

Original Research Article

Role of prebiotics and probiotics in the prevention of the gastrointestinal side effects of metformin among the type 2 diabetic patients

Sundus Khan¹, Hira Yousaf², Hina Rafiq³, Zarish Zamir⁴, Ayesha Muhammad Deen⁵,
Tayyab Mumtaz Khan^{6*}, Hina Nauman⁷, Sheema Nauman⁷, Shahrukh Khan⁵

¹Riphah International University, Islamabad, Pakistan

²University of Huddersfield, United Kingdom

³University of Agriculture Faisalabad, Punjab, Pakistan

⁴University of Lahore, Pakistan

⁵University of Veterinary and Animal Sciences, Lahore, Pakistan

⁶Rawalpindi Medical University, Rawalpindi, Pakistan

⁷Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan

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*Correspondence:

Dr. Tayyab M. Khan,

E-mail: tayyab.mkhan98@gmail.com

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ABSTRACT

Background: Diabetes mellitus (DM) is most common endocrine disorder all over the world. Metformin has been used as a first line drug, however, it has several gastrointestinal side effects. This study aims to determine the frequency of metformin induced gastrointestinal side effects among type 2 diabetic patients and role of prebiotics and probiotics in the prevention of the metformin-induced GI side effects.

Methods: This cross-sectional study was performed in a tertiary care hospital, Rawalpindi, among 130 for one year from January 2021 to December 2022. Data was collected by applying a self-structured questionnaire. Descriptive statistics were used for the data analysis. Data analysis was performed via statistical package for the social sciences (SPSS) version 25.0.

Results: The means for study variables like age, dose, and duration of therapy were 54.09 years, 1000 mg and 3.6 years respectively. Female patients had more GI side effects than male patients. Similarly, GI side effects frequency was also higher among the patients who were on metformin alone than the patients who were using metformin and combination of prebiotics and probiotics. Patients with higher dose of metformin and shorter duration of metformin therapy had higher frequency of GI symptoms. The most common GI symptom was constipation followed by diarrhea, bloating, abdominal pain, vomiting/nausea, dyspepsia, loss of appetite and flatulence.

Conclusions: Metformin induced GI symptoms were common among study population. Use of prebiotics and probiotics combination with metformin, low dose of metformin, and longer duration of metformin use were found protective against the metformin-induced GI side effects.

Keywords: Prebiotics, Probiotics, Gastrointestinal, Side effects, Metformin, Type 2 diabetic patient

INTRODUCTION

Diabetes mellitus (DM) is a most common endocrine disorder characterized by raised blood sugar levels due to

insulin deficiency or insulin resistance in body. More than 415 million people over the world have been affected by the DM and it is estimated that this number would be reached to 642 million by the end of 2040.¹ According to

World Health Organization (WHO), almost 10% (12.9 million) of Pakistani population are diabetic and from these, only 9.4 million people are diagnosed while 3.5 million people are undiagnosed. Furthermore, a huge number of people (38 million) in Pakistan are suffering from prediabetes, and more of these people are women. Every year almost 120,000 people die because of DM-related complications.^{2,3}

Different modalities have been used for the treatment of DM all over the world and these modalities included diet modification, exercise, oral antidiabetic drugs, and inulin.^{4,5} One of the most commonly prescribed antihyperglycemic drugs is metformin. Over the decades, metformin has become the first-line drug in the treatment of diabetes mellitus type 2.⁶

Metformin acts as an antidiabetic agent by decreasing blood sugar levels through different mechanisms. It reduces the hepatic production of glucose and glucose absorption in intestine. It also reduces the resistance of insulin in the body by increasing the sensitivity of the insulin.⁷

Besides its use in the management of diabetes mellitus type 2, metformin has been also used in the treatment of versatile diseases polycystic ovarian disease, gestational diabetes, pre-eclampsia, obesity, osteoarthritis, and skin diseases.⁸

Gastrointestinal (GI) side effects among the patients who use metformin have become the major barrier to the intolerance of metformin. Several studies have reported the GI side effects of metformin all over the world. It is estimated that almost 20% to 30% of metformin users face GI side effects and almost 5% of patients on metformin stop using it. Although this percentage varies in different regions.^{9,10} Different mechanisms have been suggested that lead to GI side effects while patients on metformin such as alternation in the metabolism of glucose and incretin, malabsorption of bile salts, and release of serotonin. All these lead to GI side effects and intolerance to metformin. Moreover, genetic-based intolerance to metformin has also been reported.^{11,12}

Several studies have also shown that metformin alters the microbiota of the gut that leads to metformin-induced GI side effects. Metformin use increases some gut flora such as *Akkermansia muciniphila*, *Escherichia spp*, and *Lactobacillus* while decreases other gut flora like *Intestinibacter spp*. This imbalance in the gut flora could be the cause of metformin-induced GI side effects.^{16,17} Various researches have presented that use of prebiotics and probiotics along with metformin balance the gut flora imbalance induced by alone use of metformin and consequently the metformin-induced GI side effects gets settled.^{17,18}

GI side effects of metformin and role of prebiotics and probiotics use in the prevention of metformin-induced GI

side effects are under-studied in the different regions of Pakistan, especially in the locality of this research. Therefore, this study aims to determine frequency of metformin-induced GI side effects and the role of prebiotics and probiotics in the prevention of the gastrointestinal side effects of metformin among diabetic patients in Rawalpindi, Pakistan.

METHODS

This cross-sectional study was conducted in the outdoor medicine department of a tertiary care hospital of Rawalpindi, among one hundred and thirty patients diagnosed with type 2 diabetes mellitus for one year from January 2021 to December 2022. 65 diabetic patients were on metformin only while 65 patients were on both metformin and prebiotics and probiotics combination. Study sample size was calculated by the WHO calculator. Patients were enrolled in the study by using the non-probability convenient sampling and developed inclusion and exclusion criteria. Only those patients who had aged above 40 years, had type 2 diabetes mellitus, no psychiatric diseases, will to take part in the study, and were only metformin tablets for different duration were recruited in the study. Whereas, those who had an age below 40 years, any psychiatric diseases, showed hesitation to participate, and were on different antidiabetic drugs including insulin, were excluded from the study. Informed consent was also waived from all participants before the data collection. Data was collected by using a self-designed questionnaire. This questionnaire was composed of two parts. First part was about the socio-demographic characteristics of the study population such as gender (male or female) and age. Second part was regarding the questions about the duration since the patients were using metformin and dose of metformin that patients were taking. In second part of questionnaire, question about the use of prebiotics and probiotics was also asked. Second part also had questions about the gastrointestinal (GI) side effects (diarrhea, vomiting/nausea, abdominal pain, flatulence, dyspepsia, bloating, and heartburn, loss of appetite, and constipation) of metformin that patients on metformin were facing. This questionnaire was given to each participant, and they were asked to fill in it by themselves under observation of researchers. After data collection, data analysis was performed in statistical package for the social sciences (SPSS) version 25 (Armonk, NY: IBM Corp.) by applying descriptive statistics. The frequency and percentage of qualitative data were calculated, while means of quantitative data were estimated.

RESULTS

Out of one hundred and thirty patients, 76 (58.46%) were females, whereas, 54 (41.54%) were males. The mean of age for the study population was 54.09 years with standard deviation of ± 10.67 years. The mean of duration of metformin therapy was 3.6 years with the range from 2 months to 7 years while the mean dose of metformin for study population was 1000 mg with the range from 500 mg

to 2000 mg. From the total of 130 patients 75 (57.69%) were facing metformin induced GI symptoms while 55 (42.31%) patients were free from any GI symptoms. From the 75 patients who were facing GI side effects, only 12 (16%) patients belong to that group of diabetic patients who were using prebiotics and probiotics combination together with the metformin, whereas, 63 (84%) diabetic patients were those, who were only on metformin.

Table 1 shows that GI side effects were more common females 43 (57.34%) than males 32 (42.66%).

Table 1: Comparison of frequencies and percentages of metformin induced gastrointestinal side effects based on gender.

Gender	Frequency	Percentage
Female	43	57.34
Male	32	42.66

Table 2 shows that GI side effects were more prevalent among the patients 63 (84%) who were only on metformin than the patients 12 (16%) who were on metformin plus prebiotics and probiotics combination.

Table 2: Comparison of frequencies and percentages of metformin induced gastrointestinal side effects based on use of prebiotics and probiotics use.

Drug combination	Frequency	Percentage
Only metformin	63	84
Metformin plus prebiotics and probiotics combination	12	16

Table 3 elaborates that with the high dose of metformin was associated with the higher frequency of GI side effects.

Table 3: Comparison of frequencies and percentages of metformin induced gastrointestinal side effects based on dose metformin therapy.

Metformin dose (mg)	Frequency	Percentage
500	8	10.66
750	13	17.33
1000	14	18.67
1500	16	21.33
2000	24	32.0

Table 4 manifests that patients had more GI side effects whose metformin therapy duration was less than 1 year than whose metformin therapy duration was more than 1 year.

Table 5 indicates that frequency and percentages of various metformin induced gastrointestinal side effects among diabetic patients. The most common side effect of metformin among study population was constipation

(52%). It also elaborated that the other symptoms that were related to metformin included diarrhea (45.33%), bloating and nausea (40%), abdominal pain (37.33%), vomiting/nausea (36.0%), dyspepsia (28.0%), loss of appetite (24%), and flatulence (16.0%).

Table 4: Comparison of frequencies and percentages of metformin induced gastrointestinal side effects based on duration on metformin therapy.

Duration of therapy	Frequency	Percentage
Less than 1 year	47	62.67
More than 1 year	28	37.33

Table 5: Frequencies and percentages of metformin induced gastrointestinal side effects among study population.

Variables	Frequency	Percentage
Constipation		
Yes	39	52.0
No	36	48.0
Diarrhea		
Yes	34	45.33
No	41	54.67
Bloating and heartburn		
Yes	30	40
No	45	60
Abdominal pain		
Yes	28	37.33
No	47	62.67
Vomiting/nausea		
Yes	27	36.0
No	48	64.0
Dyspepsia		
Yes	21	28.0
No	54	72.0
Loss of appetite		
Yes	18	24.0
No	57	76.0
Flatulence		
Yes	12	16.0
No	63	84.0

DISCUSSION

This study was performed to estimate the frequency of metformin induced GI symptoms among the type 2 diabetes mellitus patients in Rawalpindi, Pakistan, and current study has provided significant information about the GI symptoms of the metformin among the diabetic patients and the involvement of prebiotics and probiotics combination in the prevention of the metformin-induced GI side effects.

The percentage of metformin induced GI symptoms in current study was (57.69%). Several regions of world have presented different percentages of GI symptoms after

taking metformin. Dujic et al noticed in their study that 20-30% of patients taking metformin face GI symptoms.⁹ According to Burton et al, 88% of patients who take metformin suffer from GI symptoms.¹³ Another study suggested that 45.80% of patients who use metformin face metformin induced GI symptoms.²

This study suggested that the metformin induced GI symptoms were more prevalent among females (57.34%) as compared to males (42.66%). Another study presented similar finding that female suffer more with metformin induced GI symptoms.¹²

The use of prebiotics and probiotics along with metformin was found to linked with lower frequency of metformin-induced GI side effects in contrast to the only use of metformin among diabetic patients. This finding of the research was also backed by various studies that were performed in the different regions of the globe.¹⁶⁻¹⁸

This study also noted that metformin induced GI side effects frequency was higher with high dose of metformin. A study with consistent finding also observed that higher dose of metformin increases the frequency of GI side effects.²

Regarding the impact of duration of therapy of metformin on GI side effects, it was observed that higher patients whose duration of therapy was less than 1 year and who were in initial phase of therapy were facing more GI side effects in comparison to those patients who were on metformin for longer duration. Similar results were presented by an Indian study.¹⁰

Metformin leads to several gastrointestinal symptoms. These symptoms included constipation, diarrhea, bloating and heartburn, abdominal pain, vomiting/nausea, dyspepsia, loss of appetite, and flatulence. These findings were supported by various studies that were conducted in different parts of the world.^{13,14}

In current study most common GI side effect in current study was constipation (52.0%) while least was flatulence (16.0%). Another study also noted that most common GI side effect of metformin in constipation, however, least common side effect in it was vomiting.² Whereas, Bouchoucha et al found that diarrhea and nausea/vomiting were the most common GI side effect of metformin.¹⁵

In this study constipation was followed by diarrhea, bloating and heartburn, abdominal pain, nausea/vomiting, dyspepsia, loss of appetite, and flatulence. While in a study of Saluja et al noted that diarrhea was followed by nausea/vomiting, abdominal pain, flatulence, retching, and dysgeusia.¹⁰

This variation in the GI side effects of metformin different studies that had been conducted in discrete regions of the world could be due to diversity in the races, environmental variation, distinct lifestyles and genetics of people.

The limitations of this study included small sample size and cross-sectional design of the study. This might have caused the change in findings and because of the cross-sectional design current study could not explain how the metformin leads to gastrointestinal side effects and how use of prebiotics and probiotics combination with metformin prevent metformin-induced GI effects. Therefore, additional research work is needed with a larger sample size and different study design that could elaborate the temporal association between the metformin and gastrointestinal side effects. And to manifest that how the prebiotics and probiotics combination use with metformin stops metformin-induced GI side effects.

CONCLUSION

The study findings have suggested that metformin induced GI side effects are more common among female patients than male patients. Similarly, it is also noted that the metformin-induced GI side effects frequency was higher among the diabetic patients who were only using metformin than the diabetic patients who were using metformin with prebiotics and probiotics combination. Current study also showed that patients who were using higher dose of metformin and who were on metformin for shorter duration had more GI side effects. The most prevalent GI side effect of metformin was constipation, while least was flatulence. This study recommends that to avoid or at least to decrease the frequency of metformin induced GI side effects, metformin should be used with the combination of prebiotics and probiotics.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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