hypoglycemic drug has been added to the therapy because of poor glycemic status. The study had been started after obtaining informed consents of the participants. The experimental protocol was approved by the Institutional Ethical Committee of *IPGME&R, Kolkata.* All the participants were instructed to maintain appropriate lifestyle habits during the course of the study.

Baseline evaluation

Patients were initially screened during an outpatient clinic visit with brief medical history, review of outside medical records, physical examination, information about demographic parameters and routine blood test in collaboration with the physician. None of the patients were taking antidiabetic medication prior to their diabetes diagnosis.

HbA1c was analyzed using the high-pressure liquid chromatography (BioRad D 10, Hercules, CA). Blood glucose was determined by a glucose oxidase method (Roche, Basel, Switzerland).

Therapy and monitoring

After complete medical evaluation and HbA1c**,** FBS and PPBS tests, patients who qualified for the therapy were treated with metformin at an initial dose of 500 mg once daily and then rapidly upgraded to full dose (2000 mg/day) with following schedule: 500 mg once a day for 5 days followed by 1000 mg once a day for 5 days and finally 1000 mg twice daily, if no side effects were observed. Patients were monitored for a 12-week period. Patients were asked to come after 6 week to see compliances. Also they are asked to bring used medicine strips. The HbA1c, FBS and PPBS tests were repeated again after 3 months of therapy. Metformin treatment was well tolerated. 10 (9%) patients had mild gastrointestinal symptoms in the form of abdominal discomfort with increase bile motion, which subsided with few weeks.Two patients stopped therapy because of severe gastrointestinal side effects.

Statistical analyses

Two tailed paired and unpaired *t*-tests were performed to test the statistical significance among the data for each group and between two groups before and after treatment measures. We analysed non-parametric variables by Mann-Whitney test and Wilcoxon matched pairs test. Statistical analysis was performed using Graphpad Prism 4 software (Graphpad Software Inc., San Diego, CA, USA).

Results

Patients enrolled

113 adult patients with T2DM were enrolled in the study and 111 completed the 3 months of therapy and underwent follow-up testing. The 2 been excluded (a 45 years and 53 years old women) as they stopped therapy after 12 days. These two patients were not included for further analyses.

Baseline features

The 111 patients included 58 male and 53 female with an average age was 44.91 years. No patient was treated for diabetes at the time of the enrolment. The baseline demographic characteristics (Table 1) and the anthropometric characteristics of all patients were presented in Table 1. Indeed there was almost two times increase in the prevalence of diabetes with age group 40-60 years compare to 20-40 years age and almost ten times increase compare to age above 60 years (Table 1). The prevalence of overweight and obesity in the entire study population were almost 20% and 45%. Furthermore, central obesity was observed in 57% in patients with diabetes. Approximately 61% patients were family history positive for diabetes. Comparison of presenting symptoms was shown in Table 1. Osmotic symptoms was most common (51.3%) followed by general weakness (22.2%), Polyphagia (15.3%), weight loss (7.2%), Burning sensation in feet and palm (7.2%), Blurring of vision (4.5%), Pruritus (3.6%), Balanoposthitis (3.6%), Numbness in feet (2.7%) and Vaginitis(1.8%). We also found 21 (18.9%) patients without any symptoms.

The responder and non-responder groups did not differ significantly in term of age (45.23 ± 10.49 in the responder group, 41.33 ± 10.55 in the non-responder group, p = 0.50). At baseline, also the difference of average BMI, WC, FBS, PPBS and HbA1c values between responder and non-responder group were insignificant (Table 2).

Metformin responder and non-responder

Responder: Number of patients: 102

Characteristic	Patients (n-111)
Men:Women	58:53
Age (years)	n (%)
20-40	36 (32.4)
41-60	69 (62.1)
61 above	7 (6.3)
Family history of Diabetes	68 (61.2)
BMI (kg/m²)	
<18.5 (underweight)	7 (6.3)
18.5-22.9 (normal range)	32 (28.8)
23-24.9 (overweight)	22 (19.8)
25-29.9 (obese)	50 (45.0)
Abdominal obesity	
Waist <80 cm (female), <90 (male)	48 (43.2)
Waist> 80-89 cm (female), >90-99 cm (male)	32 (28.8)
Waist>90 cm (female), >100 cm (male)	31 (27.9)
Occupation	
Unskilled/skilled worker	45 (40.54)
Entrepreneur	14 (12.61)
Farmer	11 (9.9)
Housewife	36 (32.4)
Retired	5 (4.5)
Smoking	22 (19.8)
Smoking + alcohol	13 (11.7)
Oral tobacco	17 (15.3)
Hypertension	26 (23.4)
Osmotic symptoms	57 (51.3)
Polyphagia	17 (15.3)
Gen weakness	25 (22.2)
Weight loss	8 (7.2)
Burning sensation in feet and palm	8 (7.2)
Numbness in feet	3 (2.7)
Pruritus	4 (3.6)
Balanoposthitis	4 (3.6)
Vaginitis	2 (1.8)
Blurring of vision	6 (4.5)
Asymptomatic	21 (18.9)

Table 1: Baseline demographic characteristics of patients.

	Baseline			After 3 months		
Parameters	**Responder (n-102)**	**Non- responder (n-9)**	***P*-value**	**Responder (n-102)**	**Non- responder (n-9)**	***P*-value**
BMI (kg/m²)	25.01 (4.47)	24.38 (4.68)	0.995*	23.91 (3.71)	24.10 (4.48)	0.364
WC (cm)	91.95 (12.03)	88.67 (13.58)	0.439	90.45 (10.78)	87.98 (13.27)	0.519
FBS (mg/dL)	182.13 (40.01)	185.67 (50.41)	0.837	114.73(18.85)	186.89 (34.06)	**<0.001**
PPBS (mg/dL)	277.28 (63.53)	283.44 (71.01)	0.782	156.55 (30.79)	294.11 (63.29)	**<0.001**
HbA1c%	9.36 (1.19)	9.07 (1.20)	0.402	6.72 (0.85)	9.21 (1.04)	**<0.001**

P-value based on 2 tailed unpaired *t*-test and
**P*-value based on Mann-Whitney test
Values are given as mean (s.d.)

Table 2: Comparisons between metformin responder and non-responder at baseline.

Parameter	**Baseline**	**After 3 months**	***P*-value**	**Baseline**	**After 3 months**	***P*-value**
	Responder (n-102)			**Non-responder (n-9)**		
BMI (kg/m²)	25.01 (4.47)	23.91 (3.71)	**<0.001***	24.38 (4.68)	24.10 (4.48)	0.08
WC (cm)	91.95 (12.03)	90.45 (10.78)	**<0.001**	88.67 (13.58)	87.98 (13.27)	0.126
FBS (mg/dL)	182.13 (40.01)	114.73(18.85)	**<0.001**	185.67 (50.41)	186.89 (34.06)	0.906
PPBS (mg/dL)	277.28 (63.53)	156.55 (30.79)	**<0.001**	283.44 (71.01)	294.11 (63.29)	0.53
HbA1c%	9.36 (1.19)	6.72 (0.85)	**<0.001**	9.07 (1.20)	9.21 (1.04)	0.428

P-value based on 2 tailed paired *t*-test and
*P-value based on Wilcoxon matched pairs test
Values are given as mean (s.d.)

Table 3: Comparison of clinical parameters at baseline and after 3 months of metformin therapy of responder and non-responder patients.

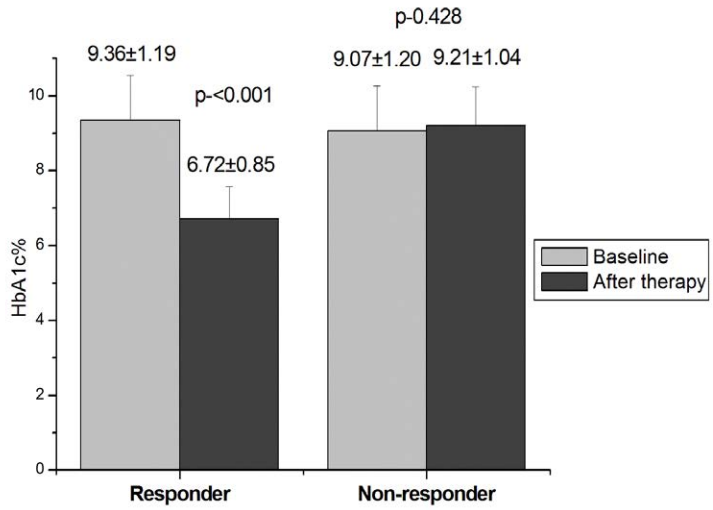

Figure 1: Comparison of mean HbA1c% in responders and non-responders group before and after therapy.

Gender a) Male–56(55%)

b) Female - 46 (45%)

According to the selection criteria, 102 patients were responders, among them 56% were male and 46% female. Improvements in BMI, WC, FBS, PPBS and HbA1c were observed during metformin treatment in 102 patients (responder). After therapy, the average BMI decreased from 25.01 kg/m^{-2} to 23.91 kg/m^{-2} (P = <0.001), was statistically significant and the changes in average WC, FBS, PPBS and HbA1c values were significantly decreased from baseline (Table 3). The histogram shows average changes in HbA1c% in responders before and after therapy (Figure 1).

Non-responder: Number of patients: 9

Gender a) Male - 2 (22%)

b) Female - 7 (78%)

According to the selection criteria, 9 patients were non responders, among them 22% were male and 78% female. The average BMI, WC, FBS, PPBS and HbA1c levels did not improve in nine patients (non-responder) (Table 4) out of 102 patients after therapy. The average HbA1c level was increased from 9.07% to 9.21% after metformin monotherapy. The graph shows average changes in HbA1c% in non-responders before and after therapy group (Figure 1). The HbA1c levels of six non-responders were increased from baseline and the value was decreased (~0.4%) in three non-responders (Figure 2).

After completion of metformin therapy, FBS, PPBS and HbA1c levels were significantly different between responders and non-responders (Table 2).

Discussion

We conducted this open-label trial study to determine the inter-patient variability in the clinical efficacy of metformin in patients

Parameter	Baseline	After 3 months	*P*-value
BMI (kg/m^2)	24.38 (4.68)	24.10 (4.48)	0.08
WC (cm)	88.67 (13.58)	87.98 (13.27)	0.126
FBS (mg/dL)	185.67 (50.41)	186.89 (34.06)	0.906
PPBS (mg/dL)	283.44 (71.01)	294.11 (63.29)	0.53
HbA1c%	9.07 (1.20)	9.21 (1.04)	0.428

P-value based on 2 tailed paired *t*-test.
Values are given as mean (s.d)

Table 4: Comparison of clinical parameters at baseline and after 3 months of metformin therapy of non-responder patients.

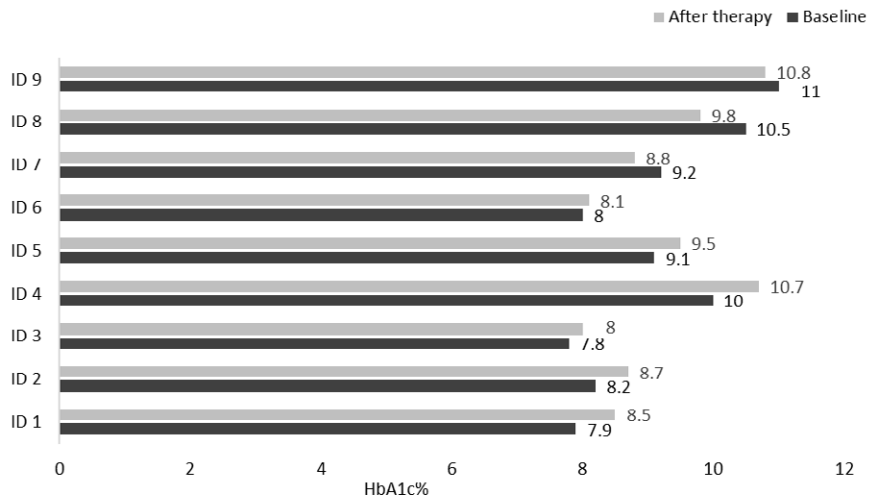

Figure 2: Changes in HbA1c% before and after therapy in 9 non-responder patients. ID-patient ID.

with T2DM in the state of West Bengal, India. Our data suggest that 8% T2DM patients are not able to improved glycemic response with metformin therapy.

Our study was designed to assess glycemic control of metformin as measured by changes in HbA1c from baseline to week 12. Three months course of metformin in dose of 2000 mg/day was associated with improvements in HbA1c, FBS and PPBS in over one third of (92%) patients with T2DM. 8% of patients did not show improvement in the HbA1c, FBS and PPBS levels. All the guidelines advocates use of metformin as 1st line agent for most T2DM therapy. Nevertheless, metformin is known to cause variable glycemic response. In responders, the improvements in average HbA1c, FBS, PPBS, BMI and WC values were significant before and after the therapy, but in non-responders group these levels did not improve after the therapy. It was previously reported that metformin was effective in a smaller dose (500 mg) in the Asian Indian population [19]. In our study, we used metformin in doses of 2000 mg/day to optimize treatment. However, some patients may not need 2000 mg/day dose but to assess a proper glycemic response, we used to increase the dose to a best possible dose.

Earlier studies reported that oral antidiabetic drug sufficiently decrease HbA1c levels by 0.5–1.5% [18]. A very recent study conducted by Mahrooz et al. showed that, decrease in HbA1c levels by more than 1% from baseline may possibly a criterion for classifying diabetic patients as metformin responders or non-responders [20]. In our study, we showed that, after metformin therapy the average decrease in HbA1c levels reached 2.41% (2.41 ± 1.17%). In addition, the mean decrease was 2.64% (2.64 ± 0.92%) among responders, whereas the value was increased 0.13% (0.13 ± 0.47%) in non-responders. The average decrease in HbA1c levels in our study is higher compare to previous study conducted by Mahrooz et al. [20]. Mahrooz et al. used metformin dose 1000 mg/day in their study whereas in our study we used 2000 mg/day. The simultaneous use of metrormin and dietary and life style modification and ethnic variation may be the probable reason for greater decrease of HbA1c level. However there is considerable variation in response to metformin, with about 35% of patients failing to achieve initial glycemic control on metformin monotherapy as reported [21,22] whereas, we found 8% (n=9) of patients were non-responder to metformin. Many questions remain regarding metformin response, which may be due to genetic or non-genetic. Till now most reproducible associations have been in known transporter genes. As we learn more about the genetics of drug response, we are finding a number of circumstances in which genetic differences can influence both the likelihood of responding and the likelihood of having a severe side effect to medication.

This study enrolled patients with well characterized T2DM. The strength of this study was selection of drug naïve patients (who never took anti-diabetic drugs), careful follow up, and ensuring drug compliance. The major limitations of this study were small number of patients and conducted in small area. Further large replicating study is needed to support our result.

Conclusions

In summary, this is the first study regarding the glycemic efficacy of metformin in treatment naïve T2DM patients from West Bengal, India. Our study revealed that, decrease in HbA1c levels by more than 1% from baseline could be considered a criterion for response to metformin. In addition, few patients were non responders to metformin therapy,

which may be combined effects of multiple gene variants in the same or converging pathways and their interaction with non-genetic factors.

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Disclosures

The authors declare that they have no conflict of interest.

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