

Association of Gastrointestinal Symptoms with Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

FARMAN ULLAH SHAH¹, MUHAMMAD SOHRAB KHAN²

¹Assistant Professor, Department of Gastroenterology, MTI Bacha Khan Medical College and Mardan Medical Complex Mardan, Khyber Pakhtunkhwa, Pakistan

²Assistant Professor, Department of Medicine, MTI Bacha Khan Medical College and Mardan Medical Complex Mardan, Khyber Pakhtunkhwa, Pakistan

Correspondence to: Dr. Muhammad Sohrab Khan, Email: sohrab_dr2002@hotmail.com

ABSTRACT

Objective: To assess how often gastrointestinal (GI) symptoms (constipation, diarrhoea, dyspepsia and bloating) occur in type 2 diabetes mellitus (T2DM) and whether they are related to glycemic control or diabetes duration.

Materials and Methods: This was a cross-sectional study which was carried out in the Department of Gastroenterology and Medicine at Mardan Medical Complex Mardan from August 2022 to January 2023. The sample size consisted of 250 adult patients with T2DM, who were sampled consecutively, and who had GI symptoms measured using an adapted version of the Diabetes Bowel Symptom questionnaire. The glycated hemoglobin (HbA1c) <7% was considered as controlled and HbA1c ≥7% as uncontrolled. The following statistical methods were utilized: chisquare, Mann-Whitney U, Spearman correlation and logistic regression.

Results: Mean age was 53.7 ± 10.0 years, 58.0% were female, mean diabetes duration was 6.9 ± 4.2 years and mean HbA1c was $8.1 \pm 1.6\%$; 74.0% had uncontrolled diabetes. GI symptoms were present in 148 (59.2%): dyspepsia 23.2%, bloating 18.8%, diarrhea 15.2% and constipation 14.8%. Of all the symptoms, any one was more common in those with uncontrolled diabetes but not significantly (62.2% vs 50.8%, $p = 0.108$). HbA1c was higher with dyspepsia (8.6% vs 7.9%, $p = 0.027$) and correlated weakly with symptom count ($\rho = 0.15$, $p = 0.017$). Bloating rose with duration, from 12.5% at <5 years to 31.4% at >10 years ($p = 0.022$). Each 1% rise in HbA1c increased the adjusted odds of any GI symptom (OR 1.21, 95% CI 1.03-1.44, $p = 0.023$).

Conclusions: GI symptoms were found in people with T2DM. The higher the HbA1c, the higher the rate of dyspepsia and overall symptom burden, and the longer the duration, the more frequent bloating, but they were not significantly divided by the 7% cut-off. They require periodic follow-up.

Keywords: Diabetes Mellitus, Type 2; Glycated Hemoglobin; Gastrointestinal Diseases; Constipation; Diarrhea; Dyspepsia

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic diseases in the world. In 2021, there were approximately 537 million adults aged 20-79 years with diabetes (10.5%)¹. One of the heavy burdens faced by Pakistan is that its second National Diabetes Survey of Pakistan (2016-2017) indicated high prevalence of 26.3% in adults².

The effects of sustained hyperglycemia are generally referred to in terms of retinopathy, nephropathy and peripheral neuropathy, and damage to small vessels and autonomic nerves has been demonstrated. However, the gastrointestinal (GI) tract is involved from the esophagus to the anorectum and its involvement is an easy-to-ignore aspect of routine diabetes management^{3,4}. Patients complain of dysphagia, nausea, early satiety, dyspepsia, bloating, abdominal pain, constipation, diarrhea and fecal incontinence. These symptoms also impact quality of life, influence the absorption of oral medications and nutrient delivery and can make glycemic control more difficult to attain⁴. The most widely recognised end point of the spectrum is gastroparesis, which is delayed gastric emptying, in the absence of mechanical obstruction⁵.

The question of whether or not the symptoms of GI follow glycemic control remains open. In a population-based survey of 15,000 adults, upper and lower GI symptoms were more prevalent in individuals with diabetes and excess upper and lower GI symptoms seemed to be associated with poor glycemic control, but not with the duration of diabetes⁶. A Korean case-control study of 190 patients with T2DM revealed that none of the diabetic factors (other than HbA1c) was independently associated with UGIS⁷. The Australian team who made the population survey later linked the GI symptoms to the extent of glycemic control and diabetic complications⁸. In Pakistan, a study conducted in Karachi found an increase in GI symptoms in diabetics compared to non-diabetics as well as a relationship to glycemic control but not the length of diabetes⁹, and a study in Lahore was conducted on gastroparesis symptoms in T2DM¹⁰. Community data about GI symptoms in diabetes is also available¹¹. A 2018 review, however, still found the link between GI symptoms and glycemic control to be indistinct⁴.

There are differences in ethnic groups, diets, treatment patterns and measurement of symptoms across populations, and to our knowledge, few local data are available in Khyber Pakhtunkhwa. Therefore, patients having T2DM attending the Departments of Gastroenterology and Medicine in Mardan Medical Complex, Mardan were studied. The aim was to find out the prevalence of constipation, diarrhea, dyspepsia and bloating and their connection with HbA1c and diabetes duration. Higher HbA1c and diabetes duration was hypothesized to be correlated with more GI symptoms.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Department of Gastroenterology and Medicine, Mardan Medical Complex, Mardan, Khyber Pakhtunkhwa, Pakistan from August 2022 to January 2023.

Ethical considerations: The study protocol was approved by the Ethical Review Committee of Bacha Khan Medical College Mardan. The procedures followed the standards of the institutional committee on human experimentation and the Declaration of Helsinki. The informed consent for the participation in the study was obtained from all the subjects and no names, initials and hospital numbers were recorded in the study data.

Sample size and sampling technique: The subjects were sampled by [non-probability consecutive sampling] method and the sample size was 250 because all eligible patients who visited the two departments during the study period were included. We validated this sample with the primary outcome. At 95% confidence, 250 patients estimate the frequency of GI symptoms to within about ±6% (observed 59.2%, 95% CI 53.1% to 65.3%).

Selection criteria: Inclusion criteria were: HbA1c measured at enrollment; T2DM of at least one year duration (per American Diabetes Association criteria). Patients were excluded if they had type 1 or gestational diabetes, a previously diagnosed GI disorder (including inflammatory bowel disease, celiac disease, peptic ulcer disease or GI malignancy), previous abdominal surgery, chronic liver disease, or advanced renal disease, hypothyroidism, acute infective gastroenteritis in the last 4 weeks, or regular use of drugs known to affect the GI motility, such as anticholinergics/opioids.

Data collection: Structured proforma were used to obtain demographic and clinical data, such as age, sex, BMI, duration of diabetes, antidiabetic drug use (metformin and insulin), hypertension and known diabetic complication. A trained interviewer administered the questionnaire developed by Diabetes Bowel Symptom Questionnaire (DBSQ) (12) to elicit GI symptoms in the past three months. The following operational definitions were used. Consistency was defined as constipation if fewer than 3 bowel movements occurred spontaneously per week or if they were hard stools and the patient was straining to have them. Diarrhea was considered any individual who had passed three or more loose or watery stools in a day. Epigastric pain or burning, early satiety or fullness after eating, as described by the Rome IV classification of gastroduodenal symptoms, were used to define dyspepsia (13). Bloating was considered as an uncomfortable feeling of fullness or bloating in the abdomen. The other symptoms on the proforma (nausea, vomiting, abdominal pain, dysphagia, fecal incontinence, heartburn or acid reflux, belching, excessive flatulence and tenesmus) were combined into other GI symptoms.

Blood was collected for HbA1c which was tested in the hospital laboratory using a Roche [analyzer model, e.g. cobas] analyzer. Glycemic control was defined as controlled (HbA1c <7%) or uncontrolled (HbA1c ≥7%), in line with the American Diabetes Association target for most adults who are not pregnant (14). The duration of diabetes was categorized as < 5 years, 5 to 10 years and >10 years.

Statistical analysis: Data were analysed using [Python 3 (SciPy and statsmodels); replace with SPSS version xx if re-run in SPSS]. For continuous variables, data are reported as mean ± SD and for categorical variables as frequencies and percentages. The normality test was performed using the Shapiro-Wilk test: Age and BMI were normally distributed, whereas HbA1c, and the duration of diabetes were not. The difference in the frequency of each GI symptom between controlled and uncontrolled groups and between duration categories was compared by using the chi-square test. Fisher exact test was used only for 2 × 2 tables with an expected value of < 5; none of these was expected to be < 5. The linear-by-linear association test was used for trend across duration groups. Crude odds ratios (OR) with 95% confidence intervals were calculated for uncontrolled versus controlled diabetes. The duration was skewed, as was HbA1c, so both were compared between patients with and without each symptom using the Mann-Whitney U test and the correlation between the number of GI symptoms per patient, and the HbA1c and duration were analyzed using Spearman's rank correlation. Univariate data were subsequently analyzed using binary logistic regression to determine factors independently associated with having any GI symptom after adjustment for age, sex, duration of diabetes, body mass index and metformin use. HbA1c was then included as a continuous variable in the primary model and as a binary variable (HbA1c ≥7% vs <7%) in a sensitivity analysis. Secondary analyses were fitted using separate models for dyspepsia and bloating, adjusted for HbA1c, age, sex, duration and use of metformin and known neuropathy. A p-value <0.05 was considered statistically significant.

RESULTS

The overall number of patients involved were 250 cases of T2DM. Their mean age was 53.7 ± 10.0 years (range 30 to 80), 145 (58.0%) were women, and the mean duration of diabetes was 6.9 ± 4.2 years. The mean HbA1c was 8.1 ± 1.6%. The baseline characteristics are shown in Table 1. Based on the HbA1c level of 7%, 65 (26.0%) patients had controlled diabetes and 185 (74.0%) had uncontrolled diabetes (Figure 1). Patients in the 5–10-year time frame were the largest group with 111 (44.4%) (Figure 2).

GI symptoms were reported by 148 patients (59.2%, 95% CI 53.1% to 65.3%), and 44 (17.6%) had two or more. Table 2 and figure 3 indicate the frequency of symptoms. Dyspepsia was the most common (23.2%), followed by bloating (18.8%), diarrhea (15.2%) and constipation (14.8%).

GI: gastrointestinal. *Nausea, vomiting, abdominal pain, dysphagia, fecal incontinence, heartburn or acid reflux, belching, excessive flatulence and tenesmus, recorded as one category. Symptoms are not mutually exclusive, so percentages may exceed 100%.

Table 1: Baseline characteristics of the study population (n = 250)

Characteristic	Value
Age (years), mean ± SD	53.7 ± 10.0
Male, n (%)	105 (42.0)
Female, n (%)	145 (58.0)
Body mass index (kg/m ²), mean ± SD	28.8 ± 4.6
Duration of diabetes (years), mean ± SD	6.9 ± 4.2
Duration category, n (%)	
<5 years	88 (35.2)
5 to 10 years	111 (44.4)
>10 years	51 (20.4)
HbA1c (%), mean ± SD	8.1 ± 1.6
Glycemic control, n (%)	
Controlled (HbA1c <7%)	65 (26.0)
Uncontrolled (HbA1c ≥7%)	185 (74.0)
Treatment, n (%)	
Metformin	206 (82.4)
Sulfonylurea	107 (42.8)
Insulin	52 (20.8)
Hypertension	98 (39.2)
Known diabetic neuropathy	36 (14.4)

SD: standard deviation; HbA1c: glycated hemoglobin.

Table 2: Frequency of gastrointestinal symptoms (n = 250)

Gastrointestinal symptom	Present, n (%)	Absent, n (%)
Any GI symptom	148 (59.2)	102 (40.8)
Constipation	37 (14.8)	213 (85.2)
Diarrhea	38 (15.2)	212 (84.8)
Dyspepsia	58 (23.2)	192 (76.8)
Bloating	47 (18.8)	203 (81.2)
Other GI symptoms*	23 (9.2)	227 (90.8)
Two or more symptoms	44 (17.6)	206 (82.4)

Table 3: Association of Gastrointestinal Symptoms with Glycemic Control

Symptom	Controlled (HbA1c <7%) n = 65	Uncontrolled (HbA1c ≥7%) n = 185	Odds ratio (95% CI)	p-value
Any GI symptom	33 (50.8)	115 (62.2)	1.59 (0.90-2.82)	0.108
Constipation	8 (12.3)	29 (15.7)	1.32 (0.57-3.07)	0.511
Diarrhea	9 (13.8)	29 (15.7)	1.16 (0.52-2.59)	0.724
Dyspepsia	10 (15.4)	48 (25.9)	1.93 (0.91-4.08)	0.083
Bloating	9 (13.8)	38 (20.5)	1.61 (0.73-3.54)	0.235

Chi-square test. OR: crude odds ratio for uncontrolled vs controlled diabetes; CI: confidence interval; p <0.05 considered significant.

Table 4: Association of Gastrointestinal Symptoms with Duration of Diabetes

Symptom	<5 years n = 88	5 to 10 years n = 111	>10 years n = 51	p-value
Any GI symptom	45 (51.1)	71 (64.0)	32 (62.7)	0.159
Constipation	11 (12.5)	17 (15.3)	9 (17.6)	0.698
Diarrhea	10 (11.4)	20 (18.0)	8 (15.7)	0.428
Dyspepsia	20 (22.7)	28 (25.2)	10 (19.6)	0.728
Bloating	11 (12.5)	20 (18.0)	16 (31.4)	0.022

Chi-square test. Values are n (%) of patients within each duration group. Linear-by-linear association for bloating, p = 0.008.

Table 5: Multivariable Logistic Regression for Factors Associated with any Gastrointestinal Symptom

Variable	Adjusted odds ratio	95% CI	p-value
HbA1c (per 1% increase)	1.21	1.03-1.44	0.023
Duration of diabetes (per year)	1.01	0.95-1.08	0.733
Female sex	1.23	0.72-2.11	0.446
Age (per year)	1.01	0.98-1.03	0.699
Body mass index (per kg/m ²)	0.98	0.93-1.04	0.578
Metformin use	1.31	0.67-2.59	0.428

CI: confidence interval. HbA1c entered as a continuous variable; all six variables were entered together.

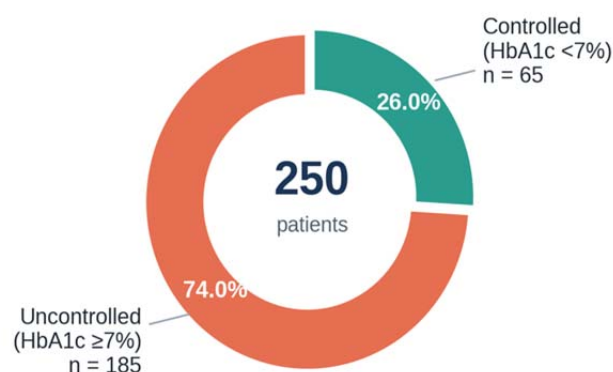


Figure 1: Distribution of patients by glycemic control (n = 250)

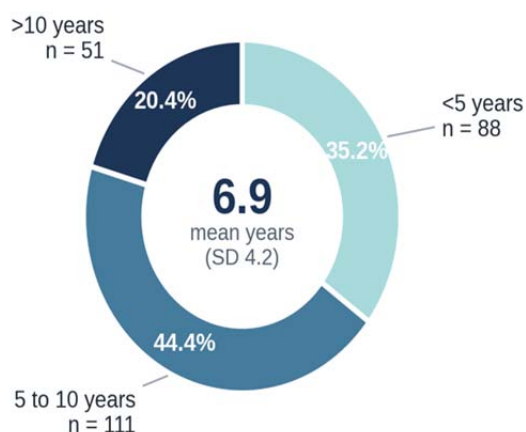


Figure 2: Distribution of patients by duration of diabetes (n = 250)

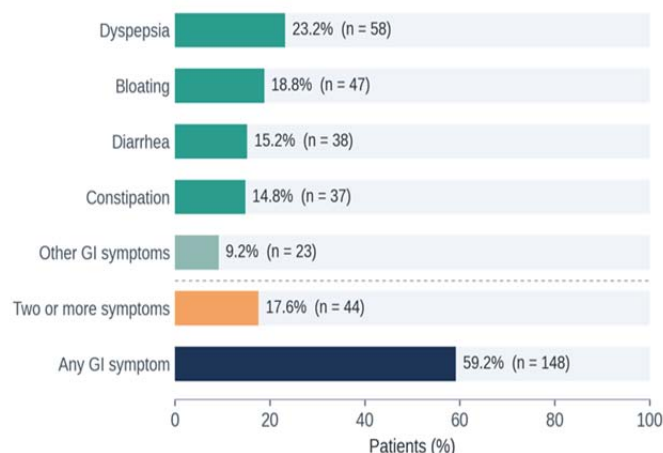


Figure 3: Distribution of gastrointestinal symptoms among patients with T2DM (n = 250)

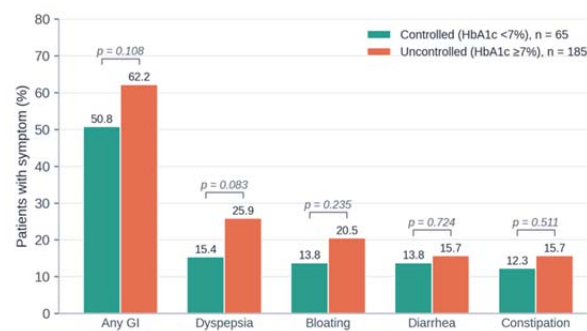


Figure 4: Frequency of gastrointestinal symptoms by glycemic control (n = 250)

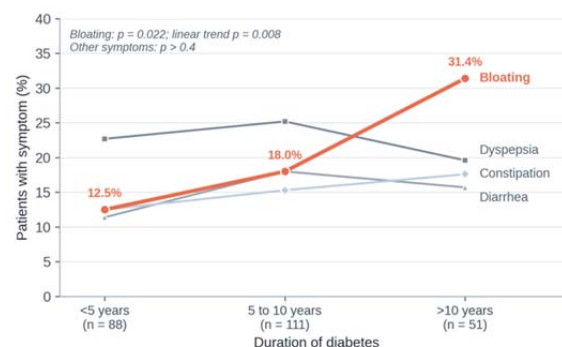


Figure 5: Frequency of gastrointestinal symptoms by duration of diabetes (n = 250)

The frequency of GI symptoms according to glycemic control is given in Table 3 and Figure 4. The presence of any GI symptom was seen in 62.2% of patients with uncontrolled diabetes and 50.8% of patients with controlled diabetes ($p = 0.108$). Each symptom occurred more commonly in the uncontrolled group; none of the differences was significant. Dyspepsia came closest (25.9% vs 15.4%; OR 1.93, 95% CI 0.91-4.08; $p = 0.083$), and two or more symptoms were reported by 20.0% vs 10.8% ($p = 0.093$). The difference was greater for the continuous values of HbA1c. Mean HbA1c was $8.3 \pm 1.7\%$ in patients with and $7.8 \pm 1.4\%$ in those without GI symptoms ($p = 0.068$). It was significantly higher in patients with dyspepsia than in those without ($8.6 \pm 1.8\%$ vs $7.9 \pm 1.5\%$, $p = 0.027$), and in patients with two or more symptoms ($8.7 \pm 1.9\%$ vs $8.0 \pm 1.5\%$, $p = 0.025$). HbA1c had weak, but significant, correlation with the number of symptoms per patient (Spearman's $\rho = 0.15$, $p = 0.017$).

Symptom frequency by duration category is displayed in both Table 4 and Figure 5. Bloating was found to be significantly associated with duration of diabetes, and increased gradually with longer duration ($p = 0.022$; linear trend $p = 0.008$) from 12.5% at diabetes < 5 years to 18.0% at diabetes 5–10 years and 31.4% at diabetes > 10 years. Patients with bloating also had a longer mean duration of diabetes (8.0 ± 4.2 vs 6.6 ± 4.1 years, $p = 0.028$). There were no significant differences in the incidences of constipation, diarrhea and dyspepsia according to the duration. The number of GI symptoms was weakly correlated with duration of diabetes, but this was not significant ($\rho = 0.12$, $p = 0.059$).

When the multivariable logistic regression model (Table 5) was used, only HbA1c was independently associated with any GI symptom. Each 1% increase raised the odds by about a fifth (adjusted OR 1.21, 95% CI 1.03-1.44, $p = 0.023$). There were no significant differences in duration of diabetes, sex, BMI or metformin use. The direction of the association was the same but no longer significant when HbA1c was entered as a binary variable (HbA1c $\geq 7\%$ vs $< 7\%$) (adjusted OR 1.63, 95% CI 0.90-2.93, $p =$

0.104). In the secondary models, HbA1c remained associated with dyspepsia (adjusted OR 1.30 per 1%, 95% CI 1.08-1.58, $p = 0.007$). Only neuropathy (adjusted OR 2.44, 95% CI 1.05-5.66, $p = 0.038$) was significant for bloating, while duration of diabetes was not ($p = 0.110$).

DISCUSSION

Cumulative data of the patients with T2DM who were recruited from a tertiary health care center in Mardan during study period were analyzed and total 250 patients were included. 59.2% of them had at least one GI symptom, which was lower than the 72% of the patients with T2DM in the Korean study⁷. Dyspepsia was the most common symptom in our series. In Lahore study, 44.6%, 41.2% and 39.9% of patients reported on fullness, nausea and bloating respectively and our frequency was 18.8%, which is less than half of the Lahore study. That study relied on the Gastroparesis Cardinal Symptoms Index, a questionnaire which specifically inquired about gastroparesis-type symptoms. Overall, there are variations in figures among studies because symptom definitions, the length of recall period, questionnaires, and case mix are not standardized⁴.

We wondered if glycemic control is associated with GI symptoms and the answer was somewhat different based on the way HbA1c was analyzed. There were no significant differences between controlled and uncontrolled for any symptom but each symptom occurred more frequently in the uncontrolled group, which was split at 7%. HbA1c was elevated in patients with dyspepsia and in those with multiple symptoms, and was correlated with the number of symptoms; it was an independent predictor of any GI symptom after adjustment, and was a continuous measure. This is consistent with the Korean study, in which only HbA1c was independently associated with upper GI symptoms⁷; the Karachi study, which found the highest risk factor for GI symptoms was the poor glycemic control⁹; and with the population based studies related to upper GI⁶ and lower GI⁸ symptoms, both of which linked poor glycemic control to GI symptoms. The less favorable outcome in the 7% cut-off could be due to the loss of information that occurs when a continuous variable is dichotomized. We also had a small controlled group of three quarters of our patients, so only 65 were used for comparison. The impact sizes were small, consistent with the belief that there is inter-population variation in the association between long-term glycemic levels and symptoms⁴.

There may be multiple mechanisms involved in an association between hyperglycemia and GI symptoms. Autonomic neuropathy that follows long-standing hyperglycemia interferes with gut motility, secretion and sensation¹⁵. Adverse early and long-term consequences of diabetes in type 1 are associated with delayed gastric emptying¹⁶. Acute hyperglycemia also causes changes in the compliance of the proximal stomach and its perception of distention¹⁷, and the stomach empties and glycemia influence one another in a bidirectional manner¹⁸. A cross-sectional design is therefore not a good choice to answer the question of the direction of causation, because poor glycemic control may trigger symptoms, and symptoms and delayed emptying may result in poorer glycemic control, relative to the timing of drug action^{4,18}. Bloating was associated independently with known neuropathy, which would be consistent with this mechanism, although neuropathy was obtained from the clinical record and not confirmed by autonomic testing in our patients.

Dyspepsia and bloating occurred in other patterns. Gastric emptying in diabetes can be delayed, fast or normal and upper GI symptoms do not well correlate with the emptying rate¹⁹. Nevertheless, there has been a systematic review and meta-analysis that has associated upper GI symptoms with delayed gastric emptying in diabetes²⁰, and referral centre data has demonstrated that upper GI symptoms are not all motor or sensory based²¹. The association of HbA1c with dyspepsia (pre and post adjustment) should be interpreted with that context. No measures

of gastric emptying have been made and gastroparesis cannot be distinguished from functional dyspepsia. In contrast, the number of days since diabetes diagnosis was linked to bloating, and neuropathy was independently associated with bloating, but not HbA1c, which is consistent with a neuropathic than a glycemic origin. The most effective way to identify diabetic gastroenteropathy is to directly ask about these symptoms and it is an underdiagnosed complication²².

Constipation and diarrhea can be due to different causes. 82.4% of our patients were taking metformin, and metformin is known to cause diarrhea, nausea, flatulence and indigestion²³ and metformin-induced GI symptoms negatively affect quality of life and medication adherence²⁴. As drug exposure is a potential confounder, we added metformin into the multivariable model which was not associated with GI symptoms (adjusted OR 1.31, $p = 0.428$). There was also no significant difference between the metformin users and non-users with regard to the frequency of diarrhea (11.4% vs 16.0%, $p = 0.435$), but only 44 patients did not take the drug. Diabetes causes intrinsic disturbances of small bowel and colonic motility, secretion and anorectal function, which also cause constipation, diarrhea and incontinence²⁵. In our data, there was no association between constipation and HbA1c level or duration of diabetes, nor was there any association between diarrhea and HbA1c or duration of diabetes. No duration effect is found as was also Bytzer et al. and Abid et al^{6,9}, where only the symptom of bloating got worse with duration.

While patients with T2DM at medical clinics are not asked about GI symptoms, 6 out of 10 of the patients had at least one symptom. They are treatable and if recognized, it can result in a re-evaluation of the drug treatment, diet recommendations, or a neuropathy evaluation or a gastroparesis evaluation. Two of the most helpful prompts in our population were: dyspepsia in a patient with an increasing HbA1c and bloating in longstanding disease or known neuropathy.

LIMITATIONS: It is a cross sectional design and causal inference is not possible. The sample was from one center and was selected [non-randomly] limiting generalizability. All symptoms were subjective and recall bias could have occurred, and glycated Hb might not have measured long-term glycemic exposure or glycemic variability. There was a small sample of patients with controlled diabetes ($n = 65$) reducing the power of the comparison of controlled versus uncontrolled diabetes, and no non-diabetic comparison group. p -values near the 0.05 threshold should be interpreted with caution as they are several non-multiplet comparisons. Gastric emptying studies, autonomic function tests, Helicobacter pylori status and psychological factors were not evaluated. It is recommended to carry out larger multicenter studies with a non-diabetic comparison group and objective motility assessment.

CONCLUSION

In this series, GI symptoms occurred in most patients (59.2%), most commonly dyspepsia, with those of T2DM.

There was no significant association with individual GI symptoms for poor glycemic control (HbA1c $\geq 7\%$). Higher HbA1c (analysed as continuous) was significantly associated with the presence of dyspepsia, and with the number of GI symptoms, and also with presence of any GI symptom after adjusting for other variables.

Increased diabetes duration was significantly associated with bloating only and known neuropathy was independently associated with bloating.

Patients with T2DM, especially those with elevated HbA1c or a longer duration of disease, should be screened for GI symptoms by clinicians and larger multicenter studies are needed to confirm these observations.

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AUTHOR CONTRIBUTIONS:

Farman Ullah Shah: Conceptualization, study design, data collection, data analysis and interpretation, manuscript drafting, critical revision, and final approval of the manuscript.

Muhammad Sohrab Khan: Literature review, data collection, data interpretation, manuscript review and editing, critical revision, and final approval of the manuscript.

Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; GI, gastrointestinal; DBSQ, Diabetes Bowel Symptom Questionnaire; SD, standard deviation; OR, odds ratio; CI, confidence interval.

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