CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3249982

Available online at: http://www.iajps.com Research Article

A QUASI-EXPERIMENTAL STUDY TO EXAMINE THE ACTION STATISTICS OF METFORMIN IN TYPE II DIABETES MELLITUS PATIENTS

M.Shamim ul Husnain[1], Sh. Sarmad Elahi[1], Zulqarnain Haider[2]

[1] Fatima Memorial Hospital, Lahore

[2] Shaikh khalifa bin Zayed Al Nahyan Medical & Dental College, Lahore

Article Received: April 2019 **Accepted:** May 2019 **Published:** June 2019

Abstract:

Aim of Study: *The main purpose of our study was to judge the action statistics of metformin in type II diabetes mellitus patients and in connection with this to examine the association of it with decrease of GIT and BMI.*

Study design: *Quasi-Experimental study*

Place and duration: *This study was carried out at Shaikh Zayed Hospital, Lahore for the time duration of one year starting from March, 2018 to February, 2019.*

Material and Methods: *A total number of 200 patients, newly diagnosed of type II diabetes mellitus (T2DM) were included in this quasi experimental study. All selected patients were treated with dose of metformin for a time period of 03 months and after that they were divided into two groups known as Responder and Non-responder assessed by reductions of HbA1c (A1C). This was calculated via hemoglobin analyzer (TC4611A TAIDoc Tech. Taiwan) by means of photometry. Same alike, BMI on the first day and after 3 months of treatment was noted on a proforma.*

Results: *All selected (200) patients of T2DM were treated with pre-decided dose of metformin for a time period of 03 months and after that they were divided into two groups known as Responder and Non-responder. There were 59.50% responder patients and 40.50% patients were non-responder. BMI at the start of the therapy was 26.09 kg/m2 which was considerably decreased to 25.4 kg/m2 after metformin treatment. Also observed that in all patients A1C was reduced due to metformin therapy. As compared to lower baseline levels of A1C as 0.61%±0.07, the glycemic control was significantly well in patients with higher baseline of A1C as 1.13% ± 0.08. While considering GIT intolerance, symptoms lacked in 140 patients amongst which there were 39.30% non-responders and rest 60.70% were responders.*

Conclusions: *After treatment with metformin found improvement in 59.5% of newly diagnosed T2DM patients for glycemic control. Whereas, 40.50% patients didn't improve which might be due to collective influences of various gene polymorphisms and their inter-action with non-genetic factors. Regardless of effects of metformin on HbA1C, it decreased the BMI of all selected patients. Furthermore, no difference found in both groups for the symptoms and signs of GIT.*

Keywords: *Body Mass Index (BMI), GIT Intolerance, Type-II Diabetes Mellitus, Metformin, Glycemic Response.*

Corresponding author:

M.Shamim ul Husnain,

Fatima Memorial Hospital, Lahore

QR code

Please cite this article in press M.Shamim ul Husnain et al., ***A Quasi-Experimental Study To Examine The Action Statistics Of Metformin In Type II Diabetes Mellitus Patients.,*** *Indo Am. J. P. Sci, 2019; 06(06).*

INTRODUCTION:

One of the main forms of diabetes is Type-2 diabetes mellitus (T2DM) and that is the reason it is found in at least 90 percent of diabetes patients [1]. It is defined by insulin resistance because of decreased insulin sensitivity in tissues of body along with reduced production of insulin. Receptors of insulin become in effective for receiving insulin and delivering it to body tissues ultimately gathering the glucose in various parts of body and in blood [2]. In 1995 occurrence of diabetes in grownups was assessed as 4% globally and upto 2025 estimated to increase to 5.4%. In 1995 patients of diabetes were 4.3 million in Pakistan and in 2025 expected to increase to 14.5 million [3]. In 2015 diabetics population of Pakistan was 7 million according to the report of International Diabetes Federation (IDF) [4]. Previously in Pakistan average prevalence of T2DM was 11.77% which has now augmented to 26.30% [5, 6].

For the management of type 2 diabetes mellitus metformin is widely used as first line mono-therapy and with suitable diet plan it decreases fasting glucose concentration by 2.78mmol/L to 3.9mmol/L which is 50mg/dL to 70mg/dL. This matches to 1.30% to 2% decrease in HbA1c values [7, 8]. The main function of metformin is to decrease the production of hepatic glucose that is why it is considered to delay or prevent starting of type 2 diabetes mellitus in the patients who are already having diabetes [9].

Furthermore, anti-diabetic medications that are associated with weight stability or gain differ from metformin as it becomes reason for weight loss [10]. Treatment with metformin is commonly related with side effects of GI which was observed in 20% to 30% patients. Symptoms of metformin GI commonly consist of abdominal pain, abdominal cramps and/or changes in intestinal motility, leading to loose motions and overt diarrhea that becomes uncontrollable sometimes, metallic taste, dyspepsia, bloating, vomiting, diarrhea and nausea. The metformin pathophysiology prompted GI intolerance is not clear, anyhow it is imagined that GI intolerance is associated to high absorption of metformin in the intestine after oral giving out of the medicine [11]. Our study was carried out to define the efficiency of metformin in reducing HbA1c. The reduction in HbA1c might be cogitated as standard for reaction to metformin. This thing shows the necessity for customized medications to sustain stringent glycemic control.

MATERIAL AND METHODS:

This study was carried out at Shaikh Zayed Hospital, Lahore for the time duration of one year starting from March, 2018 to February, 2019. A total number of 200 patients, newly diagnosed of type II diabetes mellitus (T2DM) were included in this quasi experimental study. HbA1c of the patients was from 7% to 9% and their age was from 35 years to 60 years. Diagnosed the type 2 diabetic patients on the basis of 02 hours glucose more than or equal to 200 mg/dl (≥11.1 mmol/liter) during an oral glucose tolerance test (OGTT), non-fasting plasma glucose more than 200mg/dl or HbA1c more than or equal to 6.5%, eight hours or more than eight hours of fasting resulting glucose more than or equal to 126mg/dl (≥ 7.0 mmol/liter). Excluded all those patients from our study who presented inflammatory bowel disease, peptic ulcer disease, pregnancy, congestive heart failure, cirrhosis of liver and abnormal renal functions (increased creatinine levels ≥1.4mg/dl in females and ≥1.5mg/dl in males). WHO software, based on S.K Lwanga and Lameshow, was used to calculate sample size of our study. Keeping the margin of error equal to 6% and the confidence (CI) level equal to 95%, under mentioned formula was used:

$$n = \frac{Z^2_{1-\alpha/2}\, P\,(1-P)}{d^2}$$

$Z^2_{1-\alpha/2}$	= for 95% confidence level	=	1.96
P	= Prevalence	=	57.4%
d	= Margin of error	=	6%
n	= Sample Size	=	260

Primarily a total of 260 type 2 diabetic patients were involved in the study. Nevertheless, because of later stage drop out of patients and inclusion criteria, the sample size was shrunken to 200. All the selected patients were supplied with written informed consent and patients were satisfactorily educated of post-study provisions, potential risks of the study and the discomfort it may involve, the anticipated benefits, institutional affiliations of the researcher, any possible conflicts of interest, sources of funding, methods and aims of the study. Ethics Committee of the hospital approved all these protocols. Moreover, the research and recruitment protocols were organized rendering to the Ethical Principles for Medical Research involving Human Subjects adopted in the Declaration of Helsinki by the World Medical Association [12].

Standardized forms for data collection were used to record the information obtained from the interviews of the patients. Initially started with low dose of metformin as 500mg/day for a total of 05 days and then increased the dose to 1000mg/day for next 05 days and in the case of no side effects observation, increased the dose of metformin upto 2000mg/day. To see the compliances, patients were advised for follow

up after six weeks. Patients were monitored for duration of 12 weeks. Carried out the blood sampling for A1c estimation twice during the duration of our study, once at the start of study and second after 12 weeks of metformin therapy. Categorized the patients into respondents and non-respondents after the observation of A1c reduction.

There is no recognized standard in the clinical cut-off point to distribute patients into Responders and Non-Responders. Therefore, we adopted the criteria based on our clinical experiences and previous studies lilke Responders and Non-Responders (patients whose HbA1c levels had decreased by ≥0.8% or <0.8% from the baseline within three months of metformin therapy respectively) [13,14]. A1C was calculated by HbA1C analyzer (TD4611A TAIDoc Tech. Taiwan) by means of photometry. The substance uses antigen-antibody reaction to directly verify the glycated hemoglobin in the blood. The patients were asked about the side effects of metformin which mainly included dyspepsia or abdominal pain on each visit, nausea and diarrhea. After one week of therapy with metformin if any one of the said symptoms is present, GIT intolerance was said to be present [15].

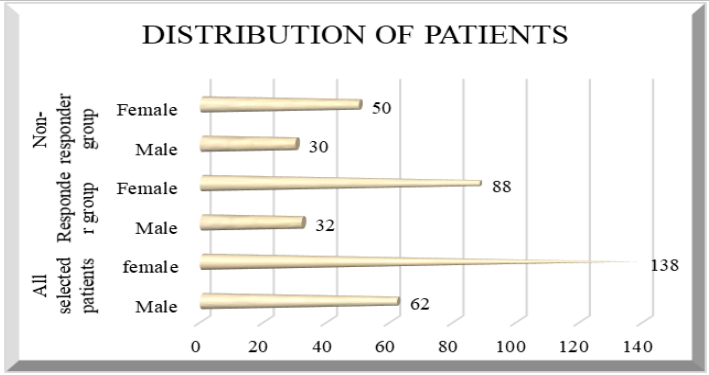
Recorded the BMI before and after 03 months of metformin therapy. Calculate the differences in the mean of the A1C and BMI via chi-square T-testing. In the response groups and in over all cases, measured the occurrence of GIT intolerance. Correlation of GIT intolerance and the cases was calculated using chi-square test with the P value 0.5% and x2 equal to 0.436.

RESULTS:

There was a total of 200 diabetic patients selected for the study. Among all selected patients there were 119 responder patients and 81 non-responder patients. After the metformin therapy patients with A1C reduction of ≥ 0.8% were grouped as Responders and those with lesser decrease of < 8% were grouped as Non-Responders. The mean age of all participants were 49 years. Mean age of responder group was 50 years and mean age was 49 years in non-responder group. Gender distribution of all selected patients was as 138 (69%) females and 62 (31%) were males. From all selected females there were 88 (64%) responders and 50 (36%) were non-responder. Amongst all selected male patients there were 32 (56%) responders and 30 (48%) were non-responders. Interview data showed that positive diabetic family background was there in 54% of patients and with out family history of diabetes was there in 36% patients.

Table No 01: Gender distribution of patients

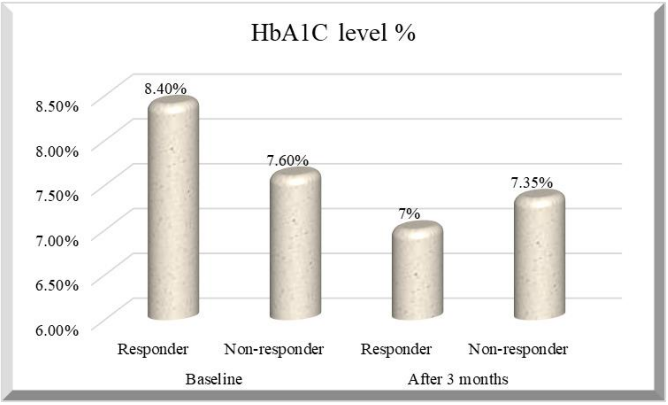
Groups	Gender	Quantity	Percentage
All selected patients	Male	62	31%
	female	138	69%
Responder group	Male	32	51.61%
	Female	88	63.77%
Non-responder group	Male	30	48.39%
	Female	50	36.23%



The average value of A1c was 8.4% in responder group and 7.6% in non-responder group at the start of study. After three months of metformin therapy this value was 7% in responder group and 7.35% in non-responder group. The variance in the average of both response groups was statistically significant.

Table No 02: Average percentage of HbA1C level

Interval	Group	HbA1C level %
Baseline	Responder	8.4%
	Non-responder	7.6%
After 3 months	Responder	7%
	Non-responder	7.35%



In this study we analyzed the effectiveness of metformin in decreasing the A1C. Group one consists of the patients with the A1C<8% and the Group two consist of the patients with comparatively A1C of ≥ 8%. The variance among the mean reductions in the A1C within both groups was found to be statistically significant with P value less than 0.0001. Decrease in A1C due to metformin was observed more if at the baseline it was more. At the start of the metformin therapy and after 12 weeks the mean value of A1C in responder group and non-responder group with the difference in the average values of both groups are shown below in table No three.

Table No 03: Differences in HbA1C in both groups

Statistics	Responder	Non-responder	P-value
	Mean±SEM	Mean±SEM	
Baseline	7.50±0.030	8.70±0.033	<0.0001
After 3 months	6.88±0.077	7.57±0.080	
Decrease in A1C	0.61±0.070	1.13±0.080	
Difference in both groups	0.51±0.110		

P value <0.05 considered significant

At the start of metformin therapy average BMI of the diabetic patients was 26.09kg/m^2 while the average BMI after 12 weeks of metformin therapy was 25.40kg/m^2. The difference before and after the metformin therapy between the median BMI was statistically dissimilar with P-value 0.00 showing the decrease of BMI after treatment. The BMI among both groups was not statistically dissimilar exposing that metformin lowering activity of BMI was same for both response groups. Results are shown below in tabular form.

Table No 04: The mean and SEM of BMI

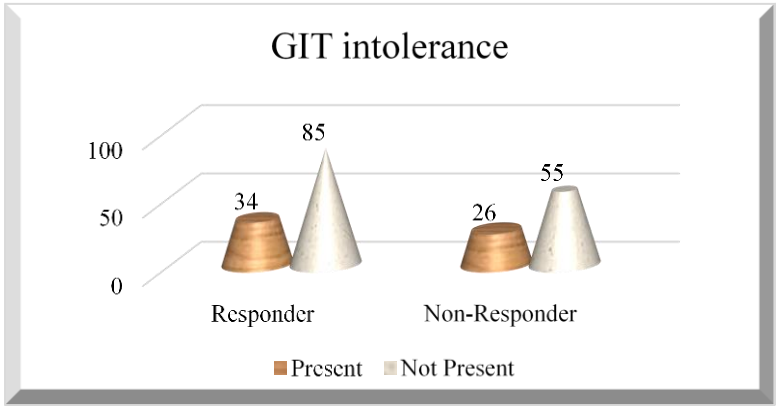
Statistics	Responder Mean±SEM	Non-responder Mean±SEM
Baseline	24.87±0.44kg/m^2	25.24±0.55 kg/m^2
After 3 months	24.63±0.39 kg/m^2	24.85±0.50 kg/m^2
Decrease in BMI	0.24±0.11 kg/m^2	0.39±0.20 kg/m^2
P-value for decrease	0.00	0.00
Difference in both groups	0.15±0.04 kg/m^2	
P-value difference	0.68	

P-value <0.05 considered significant

Side effects were reported by 61 patients among all selected patients after metformin therapy. There was 34 (56%) cases in responder group and 27 (44%) cases in non-responder group. The difference in both groups was statistically not significant with P value equal to 0.509.

Table No 05: GIT intolerance

Groups	Present		Not Present		Total
	Quantity	Percentage	Quantity	Percentage	
Responder	34	28.57%	85	71.43%	119 (100%)
Non-Responder	26	32.10%	55	67.90%	81 (100%)



DISCUSSION:

Type-2 diabetes mellitus (T2DM) is the utmost frequent shape of diabetes and metformin is the baseline medicine for its therapy. Irrespective of its prevalent use, 35% patients fail to reach initial target of glycemic control with metformin because of variable drug response [16]. In our study, Responders were 59.5% patients and Non-Responders were 40.5% patients as to metformin on the basis of decreases in A1C. If classification of patients is associated in relations of response, alike study was carried out on South Indian newly diagnosed T2DM patients where Responders were 76% patients and Non-Responders patients were 23% [8]. Though, the percentage of Non-responders was bigger in our study but this inconsistency in non-responsiveness may be accredited to other factors like compliance of patients, genetic changes and duration of diabetes which were not considered in our study.

We found reduction in BMI after 12 weeks of therapy with metformin in our study. The reduction was similar in both response groups. Our conclusion was in accordance to the earlier research done on white Americans as they discovered durable connotation of BMI with the patients. They discovered that decrease in BMI was more in Responder group as compared to Non-Responder group [17]. In an-other study carried out on German inhabitants in 2013, also presented conflicting consequences to our study [18]. Same alike consequences were obtained in a research carried out on the Australian population in 2006 and they discovered that metformin therapy had no effect in decreasing BMI of the patients whether they are

Responders or Non-Responders [19]. In a research study in Latvian population, Tarasova and her colleagues discovered that BMI was not related to any of the response group and the BMI was greater than our study. Nevertheless, more consideration should be given towards categorizing patients consistent with the degree of overweightness in comparation to total body mass, as well as to the degree of stomach overweightness [20].

The outcomes of our study presented that GIT intolerance was not related with the response group and these outcomes are in opposition to the study carried out on population from North Caucasia, North Africa and Sub-Sahara African ancestry. Significant effect of metformin therapy was found in generating GIT intolerance [21]. While, Laura and her colleagues originate no connotation among metformin therapy and the GIT intolerance [22]. The patients who are already suffering from GI problems or patients who are already using anti-diarrheal drugs should be identified as risk factor for metformin intolerance. As compared to patients who were having initial HbA1C level <8%, patients with ≥8% HbA1C initial level showed more reduction. High baseline HbA1C levels are associated with higher reductions in HbA1C levels via treatment through metformin and some other studies also support the same findings [23].

CONCLUSION:

It was concluded in our study that after treatment with metformin found improvement in 59.5% of newly diagnosed T2DM patients for glycemic control. Whereas, 40.50% patients didn't improve which might be due to collective influences of various gene polymorphisms and their inter-action with non-genetic factors. Regardless of effects of metformin on HbA1C, it decreased the BMI of all selected patients. Furthermore, no difference found in both groups for the symptoms and signs of GIT.

REFERENCES:

1. Soumya D, Srilatha B. Late stage complications of diabetes and insulin resistance. J Diabetes Metab. 2012;2(9):1-7.
2. Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy a meta-regression analysis. Diabetes Care. 2006;29(9): 2137-2139. doi: 10.2337/dc06-1120.
3. Basit A, Danish Alvi SF, Fawwad A, Ahmed K, Yakoob Ahmedani M, et al. Temporal changes in the prevalence of diabetes, impaired fasting glucose and its associated risk factors in the rural area of Baluchistan. Diabetes Res Clin Pract. 2011;94(3):456-462. doi: 10.1016/j. diabres.2011.08.009.
4. Zafar J, Bhatti F, Akhtar N, Rasheed U, Bashir R, Humayun S. Prevalence and risk factors for diabetes mellitus in a selected urban population of a city in Punjab. J Pak Med Assoc. 2011; 61:40-47.
5. S. A. Meo, I. Zia, I. A. Bukhari, Arain SA. Type 2 diabetes mellitus in Pakistan: Current prevalence and future forecast. J Pak Med Assoc. 2016;66(12):1637-1642.
6. Basit A, Fawwad A, Qureshi H, Shera AS. Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016-2017. BMJ open. 2018; 8(8): e020961.
7. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy a consensus statement from the American Diabetes Association and the European Association for the study of diabetes. Diabetes Care. 2006;29(8):1963-1972. doi: 10.2337/dc06-9912.
8. Umamaheswaran G, Praveen RG, Arunkumar AS, Das AK, Shewade DG, Adithan C. Genetic analysis of OCT1 gene polymorphisms in an Indian population. Indian J Hum Genet. 2011;17(3):164-168. doi: 10.4103/09716866.92094.
9. Kirpichnikov D, Mcfarlane SI, Sowers JR. Heart failure in diabetic patients: utility of βblockade. J Card Fail. 2003;9(4):333-344.
10. Bray GA, Ryan DH. Medical therapy for the patient with obesity. Circulation 2012;125(13):1695-1703. doi:10.1161/ CIRCULATIONAHA.111.026567.
11. Hermans M, Ahn SA, Rousseau M. What is the phenotype of patients with gastrointestinal intolerance to metformin? Diabetes Metab. 2013;39(4):322-329. doi: 10.1016/j.diabet.2013.05.005.
12. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194. doi: 10.1001/ jama.2013.281053
13. Shikata E, Yamamoto R, Takane H, Shigemasa C, Ikeda T, Otsubo K, et al. Human organic cation transporter (OCT1 and OCT2) gene polymorphisms and therapeutic effects of metformin. J Hum Genet. 2007;52(2):117-122. doi: 10.1007/ s10038-006-0087-0.

14. Tkac I, Javorsky M, Klimcakova L, Zidzik J, Gal'a I, Babjakova E, et al. A pharmacogenetic association between a variation in calpain 10 (CAPN10) gene and the response to metformin treatment in patients with type 2 diabetes. Eur J Clin Pharmacol. 2015;71(1):59-63. doi: 10.1007/s00228-014-1774-y.
15. Siavash M, Tabbakhian M, Sabzghabaee AM, Razavi N. Severity of Gastrointestinal Side Effects of Metformin Tablet Compared to Metformin Capsule in Type 2 Diabetes Mellitus Patients. J Res Pharm Pract. 2017;6(2):73-76. doi: [10.4103/jrpp.JRPP_17_2]
16. Goswami S, Yee SW, Stocker S, Mosley JD, Kubo M, Castro R, et al. Genetic variants in transcription factors are associated with the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2014;96(3):370-379. doi: 10.1038/clpt.2014.109.
17. Dujic T, Zhou K, Donnelly LA, Tavendale R, Palmer CN, Pearson ER. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study. Diabetes. 2015;64(5):1786-1793. doi: 10.2337/db14-1388.
18. Seifarth C, Schehler B, Schneider H. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. Exp Clin Endocrinol Diabetes. 2013;121(01):27-31. doi: 10.1055/s-0032-1327734.
19. Ong CR, Molyneaux LM, Constantino MI, Twigg SM, Yue DK. Long-term efficacy of metformin therapy in nonobese individuals with type 2 diabetes. Diabetes Care. 2006;29(11):2361-2364. doi:10.2337/dc06-0827.
20. Tarasova L, Kalnina I, Geldnere K, Bumbure A, Ritenberga R, Nikitina-Zake L, et al. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion 1 transporter protein genes with the gastrointestinal side effects and lower BMI in metformintreated type 2 diabetes patients. Pharmacogenet Genomics. 2012;22(9):659-666. doi:10.1097/FPC.0b013e3283561666.
21. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy a consensus statement from the American Diabetes Association and the European Association for the study of diabetes. Diabetes Care. 2006;29(8):1963-1972.
22. Mccreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia. 2016;59(3):426-435. doi: 10.1007/s00125-015-3844-9.
23. Van Gaal L, Scheen A. Weight management in type 2 diabetes: current and emerging approaches to treatment. Diabetes Care. 2015;38(6):1161-1172. doi:10.2337/dc14-1630.