MANAGEMENT OF METFORMIN INDUCED GIT PROBLEMS

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Clinical Trial Registration No: Madeeha Fatima, Saleha Sadeeqa (2018): Management of metformin-induced gastrointestinal problems.
ISRCTN40695995 https://doi.org/10.1186/ISRCTN40695995

Word count: 2579

Abstract

OBJECTIVE: Metformin has been suggested as first-line therapy for Type 2 diabetes mellitus. However, its use has some barriers as a complex administration regimen and gastrointestinal side-effects. The objective of the study is to evaluate the effect of metformin induced GIT problems on different doses of metformin and their management.

RESEARCH DESIGN AND METHODS: The research consisted of 2 parts. In first phase a cross sectional research design was used. In second phase experimental research design was used. The total sample size was 300(N=300) patients. Statistical package for science version 21st (SPSS-21) was used for statistical analysis.

RESULTS: The comparison among three doses (500mg, 850mg and 1000mg) of metformin showed significant result (P=0.006 P=0.000; P=0.022 for 500mg, 850mg & 1000mg respectively). Furthermore, a significant difference existed between the way of intake and frequency of metformin. Difference between the pre and post intervention of omeprazole and pantoperazole showed significant value (P<0.001 and 0.001 respectively). Moreover, significant difference existed between pre and post treatment with omeprazole and pantoperazole on blood sugar level (P<0.001). The patients showed more tolerance of metformin with meals (P<0.001). There is significant difference between pharmacological and non pharmacological treatment on symptoms (p=0.007).

CONCLUSIONS: The study concluded that the GIT problems increase with the increase in dose and frequency of metformin. Metformin is best tolerated if taken with meals. , treatment with PPIs (i.e. omeprazole and pantoprazole) reduces the symptoms most likely dyspepsia, heartburn, indigestion, & abdominal pain. Further, PPIs showed no effect on the efficacy of metformin..

Introduction

The term diabetes mellitus portrays multiple aetiological metabolic disorder that are characterized by chronic hyperglycaemia along with disruption in the metabolism of fat, carbohydrate and protein which results in the defects of secretion of insulin, action of insulin, or both(1). Worldwide Type II diabetes is a health problem. It is affecting individual more than 415 million and by end of 2040 is expected to reach 642 million individuals. World Health Organization (WHO) reported that 12.9 million persons (10 percent of the population) of Pakistan are diabetic patients (2). According to the guidelines of WHO for the diabetes treatment the major components are: diet (if possible along with exercise), hypoglycaemic oral therapy and treatment with insulin (3).

Metformin has been suggested as first-line therapy for Type 2 Diabetes mellitus. This is because of its efficacy, safety, reduced cost, and potential cardiovascular benefit (4). The monotherapy of the drug typically decrease HbA1C levels by _1.5% (5) . BG work by reducing gluconeogenesis and by augmenting the glucose peripheral utilization (3). Its use has some barriers as a complex administration regimen and gastrointestinal side-effects. Dyspepsia, abdominal distension, nausea, constipation, flatulence, abdominal pain (6). The mode of action of gastrointestinal side effects and their significant inter-individual differences are unknown. The therapy of metformin should be started with the medication single dose usually 500 mg. the maximum daily recommended dose of metformin is 2550 mg (7). The objective of the study is to evaluate the effect of metformin induced GIT problems on different doses of metformin and their management.

Research Design and methods

The research consisted of 2 parts. In first phase a cross sectional research design was used. In second phase experimental research design was used. The study was conducted in Allied Hospital Faisalabad, Faisalabad Diabetic Center and Diabetic Institute Pakistan Lahore from June 2017 to November 2017. In this study convenient sampling technique was used. The total sample size was 300(N=300) patients. In the study both genders male and female participated. The age ranges from 26-85 years of the participants. Patient having type 2 diabeties were included in the study. Those patients who were using metformin as an anti diabetic drug were considered.

Type 1 diabetes patients were excluded in the sample. Patients of having age less than 26 and greater than 85 were not included in the study. Patient who were taking drug other than metformin were excluded. Patients taking insulin were not considered.

Study Instruments

Inform consent

A consent form both in English (Annexure A) and Urdu (Annexure B) was designed to get the consent of the participants. In this form the researcher completely highlighted the nature, aims and objectives of the study. The rights of participant were also described and was also mentioned that whenever the participant can leave the study without any prior.

Demographic information form

The demographic information form was composed to get the personal and factual information of the participants. The form consisted of participant name, address, gender, contact number, age, weight, and height (Annexure C).

Medical history form

A medical history form was designed in order to get the medical related information of the patient. It includes the prescription of medicine, doses of medicine, frequency to take medicine, way of intake and any other medical issue. The same form included the number of symptoms that participant has experienced (Annexure C).

Data Collection Procedure

This study consisted of two phases. The first phase is quantitative study in which cross sectional research design was used. Data was collected from the patients by visiting the Out Patient department of different government and private hospitals. In this study diabetic patients using metformin of different doses (500mg, 850mg & 1000mg) were taken. Patients who have got the symptoms of metformin induced gastrointestinal problems were noted. The symptoms were then linked with dose, frequency and way of intake of metformin.

In the second phase of the study experimental design was used. In this phase patients taking metformin having gastrointestinal symptoms were divided into three groups. Each group consisted of 20 participants. The participants were subjected to PPIs in order to see the effectiveness of proton pump inhibitors i.e. omeprazole and pantoprazole. The first group of participants were given omeprazole 40mg. Similarly the second group was subjected to pantoperazole 40mg. In this phase the initial symptom of the patient were recorded and intervention is produced and then after intervention the level and severity of the symptom again checked by directly interviewing the participants on their follow-up and noted. Their blood sugar levels were also noted. In this way the effectiveness of the medicine is checked. The third group of the patients were subjected to non pharmacological treatment i.e. intervene to take metformin during meal and the outcomes are recorded.

Data analysis

Statistical package for science version 21st (SPSS-21) was used for statistical analysis. Independent sample T test was utilized to assess the difference between groups, and intake of medicine. In the second phase of the study repeated measure t-test was used to check the effectiveness of medicine by comparing the severity of symptoms before and after taking the medicine. P-value ≤ 0.05 was taken as significant.

Ethical consideration

Approval was taken by Lahore College for Women University (LCWU) Board of Studies (BOS) and Advance Study Research Board (ASRB). The study was approved by the secretariat ethical review committee Punjab Medical College Faisalabad. The approval number was PMC/PHRC/ERC/2017/11. All the ethical considerations were taken into account. The written permission from the concerned authorities of hospitals and diabetic centers were also be taken. The research design/protocol and the Performa along with consent form were also approved from the ethical committee of the hospitals. The consent of the participants was also being taken. The ethical approval letters are attached herewith as a supplementary material.

Results

Table 1 Comparison of different doses of metformin on symptoms

Results showed that a significant difference exist between patients who are taking 500mg dose and who are taking 850mg dose of metformin (p=0.006). Further the table shows that those patients who are taking 850mg dose of drug are facing more GIT problems as compared to those patients who are taking 500mg of drug.

Moreover, results showed that there is a significant difference between those patients who are taking 500mg dose of metformin and those patients who are taking 1000mg dose of metformin (p=0.000). Moreover, the table shows that those patient who are taking 1000mg dose of drug face more GIT problems than those patients taking 500mg dose of the drug.

Furthermore, results showed that a significant difference exist between the patient who are taking 850mg dose of metformin and patient who are taking 1000mg dose of metformin (p=0.022). Those patient who are taking 1000mg dose of medicine face more GIT problems as compared to those patients who are taking 850mg dose of medicine. Hence, it means as the dose increases the gastrointestinal problems with metformin increases.

Dose	N	M	S.D	df	t-value	p-value
500mg	141	0.54	0.945	164	-2.784	0.006
850mg	25	1.12	1.054			
500mg	141	0.54	0.945	200	-7.749	0.000
1000mg	61	1.80	1.302			
850mg	25	1.12	1.054	84	-2.328	0.022
1000mg	61	1.80	1.302			

Table 1 Comparison of different doses of metformin on symptoms

Table 2 Comparison of frequency of metformin on symptoms

Results showed a significant difference between those patients who are taking metformin once a day and those patients who are taking metformin twice a day (p=0.000). Moreover, the graph shows that the patient who are taking metformin twice a day experience more GIT problems as compared to those patients taking metformin once a day.

Moreover, results showed that a significant difference exist between those patients who are taking metformin once a day and those patients taking metformin thrice a day (p=0.000). Further, the graph shows that patients taking metformin thrice a day experience more GIT problems than those patients taking metformin once a day.

Further, results showed a significant difference between those patients who are taking metformin twice a day and those patients taking metformin thrice a day (p=0.023). Moreover, it shows that patients taking metformin thrice a day experience more GIT problems than those patients taking metformin twice a day.

Frequency	N	M	S.D	df	t-value	p-value
Once a day	33	0.12	0.415	209	-4.188	0.000
Twice a day	178	1.02	1.221			
Once a day	33	0.12	0.415	47	-7.403	0.000
Thrice aday	16	1.75	1.125			
Twice a day	178	1.02	1.221	192	-2.943	0.023
Thrice aday	16	1.75	1.125			

Table 2 Comparison of frequency of metformin on symptoms

Table 3 Comparison of way of intake on symptoms

Results showed a significant difference between the way of intake of medicine (before meal and during meal). Those patients who are taking metformin before meal experience more GIT problems as compared to patients taking metformin during meal (p=0.000).

The table also showed that there exists a significant difference between the way of intake of metformin (during meal and after meal). Those patients who are taking metformin after meal experience more GIT problems as compared to patients taking metformin during meal (p=0.000).

Results also showed that there exists non significant difference between the way of intake of metformin (before meal and after meal) which shows that both patient experience GIT problems irrespective of the way of intake of medicine (p=0.759).

Way of intake	N	M	S.D	df	t-value	p-value
Before	29	1.24	1.244			
During	89	0.38	0.873	116	4.121	0.000
During	89	0.38	0.873			
After	109	1.32	1.239	196	-6.032	0.000
Before	29	1.24	1.244			
After	109	1.32	1.239	136	-0.308	0.759

Table 3 Comparison of way of intake on symptoms

Table 4 Difference between pre and post intervention on symptoms

Results showed that there is significant difference between the omeprazole treatment (before & after). The symptoms were improved after the therapy (p=0.000). The table also reflects, there is significant difference between the pantoprazole treatment (before & after). The symptoms were improved after the therapy (p=0.001). Further, there is significant difference between before

and after giving metformin with meals (non pharmacological treatment) (p=0.000). The patients shows more tolerance of metformin with meals.

Intervention	M	S.D	t-value	p-value
Before giving omeprazole	2.40	0.883	14.236	0.000
After giving omeprazole	0.80	0.696		
Before giving pantoprazole	2.60	0.883	11.000	0.001
After giving pantoprazole	0.95	0.759		
Before giving metformin with meals	1.45	0.686	8.904	0.000
After giving metformin with meals	0.35	0.587		

Table 4 Difference between pre and post interventions on symptoms

Table 5 Difference between pre and post exposure of intervention on blood sugar level

Results showed that there is a significant difference between the random blood sugar level by the omeprazole treatment (before & after) (p=0.000). The efficacy of metformin was not affected by the use of omeprazole. Results also depicts that there is a significant difference between

the random blood sugar level by the pantoprazole treatment (before & after) (p=0.000). The efficacy of metformin was not affected by the use of pantoprazole.

Intervention	M	S.D	t-value	p-value
Before giving omeprazole	194.70	40.603	3.324	0.000
After giving omeprazole	181.20	41.159		
Before giving pantoprazole	218.20	35.944	5.486	0.000
After giving pantoprazole	205.90	37.928		

Table 5 Difference between pre and post exposure of intervention on blood sugar level

Table6 Difference between pharmacological and non pharmacological treatment on symptoms

Results showed that there is significant difference between pharmacological and non pharmacological treatment on symptoms (p=0.007). The table shows that those patients receiving pharmacological treatment experience more symptoms as compared to those patients who are receiving non pharmacological treatment.

treatment	M	S.D	df	t-value	p-value
Pharmacological	0.88	0.723	58	2.814	0.007
non pharmacological	0.35	0.587			

Table 6 Difference between pharmacological and non pharmacological treatment on symptoms

Dicussion

First-line oral medication is metformin which is recommended for type 2 diabetic patients for control of hyperglycemia. As all drugs have some side effects similarly metformin induces the gastrointestinal problems. The present study was conducted to assess metformin induced gastrointestinal problems and its management. The participants taking different doses of metformin were taken in order to check the effect of drug and gastrointestinal problems. Different groups were subjected to different classes of proton pump inhibitors and metformin given with meal.

The result of the present study showed that those patients who were taking 850mg dose of drug were facing more GIT problems as compared to those patients who were taking 500mg of drug. Similarly, those patients who were taking 1000mg dose of drug faced more GIT problems than those patients taking 500mg dose of the drug. These results are consistent with those of Jacobsen et al, 2009 & Jadzinsky 2009, Kirpichnikov 2002 in which patients were subjected to different doses of metformin twice a day (7,8,9). The patients experience adverse effects most commonly related to gastrointestinal tract which increased with increasing dosage.

But a study done by Dandona (1983) is contradictory which reported that adverse effects were not related to the dose of metformin. Patients taking different doses of metformin were observed and results showed that the frequency or severity of adverse effect was irrespective of the dose of metformin (10).

The next result depicted that there existed a significant difference between the way of intake of metformin (during meal and after meal). Those patients who were taking metformin after

meal experience more GIT problems as compared to patients taking metformin during meal. These results are consistent with those of Burton (2015) and Nathan (2009) which showed that Metformin showed best tolerance when taken with a meal (11,5).

The findings of the study showed that the symptoms were improved when patients were given proton pump inhibitors. There existed a significant difference between the symptoms before and after the treatment with PPI. Machado-Alba et al.,(2013) investigated in their study that PPIs were used in diabetic patients receiving ant-diabetic drugs (metformin) (12). Ding (2014) found in their study that metformin cause gastrointestinal problems. PPIs are the first choice drugs used in gastrointestinal problems. This study also found that PPIs were frequently used with metformin but has limited systematic data (13). Bashford et al., (1998) study depicted that PPIs could be used for dyspeptic symptoms and other gastrointestinal problems (14). But a study conducted by Chen et al (2016) showed that concomitant use of metformin and PPI are not safe and lead to increased risk of hospitalization and even death (15).

The study also found that there existed a significant difference between the random blood sugar level by the PPI treatment i.e. before & after giving PPIs. PPI do not interfere with the efficacy of metformin. The random blood sugar levels were found to be reduced. These results are in consistent with Flory and his coworkers in 2015, and Crouch with his fellows in 2012 who found that PPI therapy lowers the HbA1c levels and can be used as adjunctive therapy in diabetic patients (16, 17). But Dujic and his colleagues in 2016 conducted a study that drugs (e.g. PPI) which interfere with OCT 1 transport plays important role in metformin intolerance (18).

This study evaluates the metformin induced GI intolerance. The present study is a unique contribution in terms of management of adverse effects produced by metformin by pharmacologically i.e. using proton pump inhibitors and non pharmacologically (by changing way

of intake of metformin). Moreover, frequency of metformin usage on GI symptoms is a significant result produced in this study. Furthermore, the study depicted pharmacological and non pharmacological comparison on the intensity of symptoms. The result of the study will be useful for the awareness of diabetic patients in improving their quality of life.

The literature review infers that metformin causes gastrointestinal problems and even lead to drug discontinuation. There is no experimental data that provide explanation for patient dependant adverse effects. Moreover, there is no treatment or further approach to improve the tolerance of metformin. Preference is given if metformin is taken with meals and dose is slowly titrated to avoid these GI effects but these recommendations are not supported by any solid evidence i.e. no randomized trials are found in this regard.

However our study has some limitations. In the present study only one type of diabetes is taken. The group size was limited. The research lacked HbA1C level after the pharmacological therapy. Financial issue and time constraint were the stumbling blocks in the way of research. Difficulties were faced to communicate with patients and to have their consent in the collection of the data.

Conclusion

The study concluded that the GIT problems increase with the increase in dose and frequency of metformin. Further, symptoms are also seen if metformin is taken before or after meal. Metformin is best tolerated if taken with meals. Furthermore, comparison of pharmacological and non pharmacological treatment is done which showed that metformin taken with meals decreases the incidence of GI intolerance. Moreover, treatment with PPIs (i.e. omeprazole and pantoprazole) reduces the symptoms most likely dyspepsia, heartburn, indigestion, & abdominal pain. The study also found that there has been no effect of PPIs on the efficacy of metformin.

Acknowledgement: The author thank the cooperation of the management and the ethical committee of Allied hospital Faisalabad, Faisalabad Diabetic center and Diabetic Institute Pakistan Lahore who allowed the author to conduct and complete the research work.

Funding: The study is self-funded

Conflict of interest: No conflict of interest associated with this work.

Contribution of Authors: Madeeha Fatima designed the study, researched the data, contributed to the discussion, performed data analysis and wrote the manuscript. Dr. Saleha Sadeeqa supervised and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and declares that the author did this work personally and did not fraudulently obtain the data being presented.

References

1. Consultation, W.H.O 1999. Definition, diagnosis and classification of diabetes mellitus and its complications.*Clinical picture of Diabetes II, 2*(12), 11-15.
2. Akhtar, S., Khan, Z., Rafiq, M. and Khan, A., 2016. Prevalence of Type II diabetes in District Dir Lower in Pakistan. *Pakistan Journal of Medical Sciences*, *32*(3), 622.
3. Organization, W. H. 1994. "Management of diabetes mellitus: Standards of care and clinical practice guidelines."
4. Scarpello, J.H. and Howlett, H.C., 2008. Metformin therapy and clinical uses. *Diabetes and Vascular Disease Research*, *5*(3), 157-167.

5. Nathan, D.M., Buse, J.B., Davidson, M.B., Ferrannini, E., Holman, R.R., Sherwin, R. and Zinman, B., 2009. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes care*, *32*(1), 193-203.
6. Davidson, J. and Howlett, H., 2004. New prolonged-release metformin improves gastrointestinal tolerability. *The British Journal of Diabetes & Vascular Disease*, *4*(4), 273-277.
7. Kirpichnikov, D., McFarlane, S.I. and Sowers, J.R., 2002. Metformin: an update. *Annals of internal medicine*, *137*(1), 25-33.
8. Jacobsen, I.B., Henriksen, J.E. and Beck-Nielsen, H., 2009. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. *Basic & clinical pharmacology & toxicology*, *105*(3), 145-149.
9. Jadzinsky, M., Pfützner, A., Paz-Pacheco, E., Xu, Z., Allen, E. and Chen, R., 2009. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes, Obesity and Metabolism*, *11*(6), 611-622.
10. Dandona, P., Fonseca, V., Mier, A. and Beckett, A.G., 1983. Diarrhea and metformin in a diabetic clinic. *Diabetes care*, *6*(5), 472-474.
11. Burton, J. H., Johnson, M., Johnson, J., Hsia, D. S., Greenway, F. L., & Heiman, M. L. 2015. Addition of a gastrointestinal microbiome modulator to metformin improves metformin tolerance and fasting glucose levels. *JOURNAL OF DIABETES SCIENCE AND TECHNOLOGY*, *9*(4), 808-814.

12. Machado-Alba, J., Fernández, A., Castrillón, J.D., Campo, C.F., Echeverri, L.F., Gaviria, A., Londoño, M.J., Ochoa, S.A. and Ruíz, J.O., 2013. Prescribing patterns and economic costs of proton pump inhibitors in Colombia. *Colombia Médica*, *44*(1), 13-18.
13. Ding, Y., Jia, Y., Song, Y., Lu, C., Li, Y., Chen, M., Wang, M. and Wen, A., 2014. The effect of lansoprazole, an OCT inhibitor, on metformin pharmacokinetics in healthy subjects. *European journal of clinical pharmacology*, *70*(2),141-146.
14. Bashford, J.N., Norwood, J. and Chapman, S.R., 1998. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. *Bmj*, *317*(7156),452-456.
15. Chen, C.B., Lin, M., Eurich, D.T. and Johnson, J.A., 2016. Safety of concomitant metformin and proton pump inhibitor use: a population retrospective cohort study. *Clinical therapeutics*, *38*(6), 1392-1400.
16. Flory, J., Haynes, K., Leonard, C.E. and Hennessy, S., 2015. Proton pump inhibitors do not impair the effectiveness of metformin in patients with diabetes. *British journal of clinical pharmacology*, *79*(2), 330-336.
17. Crouch, M.A., Mefford, I.N. and Wade, E.U., 2012. Proton pump inhibitor therapy associated with lower glycosylated hemoglobin levels in type 2 diabetes. *The Journal of the American Board of Family Medicine*, *25*(1), 50-54.
18. Dujic, T., Causevic, A., Bego, T., Malenica, M., Velija-Asimi, Z., Pearson, E.R. and Semiz, S., 2016. Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes. *Diabetic Medicine*, *33*(4), 511-514.