DOI:https://doi.org/10.54393/pbmj.v5i7.691

PAKISTAN BIOMEDICAL JOURNAL

https://www.pakistanbmj.com/journal/index.php/pbmj/index

Volume 5, Issue 7 (July 2022)

Original Article

Glycemic Response to Metformin and its Association with Age and Gender in Type II Diabetes

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ARTICLE INFO

Key Words:

Metformin, Type –II diabetes, gender, glycemic response

How to Cite:

Hakim, Z. ., Khan , A. ., Waheed, A. ., Hafeez, A. ., Khohkar, A. ., & Hakim, B. . (2022). Glycemic Response to Metformin and Its Association with Age and Gender in Type II Diabetes: Glycemic Response to Metformin. Pakistan BioMedical Journal, 5(7). https://doi.org/10.54393/pbmj.v5i7.691

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Received Date: 15th July, 2022
Acceptance Date: 22nd July, 2022
Published Date: 31st July, 2022

ABSTRACT

Diabetes Mellitus has become a global health concern due to its continued rise in prevalence. According to International Diabetic Federation (IDF), Type II diabetes mellitus (T2DM) currently affects 462 million people worldwide and is expected to grow from this figure to 642 million by 2040. **Objective:** The study was conducted to evaluate the glycemic response to metformin in Type-II diabetes and assess its association with age and gender. **Methods:** A cross sectional study was conducted at the Pharmacology Department of Riphah International University from Jan 2020 to Dec 2021.Type-II diabetic patients (n=200) on metformin monotherapy fulfilling the inclusion criteria were enrolled and followed up till three months. Baseline parameters were documented and reduction in HbA1c was determined. Numerical and categorical data was analyzed by chi-square and t-test using SPPS 23. **Results:** Our study demonstrates that 52% (104) of the patients were metformin responders while 48% (96) were non-responders. The reduction in HbA1c was significantly greater in responders than non- responders (- 1.58±1.07 % VS -0.32±0.35 %). Out of 85 males, 46 (54%) responded to metformin optimally while only half (50%) of the female subjects produced desirable response. However, there was no effect of gender on metformin response status with p=0.60 and changes in HbA1c levels over time were not significantly different in either sex. The mean age of responders and non-responders was found to be 48.23±9.64 years and 44.13±7.82 respectively. The effect of age on response of metformin and mean change in HbA1c among different age groups was found to be statistically significant with p=0.03 and p=0.04 respectively. **Conclusion:** There exists variability in response to metformin in type-II diabetes which is associated with age of the patient but remains un-influenced by gender of the patient.

INTRODUCTION

Diabetes Mellitus has become a global health concern due to its continued rise in prevalence. According to International Diabetic Federation (IDF), Type II diabetes mellitus (T2DM) currently affects 462 million people worldwide and is expected to grow from this figure to 642 million by 2040 [1]. World Health Organization predicts that this rapidly rising burden would largely be bore by low income developing countries including Pakistan. Pakistan presently ranks 7th with T2DM prevalence of 16.98% [2] and may go up to 4th spot in the coming decade. Diabetes, a chronic debilitating disease is associated with various micro and macrovascular complications. It can only be managed by early diagnosis and timely initiation of self-management and pharmacotherapy. All therapeutic measures aim at providing effective glycemic control to delay disease progression and prevent complications. Despite the availability of different oral anti diabetic drugs, many international organizations have recommended metformin as the first line treatment of T2DM due to its effectiveness, low cost and safety profile [3]. Metformin produces its pharmacological action by enhancing glucose uptake in peripheral tissue (skeletal tissue) and inhibition of

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intestinal glucose absorption. At the molecular level, it inhibits the activity of mitochondrial respiratory chain complex I, resulting in activation of AMP-activated protein kinase (AMPK) and the subsequent suppression of hepatic gluconeogenesis [4]. Heterogeneity in the response to metformin is one of the most important predicament in the efficacy of the drug. About 35 -40% of patients on metformin monotherapy fail to respond optimally [5] making achievement of glycemic targets a challenge. Numerous genetic and phenotypic factors such as hormones, age, gender, weight, insufficient dose, nonadherence, drug-drug interactions, socioeconomic and psychological status interact in a multi-dimensional manner to contribute to this inter-individual variability [6]. Age and gender based differences in the appearance of diabetes and its treatment have been accumulated over time. Many old and new anti-diabetic drugs have shown gender related differences in their actions and effects. Women usually receive low doses of metformin as compared to men but report more gastrointestinal side effects [7]. Studies have also documented greater body weight reduction in females while men experienced greater HbA1c decrease on metformin [8]. Younger patients under 65 years have also demonstrated poorer glycemic control than older ones [9]. Studies identifying the potential role of gender and age in response to antidiabetic treatment are not only limited worldwide, they are almost non-existent in Pakistan. Therefore, this study was designed to determine the impact of gender and age on glycemic response of metformin.

METHODS

A cross sectional analytical study was conducted at the Department of Pharmacology and Therapeutics, Islamic International Medical College of Riphah International University, Islamabad. The study was conducted in accordance with the current Good Clinical Practices and the Declaration of Helsinki after approval from the Ethical Review Board of the institute [10]. Type -II unrelated diabetic patients of either gender started on metformin monotherapy and aged between 35 and 70 years were enrolled in the study after written informed consent. Patients were clinically diagnosed according to American Diabetic Association fulfilling one of the criteria; fasting blood glucose ≥126 mg/dl, two hours' glucose ≥200 mg/dl during an oral glucose tolerance test (OGTT), non-fasting plasma glucose > 200 mg/dl or HbA1c≥ 6.5%. Exclusion criteria was Type-I diabetes, pregnant and lactating women, hepatic, renal and cardiac abnormalities and individuals on concurrent treatment that act as substrates or inhibitors of MATE transporters [11]. Sample size of 216 was calculated using the WHO sample size calculator taking 95% as confidence interval and 5% as level of significance. However, because of inclusion criteria and later stage drop out, the sample size was reduced to 200.Patients on metformin monotherapy were followed up for three consecutive months. At the time of induction, all relevant baseline characteristics such as gender, age, weight, height and BMI were collected. Venous blood was withdrawn from each participant under sterile conditions for HbA1c evaluation. HbA1c estimation was done twice in the project once at the initiation of metformin and then after completion of three months of therapy. Based upon the reduction in HbA1c from baseline, the participants were divided into metformin responders and non-responders. In the light of clinical experience and previous researches, >0.8 % and <0.8% reduction in HbA1c levels was selected as the criteria for classifying patients as responders and non-responders [12,13]. HbA1c was quantified by Bio-Rad D-10 Hb testing system which uses the HPLC ion exchange for determination of glycated hemoglobin in the sample. The data was analyzed using Microsoft SPSS-23. Descriptive statistics was used with the mean ± SD in groups. To compare differences between continuous variables, independent and paired samples' t -test was used. Chi-square was employed to compare categorical variables. One-way ANOVA and post hoc tukey test was applied to compare changes in HbA1c levels of multiple groups. $p<0.05$ was considered significant.

RESULTS

Based on established inclusion and exclusion criteria, 200 type II diabetic patients were enrolled in the study. The baseline clinical parameters of the study subjects are given in table1.

Age (years)	46.25 ±9.02
Gender	
Female	115
Male	85
Weight (kg)	66.54±10.22
Height (m2)	2.17±0.36
BMI(kg/m2)	29.76±5.77
Creatinine level	0.87 ±0.20
HbA1c %	9.19±1.56

Table 1: Baseline Characteristics of the study population(n=200)

Changes in HbA1c in response to metformin: According to the statistical analysis of HbA1c, 104 (52%) patients were classified as responders whereas the remaining 96(48%) patients fail to respond optimally. The difference between HbA1c levels at baseline and after 3 months was significantly different ($p<0.05$) in both responders and non-responders. The reduction in HbA1c levels was much higher (statistically significant) in responders than non-responders.(Figure 1)

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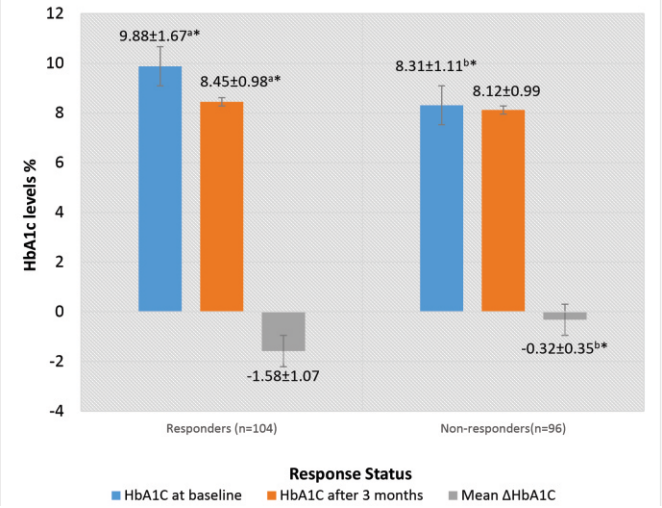

*p > 0.05 is significant
a* when baseline HbA1c compared with HbA1c at 3 months
b* when HbA1c levels compared with responders and non-responders

Figure 1: Comparison of mean HbA1c values at two different intervals between metformin responders and non-responders (n=200)

Relation of Gender with Response of Metformin: Out of a total sample size of 200 patients, 58% (n=115) were females and 42 % (n=85) were males. Among the responders 58 (56%) females and 46(44%) males were enjoying the glycemic effects of metformin as compared to 57 (60%) females and 39 (40%) males who were metformin non responders. Amongst all the females and males, responders were 50% and 54 % respectively. Chi-square showed that there is no significant difference in metformin response in either sex, x2 =0.26 and p value=0.60 (Table 2).

Gender		Response		Total
		Responder	NON Responder	
Female	Count	58	57	115
	% within GENDER	50.4%	49.6%	100.0%
	% within RESPONSE	55.8%	59.4%	57.5%
Male	Count	46	39	85
	% within GENDER	54.1%	45.9%	100.0%
	% within RESPONSE	44.2%	40.6%	42.5%
Total	Count	104	96	200
	% of Total	52.0%	48.0%	100.0%

Table 2: Cross tabulation between gender and metformin response

There was greater reduction in HbA1c after metformin therapy among males but it was not found to be significant in comparison with females, p> 0.05 (Figure 2)

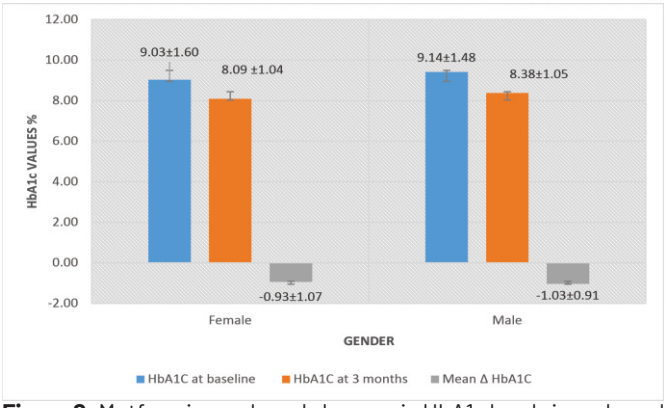

Figure 2: Metformin produced changes in HbA1c levels in male and female patients

Relation of Age with Response of Metformin: On the basis of age, all the patients were divided into 5 groups and metformin response status was assessed in each group as shown in Table 3. The mean age of responders was 48.23±9.64 years and non- responders was 44.13±7.82 years. A chi-square test of independence was performed to examine the relation between age and ability to respond to metformin. The relation between these variables was significant, p =0.03.

Gender		Metformin Response Status		Total
		Responder	NON Responder	
Age 18-35	Count	5	6	11
	% within Age Groups	45.5%	54.5%	100.0%
	% within Response	4.8%	6.3%	5.5%
Age 36-45	Count	34	47	81
	% within Age Groups	42.0%	58.0%	100.0%
	% within Response	32.7%	49.0%	40.5%
Age 46-55	Count	41	35	76
	% within Age Groups	53.9%	46.1%	100.0%
	% within Response	39.4%	36.5%	38.0%
Age 56-65	Count	19	7	26
	% within Age Groups	73.1%	26.9%	100.0%
	% within Response	18.3%	7.3%	13.0%
Age 65 and above	Count	5	1	6
	% within Age Groups	83.3%	16.7%	100.0%
	% within Response	4.8%	1.0%	3.0%
Total	Count	104	96	200
	% within Age Groups	52.0%	48.0%	100.0%
	% of Total	52.0%	48.0%	100.0%

Table 3: Frequency of metformin responders and non-responders in different age groups

Table 4 shows mean change in HbA1c obtained after three months of metformin monotherapy in different age groups. One-way ANOVA and post hoc tukey tests showed that there was significant difference in mean ΔHbA1c among different age groups, p<0.048.

DOI:https://doi.org/10.54393/pbmj.v5i7.691

Age Groups (years)	N=200	Mean ΔHbA1c %
Age 18-35	11	-.81
Age 36-45	81	-.76
Age 46-55	76	-1.05
Age 56-65	26	-1.34
Age 65 and above	6	-1.55

Table 4: Mean ΔHbA1c % in different age groups

DISCUSSION

Achievement of glycemic control is one of the main principle of successful management of T2DM. Even in the presence of treatment recommendations and guidelines, only half of the patients reach their target goals with oral antidiabetic drugs (OAD). Metformin, the first line OAD also exhibits wide interindividual variability in therapeutic response making its efficient prescription and dosing difficult. There is no fixed criterion for characterizing metformin users into responders and non-responders. Studies have identified that OAD produce an estimated decrease of 0.5-1.5% in HbA1c levels [14]. Therefore, a cut off value of ≥0.8% reduction in HbA1c levels was considered as response to metformin therapy [12]. Following metformin monotherapy, HbA1c levels decreased in average by -0.97±1.01% in entire study participants. Fifty-eight females and 46 males responded to metformin optimally while 39 males and 57 females showed an inappropriate response. Classification of study subjects according to response status is comparable to a similar study carried out by Rashid et al., in Pakistan where 59% of patients were labelled as responders and 41 % as non-responders [12]. The baseline HBA1c levels were significantly higher in responders as compared to non-responders in our study (9.88±1.67 % VS 8.31±1.11%). Parallel to this, the mean change in HbA1c in responders was statistically greater than that in non-responders (-1.58± 1.07 VS -0.32±0.35). This backs the finding that higher baseline A1C levels are associated with greater reduction in HbA1c with metformin [15]. Wilding et al., found out that changes in A1C levels at 6 months were more marked in diabetic patients with higher baseline levels (≥9.0%) compared with patients with baseline values (7.5-9.0%) [16]. Thus our study adds to the positive correlation between baseline HbA1c and subsequent reductions in HbA1c levels. There is dearth of studies globally describing gender specific effects of metformin treatment on glycemic response. Results of our study showed that male were more likely to achieve desirable glycemic goals as represented by higher percentage (54% VS 50%) of responders. This is in accordance with the cross sectional research of Cambra et.al, who indicated poorer glycemic control of women in type –II diabetes [9]. However, the decrease in HBA1c levels achieved after three months of metformin monotherapy in our research were similar in both men and women. Non-significant decrement in HbA1c value was seen across both genders in a research done on Indian population [17]. Thus, our project found no gender based differences in response to metformin in type –II diabetes. These findings were consistent with many extensive studies conducted in Texas and United Kingdom demonstrating no significant association between gender and HbA1c levels [18]. However, Schutt et al, conducted a multicenter research of 1908 patients to investigate the effect of different patient characteristics on response to antidiabetic treatment. According to their analysis, metformin displayed significantly greater HbA1c reductions in men as compared to women (– 0.7 ± 0.03 % VS – 0.6 ± 0.03 %) with p <0.05 [8]. The reason for this different outcome can be attributed to difference in energy and glucose metabolism, psychological factors and adherence to therapy. The outcome of metformin therapy is also connected with many other individual factors like age but the relevant role of age has not been addressed so far. Current study unveiled significant relation of age with treatment response and the magnitude of association seemed different between different age groups with the maximum change in HbA1c levels seen in age group 65 years and above. These results are in agreement with a population based study (n=32,638) of South European Region. They investigated gender and age based differences in glucose lowering effect of metformin and observed patients younger than 65 years with poorer glycemic control than older age groups [8]. Cook et al., also identified younger age and high BMI as predictors of inadequate control (HbA1c level < 7.0%) [19]. Same biological factors were recognized in 3553 diabetic patients in United Kingdom with lower probability of attaining target levels [20]. However, Aschner et al., and Donnelly et al., found no significant association of age with therapeutic response of metformin [21,22]. Thus, in the light of above findings, it is recommended to consider diverse response modifying clinical factors when designing and evaluating diabetic patient's treatment. However, further studies are required to identify the effect of different genetic and demographic factors on pharmacokinetics, pharmacodynamics and adverse effects of OADs. This will improve the individualization of diabetes treatment and contribute to better therapeutic outcomes.

CONCLUSION

The study revealed that variability in metformin response is quite prevalent in our country and can be assessed through change in HbA1c levels over time. This difference in effectiveness of metformin may be attributed to genetic and non- genetic factors. A positive association with age was documented with no effect of gender on its glucose

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lowering action. Thus, a large portion of type 2 diabetic patients could benefit by reducing age inequalities from treatment regimens.

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