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ORIGINAL ARTICLE

Association of Helicobacter pylori infection with metformin intolerance in type 2 diabetic patients.

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ABSTRACT… Objective: To observe the association of Helicobacter Pylori infection with metformin intolerance in type2 diabetic patients. **Study Design:** Observational, Cross Sectional study. **Setting:** Out Patients of Shifa Foundation Falahee Clinics. **Period:** August 2017 to January 2018. **Material & Methods:** Type 2 diabetes mellitus (DM) patients above 30 years of age taking metformin were recruited according to inclusion criteria. These patients were labelled metformin intolerant or metformin tolerant on the basis of their gastrointestinal (GI) symptoms. Both groups were tested for the presence of Helicobacter Pylori (H. pylori) infection using urea breath test (UBT). SPSS 23 was used for data entry and analysis. Descriptive statistics were analysed for demographic and other variables and cross tabulation performed to link the variables using chi square and Fischer's exact test. Results were expressed as p-value, which when <0.05 with 95% confidence interval, was considered statistically significant. **Results:** Out of 57 patients, female gender, age above 50 years and residence in Rawalpindi showed higher frequencies. Majority of them were found intolerant to metformin use. Urea breath test were found positive in majority of metformin intolerant patients (p value $=0.04$). Dyspepsia was most frequent symptom among metformin intolerants. Duration of diabetes mellitus, of metformin use and dose of metformin did not affect the tolerance status of metformin and urea breath test results. **Conclusion:** The screening for H. pylori should be considered in all Metformin intolerant diabetic patients. It is likely to improve drug compliance.

Key words: Helicobacter Pylori Infection, Metformin Intolerance, Urea Breath Test.

INTRODUCTION

Metformin is an effective agent with a good safety profile that is widely used as a first-line treatment for type 2 diabetes, yet its mechanisms of action and variability in terms of efficacy and side effects remain poorly understood. Although the liver is recognized as a major site of metformin metabolism, we believe that metformin response and tolerance is intrinsically linked with the gut.[1] GI adverse effects typically encountered with metformin therapy include diarrhea, nausea, flatulence/bloating, indigestion, vomiting and abdominal discomfort, with diarrhea and nausea being the most common.[2]

Observational studies show lower rates of use of metformin than would be expected from clinical guidelines, so metformin is positively viewed by patients and providers, but gastrointestinal side effects are a barrier to its use.[3]

Helicobacter pylori infection is amongst the most prevalent infections in humans worldwide, and is a significant source of morbidity and mortality. H. pylori is a gram-negative bacterium, which colonizes the gastric epithelium and induces chronic inflammation of the gastric mucosa.[4] H. pylori related GI symptoms like pain, burning epigastrium, bloating and nausea etc. are attributed to varying degrees of inflammation of gastric mucosa by H. Pylori. Han X and colleagues according to their research findings suggested that H. pylori infection was associated with the risk of type 2 diabetes in a middle-age and old-age Chinese population[5], so this may be considered another gastrointestinal effect of

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helicobacter pylori infection.

Urea breath test has high sensitivity and specificity for detection of H. pylori infection and for asymptomatic subjects is considered as gold standard.[6]

Mostly Helicobacter pylori and metformin intolerance are taken as separate entity, but they resemble each other regarding spectrum of clinical presentation. Our clinical observations and some previous research[7] led us hypothesize that H. pylori is one of the most important factor responsible for metformin intolerance in diabetic patients so we planned this study to confirm the association between two. In this way, identification and eradication of H. Pylori can be achieved and metformin tolerance can be enhanced, hence the utilization of this valuable drug in diabetic patients.

MATERIAL & METHODS

It was an Observational, Cross Sectional study conducted at Shifa Foundation Falahee out door clinic from August 2017 to January 2018 after due approval from IRB & Ethics Committee (IRB no: 663-111-2016). Taking 5% absolute precision, 95% confidence interval and 10% drop outs, total sample size was calculated to be 80. Written informed consent was taken from each patient. Type 2 diabetic patients above 30 years of age taking metformin as antidiabetic drug were included in study. Patients on long term steroids, NSAIDS, anticholinergics, using proton pump inhibitors, patients with pregnancy; history of gallstones, hiatal hernia, gut resection, end stage renal and liver disease and taking anticancer drugs were excluded from the study.

Patients were asked for gastrointestinal symptoms which were; dyspepsia (burning epigastrium, gastro-oesophageal reflux), flatulence/bloating and diarrhoea, and were segregated into two groups: those patients who developed any of these gastrointestinal symptoms first time after starting metformin OR their pre-existing milder symptoms (any of above 3) worsened on metformin, were labelled as metformin intolerant group. And the other metformin taking patients having any spectrum of gastrointestinal symptoms (any of above 3) prior to metformin use and their symptoms remained unchanged on metformin, were labelled as metformin tolerant group. Both groups were tested for the presence of Helicobacter Pylori infection using urea breath test (UBT). In the UBT, one baseline breath sample was collected followed by oral administration of 75 mg of ^{13}C-urea ((Isotec, Miamisburg, Germany). Following the dose of ^{13}C-urea, another breath samples were collected at 30 minutes. The breath sample was examined for $^{13}CO_2/^{12}CO_2$ ratio using BreathMATplus mass spectrometer (Thermo Finnigan, Germany) and result was considered positive by a cut-off of more than 5%. A positive result indicated presence of H. pylori, while negative result implied absence of H. pylori.

SPSS 23 was used for data entry and analysis. Descriptive statistics were analysed for demographic characteristics and other study variables and were expressed as frequencies and percentages while Chi square and Fischer's exact test were performed to see the association of variables. Results were expressed as p value, which less than 0.05 with 95% confidence interval was considered statistically significant.

RESULTS

A total of 80 patients were recruited for this research. 9 patients lost to follow up and 14 Performa were rejected due to incomplete information. An analysis was performed on 57 patients. Majority patients belonged to Rawalpindi, age group above 50 years and female gender. Most of the patients had diabetes duration in range of one to five years. 50.9% patients were using metformin for more than 24 months. 87.7% patients were using metformin in doses between 1 to 2 gram. 96.5% patients were compliant to metformin therapy Table-I.

When metformin tolerance status was assessed, 40(70.2%) were found to be metformin intolerant while 17(29.8%) were tolerant to metformin use. About gastro intestinal symptoms in all study subjects, flatulence/bloating was most frequent (50 out of 57), followed by dyspepsia (45 out of

57) and then diarrhea (15 out of 57). However, among metformin intolerant patients, dyspepsia was most frequent followed by flatulence/bloating and then diarrhea.

Out of 57 patients, 40(70.2%) had their urea breath test positive while 17 (29.8%) had negative test. Cross tabulation among status of metformin tolerance and urea breath test using chi square and Fischer's exact test revealed that among the 17 tolerant patients, 10(58.8%) had negative UBT, and 7 (41.2%) had positive UBT, while among 40 intolerant patients, 33(82.55) had positive UBT and 7 (17.5%) had negative UBT test (p=0.004). (Table-II)

Characteristics		Frequency (%)
Age (Years)	30-40	13 (22.8)
	40-50	17 (29.8)
	>50	27 (47.4)
Gender	Male	20 (35.1)
	Female	37 (64.9)
Residence (city)	Rawalpindi	26 (45.6)
	Islamabad	10 (17.5)
	Others	21 (36.8)
Duration of diabetes (Years)	<1	14 (24.6)
	1-5	30 (52.6)
	>5	13 (22.8)
Duration of Metformin use (Months)	<6	12 (21.1)
	6-24	16 (28.1)
	>24	29 (50.9)
Metformin dose (Gram)	<1	6 (10.5)
	1-2	51 (89.5)
Metformin tolerance status	Tolerant	17 (29.8)
	Intolerant	40 (72.2)
Urea breath test	Positive	40 (72.2)
	Negative	17 (29.8)

Table-I. Characteristics of participants (n=57)

Status of Metformin Tolerance	Urea Breath Test		P-Value
	Positive	Negative	
Tolerant	7(41.2%)	10(58.8%)	0.004
Intolerant	33(82.5%)	7(17.5%)	

Table-II. Association of status of metformin tolerance with results of urea breath test.

However, all 3 GI symptoms (flatulence/bloating, diarrhea, dyspepsia) were independently related to the positive result of urea breath test. (Table-III)

GI Symptom	Variable	Urea Breath Test		P-Value
		Positive	Negative	
Metformin related Dyspepsia	Yes (Intolerant) (39)	32	7	0.005
	No (Tolerant) (18)	8	10	
Metformin related Diarrhea	Yes (Intolerant) (14)	14	0	0.007
	No (Tolerant) (43)	26	17	
Metformin related flatulence/ bloating	Yes (Intolerant) (35)	31	4	0.001
	No (Tolerant) (22)	9	13	

Table-III. Association of gastrointestinal symptoms with results of urea breath test (n=57).

Age was not found to be correlated with any gastrointestinal symptoms, status of tolerance of metformin or result of urea breath test (p value = >0.05). Regarding gender, female patients were found to have more symptoms of flatulence then males (p value = 0.015) while rest of GI symptoms were not different among the two. Regarding overall tolerance to metformin, female patients had more intolerance then the males (p value = 0.019) but gender did not affect the result of urea breath test (p value = 0.98).

Duration of diabetes and metformin and dose of metformin did not affect status of metformin tolerance and UBT results. (p value = > 0.05)

DISCUSSION

This is a common observation that diabetic patients develop new or worsening of GI symptoms after Metformin treatment.[7] H. pylori infection poses the similar symptoms like excessive burping, nausea, pain abdomen; as the use of metformin[1,2], so most of the time these symptoms are attributed to the metformin use, while presence of H. pylori might be the case.

The debate on Metformin related gastrointestinal effects and its correlation with the presence of helicobacter pylori in gut, has been started in recent years as Huang Y and colleagues demonstrated the co-existence of metformin intolerance and Helicobacter pylori in diabetic patients.[8] Our study results endorsed Huang Y et al finding that metformin intolerance in diabetic patients was associated with the presence of helicobacter pylori infection in them as proved by positive urea breath test.

Contrary to this, Tseng CH[9] demonstrated direct antimicrobial effect of metformin on H. pylori, while they were studying the effect of metformin on H. pylori in the guts of mice. Whereas clinically metformin is known to cause or worsen GI symptoms not relieving it. So these findings of Tseng might need elaboration on some other perspectives like; in-vivo and in-vitro differences (which do not necessarily reflect all aspects of the organism as a whole)[10]; animal and human differences, which might exist in this situation. There may be dosing or certain other issues with the research on mouse; like the metformin effect as anticancer therapy was suggested by some animal studies[11,12,13,14,15] then Yousef M and colleagues critically analyzed it by noticing that the concentration of metformin used in in vitro studies was quite higher as compared to their concentration in human blood. So Yousef M and colleagues suggested researchers to plan future in vitro studies using metformin dose in the same range to be physiologically/pharmacologically relevant with the in vivo levels so to better investigate the mechanism of action.[16] Such mechanism are likely to exist in the animal based demonstration of antimicrobial effect of metformin against Helicobacter pylori also.

Further, if metformin has antimicrobial effect for Helicobacter pylori infection, then the wide spread use of metformin as first line anti diabetic agent must have decreased the prevalence of helicobacter pylori in diabetic patients significantly silently, but this is not the case as in a recent study, Kouitcheu Mabeku and colleagues showed in their study that H. pylori infection was found in 73.11% of diabetic patients versus 58.05% in non-diabetic participants, this difference was found to be significant (OR = 1.472, p = 0.0279).[17] The same has also been supported by other research.[18]

Our study showed more metformin intolerance in females, literature favors this difference based on gender. A higher proportion of women reporting metformin-associated adverse drug reactions is seen, particularly at early stages after initiation.[19]

Regarding effect of metformin dose on its GI side effects, Kento K etal showed that the gastro-intestinal symptoms were not affected by the dosage or dosing frequency of metformin.[20] Our study results endorsed Kento findings. This is generally thought that beginners of metformin therapy more suffer GI effects, but some researcher mentioned that these side effects may also occur even after prolonged treatment with metformin.[21] Our study also endorsed that duration of metformin use don't affect side effects.

Small data is the limitation of this study and also metformin intolerance was taken as subjective assessment, it would be better if we could measure intolerance in future using more specific laboratory tools.

CONCLUSION

Metformin intolerance in diabetic patients is linked to the presence of H. pylori infection in them, so the screening for helicobacter pylori should be considered in all Metformin intolerant diabetic patients. It is likely to improve metformin compliance and diabetes control.

REFERENCES

1. McCreight LJ, Bailey CJ, Pearson ER. **Metformin and the gastrointestinal tract.** Diabetologia. 2016; 59(3):426–35. DOI: 10.1007/s00125-015-3844-9

2. Bonnet F, Scheen A. **Understanding and overcoming metformin gastrointestinal intolerance.** Diabetes, Obes Metab. 2017; 19(4):473–81. DOI: 10.1111/dom.12854

3. Flory JH, Keating S, Guelce D, Mushlin AI. **Overcoming barriers to the use of metformin: Patient and provider perspectives.** Patient Prefer Adherence. 2019; 13:1433–41. doi: 10.2147/PPA.S211614

4. Soveri LM, Osterlund P, Ruotsalainen T, Poussa T, Rautelin H, Bono P. **Helicobacter pylori and gastrointestinal symptoms in diagnostics and adjuvant chemotherapy of colorectal cancer.** Oncol Lett. 2014; 7(2):553-559. doi: 10.3892/ol.2013.1714

5. Li JZ, Li JY, Wu TF, Xu JH, Huang CZ, Cheng D, et al. **Helicobacter pylori infection is associated with type 2 diabetes, not type 1 diabetes: An updated meta-analysis.** Gastroenterol Res Pract. 2017; 2017. doi: 10.1155/2017/5715403

6. Abadi ATB. **Diagnosis of helicobacter pylori using invasive and noninvasive approaches.** J Pathog. 2018;2018:1–13. DOI: 10.1155/2018/9064952

7. Fatima M, Sadeeqa S, Nazir SUR. **Metformin and its gastrointestinal problems: A review.** Biomed Res. 2018; 29(11):2285–9. DOI:10.4066/BIOMEDICALRESEARCH.40-18-526

8. Huang Y, Sun J, Wang X, Tao X, Wang H, Tan W. **Helicobacter pylori infection decreases metformin tolerance in patients with type 2 diabetes mellitus.** Diabetes Technol Ther. 2015; 17(2):128–33. DOI: 10.1089/dia.2014.0203

9. Tseng CH. **Metformin and helicobacter pylori infection in patients with type 2 diabetes.** Diabetes Care. 2018; 41(4):e42–3. https://doi.org/10.2337/dc17-2551

10. Aljofan M, Riethmacher D. **Anticancer activity of metformin: A systematic review of the literature.** Futur Sci OA. 2019; 5(8). DOI: 10.2144/fsoa-2019-0053

11. Mallik R, Chowdhury TA. **Metformin in cancer.** Diabetes Res Clin Pract. 2018; 143:409–19. DOI: 10.1016/j.diabres.2018.05.023

12. Amaral I, Silva C, Correia-Branco A, Martel F. **Effect of metformin on estrogen and progesterone receptor-positive (MCF-7) and triple-negative (MDA-MB-231) breast cancer cells.** Biomed Pharmacother. 2018; 102(1 mM):94–101. DOI: 10.1016/j.biopha.2018.03.008

13. Tan M, Wu A, Liao N, Liu M, Guo Q, Yi J, et al. **Inhibiting ROS-TFE3-dependent autophagy enhances the therapeutic response to metformin in breast cancer.** Free Radic Res. 2018; 52(8):872–86. doi.org/10.1080/10715762.2018.1485075

14. Devadasu VR, Alshammari TM, Aljofan M. **Current advances in the utilization of nanotechnology for the diagnosis and treatment of diabetes.** Int J Diabetes Dev Ctries. 2018; 38(1):11–9. DOI:10.1007/s13410-017-0558-1

15. He Y, Tan X, Hu H, Wang Q, Hu X, Cai X, et al. **Metformin inhibits the migration and invasion of esophageal squamous cell carcinoma cells by downregulating the protein kinase B signaling pathway.** Oncol Lett. 2018; 15(3):2939–45. DOI: 10.3892/ol.2017.7699

16. Yousef M, Tsiani E. **Metformin in lung cancer: Review of in vitro and in vivo animal studies.** Cancers (Basel). 2017;9(5):1–16. doi: 10.3390/cancers9050045

17. Kouitcheu Mabeku LB, Noundjeu Ngamga ML, Leundji H. **Helicobacter pylori infection, a risk factor for Type 2 diabetes mellitus: A hospital-based cross-sectional study among dyspeptic patients in Douala-Cameroon.** Sci Rep [Internet]. 2020; 10(1):1–11. Available from: https://doi.org/10.1038/s41598-020-69208-3. DOI: 10.1038/s41598-020-69208-3

18. Wan Z, Song L, Hu L, Hu M, Lei X, Huang Y, et al. **Helicobacter pylori infection is associated with diabetes among Chinese adults.** J Diabetes Investig. 2020; 11(1):199–205. DOI: 10.1111/jdi.13102

19. de Vries ST, Denig P, Ekhart C, Mol PGM, van Puijenbroek EP. **Sex differences in adverse drug reactions of metformin: A longitudinal survey study.** Drug Saf [Internet]. 2020; 43(5):489–95. doi: 10.1007/s40264-020-00913-8

20. Kanto K, Ito H, Noso S, Babaya N, Hiromine Y, Taketomo Y, et al. **Effects of dosage and dosing frequency on the efficacy and safety of high-dose metformin in Japanese patients with type 2 diabetes mellitus.** J Diabetes Investig. 2018; 9(3):587–93. doi: 10.1111/jdi.12755

21. Saluja M, Pareek KK, Swami YK. **Study of diversity of metformin related gastrointestinal side effects.** J Assoc Physicians India. 2020; 68(8):36–8. PMID: 32738838.

AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Ammarah Saeed	Statistical analysis.	
3	Nadia Saeed	SPSS sheetpreparation and initial analysis, Last review.	
4	Rahila Aamir	Mendley referencing, Discussion review.	
5	Naeem Saleem	Synopsis Writing.	
6	Mahnoor Aitzaz	Collected and arranged reference studies.