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Original Article

Diagnostic Upper Gastrointestinal Endoscopy and Prevalence of *Helicobacter Pylori* Infection in Dyspeptic Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Multisystem involvement is a norm in Type 2 diabetes mellitus (T2DM). Dyspepsia is a common gastrointestinal (GI) tract symptom in people with diabetes. We aimed to study the esophageal, gastric, and duodenal mucosal changes; presence of *Helicobacter pylori* (HP) infection; and its significance in dyspeptic diabetes patients. **Materials and Methods:** A prospective observational study done on 287 patients (147 patient with diabetes and 140 nondiabetic controls) with dyspepsia of more than 6 months duration. All patients underwent upper GI endoscopy and evaluation for HP infection. Gross and histopathological examination (HPE) features of biopsies from the esophagus, stomach (fundus, body, and antrum), and duodenum were analyzed and rapid urease test as well as HPE was done for HP detection. Statistical analysis was done and results were expressed as mean ± standard deviation. $P < 0.05$ was considered to be statistically significant. **Results:** Average age for dyspeptic T2DM patients was 56.0 ± 8.44 years. Total 67.35% diabetes patients were addicted to tobacco. Epigastric pain and heartburn were the most common symptoms. Antral gastritis was the most common gross (75.08%) and HPE (70.38%) finding in patients with diabetes. In all, 44.21% patients with diabetes tested positive for HP infection, and there was a statistically significant association of HP with T2DM when compared with nondiabetics ($P < 0.00001$). However, HP infection did not correlate significantly with either glycosylated hemoglobin (HbA1c) or duration of T2DM. **Conclusion:** Antral gastritis was a common finding in dyspeptic diabetic patients. HP infection although associated with T2DM dyspeptic patients, was not associated with either uncontrolled sugar levels or duration of diabetes.

Keywords: *Gastritis, Helicobacter pylori, hemoglobin – glycosylated, rapid urease test, type 2 diabetes mellitus*

Introduction

Dyspepsia, which encompasses a variety of specific symptoms such as heartburn, epigastric discomfort, bloating, anorexia, early satiety, belching or regurgitation, and nausea,[1] is a frequently encountered symptom in patients with diabetes.[2] Patients with type 2 diabetes mellitus (T2DM) suffer from various micro/macrovascular as well as other systemic complications including those of the upper gastrointestinal (GI) tract. The pathogenesis of GI symptoms in T2DM, which are usually attributed to neurological impairment, especially autonomic neuropathy, has not been clearly elucidated. There also appears to be increased association of *Helicobacter pylori* (HP) infection with diabetes mellitus. Many studies have been done to prove this and there are

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conflicting results. The association between HP and T2DM was first introduced in 1989 and It was proposed that the prevalence of HP is significantly higher among patients with diabetes (62% vs. 21%).[3] In contrast, some studies have shown no such relationship.[4]

Upper GI endoscopy (UGIE) is essential in diagnosing the cause of dyspepsia in patients with diabetes. Although the correlation between mucosal alterations and symptom pattern is difficult, endoscopy still remains the initial investigation of choice for clinically relevant abnormalities that need proper detection and biopsy.[5]

We aim to study the gross endoscopic and histological gastroduodenal mucosal changes in T2DM patients with chronic nonulcer dyspepsia and ascertain whether any correlation exists between T2DM and HP infection.

Materials and Methods

This was a prospective observational study done at a tertiary care hospital in Maharashtra, India, over a period of 2 years (September 2015 to September 2017). Clearance was taken from the Institutional Ethics Committee before commencing the study. Written and informed consent regarding the purpose, procedures, and risks was obtained from all patients.

A total of 1546 patients were referred for UGIE. Of these, 422 patients were undergoing endoscopy for complaints of dyspepsia. Dyspepsia was diagnosed and patients were selected (as per Rome III (for initial 9 months) and then Rome IV for the rest of the study period) if they had symptoms of bothersome postprandial fullness, early satiation, epigastric pain, and burning for the last 3 months with symptom onset at least 6 months before the study. Bothersome symptoms was defined as – severe enough to impact on daily activities or semi-quantitatively as ≥2 on a 5-point scale of the effect exerted by these symptoms on daily activities.[6] Of these, peptic ulcer disease was found in 112 patients on endoscopy and hence these were excluded from the study. Of the remaining 310 patients, 152 patients had T2DM and the remaining 158 did not have T2DM. The following criteria were followed for selection of cases with T2DM: random blood glucose levels of more than 200 mg/dl; fasting blood glucose of more than 126 mg/dl; glycosylated hemoglobin level >6.5%; and/or patients on oral hypoglycemic agents/insulin. Patients <18 years of age, pregnant females, patients with diabetic ketoacidosis, chronic kidney and liver diseases and with history of use of nonspecific anti-inflammatory drugs in the past 1 month or history of malignancy of upper GI tract, peptic ulcers, upper GI bleed, recent major intra-abdominal surgery, treatment of HP infection with proton-pump inhibitors, and antibiotics in the immediate past 4 weeks were excluded from the study. 5 diabetes and 18 nondiabetes patients were thus excluded. Hence, a total of 287 patients which included 147 diabetes patients and 140 nondiabetes patients (as controls) were enrolled in the study.

Data were collected by conducting personal interview and doing a complete physical examination of the participants of the study. A structured pro forma was used and filled after interviewing and examining the patient. The following information was collected for all the participants: age, gender, duration of T2DM, fasting and postprandial blood sugar levels, hemoglobin A1c (HbA1c) levels, dyspepsia symptoms, and their duration.

UGIE was performed on all the study participants using a video gastroscope. Gross features of the upper GI tract were noted and biopsies were obtained from the esophagus, stomach (antrum, body, and fundus), and second part of the duodenum. One antral and one corpus biopsy sample each were used for rapid urease test (RUT) (for high yield). All the biopsy samples were also sent for histopathological examination (HPE). Commercially available RUT kit, manufactured by Halifax Research Laboratory, Kolkata, under the trade name of Pylo Dry, was used. The biopsy specimen was placed in yellow-colored media with a drop of distilled water and then sealed. Pink color change of the media from yellow indicated a positive test for HP. The test was read at 2, 4, 8, and 16 h post test.

Statistics

Collected data were compiled in Microsoft Excel 2010 and analyzed using IBM SPSS (Statistical Program for the Social Sciences) software version 15, OpenEpi Software Version 2.3. Chi-square, Student's *t*-test, and Fisher's exact tests were used wherever applicable. All tests applied were two-tailed, with a confidence level of 95% ($P < 0.05$) considered statistically significant.

Results

Of the total 287 dyspeptic patients studied, 160 (55.75%) were male and 127 (44.25%) were female. About 19% females were postmenopausal. Average body mass index was 25.2 ± 4.0. A total of 174 (60.62%) out of 287 patients were addicted to tobacco either in the chewable form or as cigarettes. Average duration of dyspeptic symptoms was about 7 months. Table 1 shows the demographic, clinical, and endoscopic differences between T2DM patients and nondiabetic controls. Epigastric pain and heartburn were the most common symptoms in more than 90% patients. Figure 1 shows different symptoms of dyspepsia in the study population. Both the patients with diabetes and those without diabetes had similar spectrum of symptoms. Of the total 287 patients with

Table 1: Comparison of demographic and clinical characteristics of patients with and without type 2 diabetes mellitus

Parameter	With type 2 DM (*n*=147) (%)	Without type 2 DM (*n*=140) (%)	*P*
Age (years)	56.0±8.44	42.81±12.12	<0.00001 (Student's *t*-test)
Gender	Male: 88 (59.86)	Male: 72 (51.42)	
	Female: 59 (40.14)	Female: 68 (48.57)	
BMI	26.4±3.5	23.9±4.5	<0.00001 (Student's *t*-test)
Postmenopausal females	35 (59.32)	20 (14.28)	
Addictions			
Smoking/tobacco	99 (67.35)	75 (53.57)	0.01696 (Chi-square test)
None	48 (32.65)	65 (46.43)	
Duration of addiction (years)	16.25±4.41	8.2±3.57	
Duration of type 2 DM (years)	7.59±5.42	-	
Treatment for type 2 DM			
On OHA	126 (85.71)		
On insulin	18 (12.24)	-	
On insulin + OHA	3 (2.04)		
FBS (mg/dL)	145.85±29.24	93.94±4.84	<0.00001 (Student's *t*-test)
PPBS (mg/dL)	251±44.51	108±5.12	<0.00001 (Student's *t*-test)
HbA1c (%)	8.4±1.0	4.9±0.2	<0.00001 (Student's *t*-test)
Duration of dyspepsia (months)	8.01±5.67	6.10±3.37	<0.00001 (Student's *t*-test)
Gross endoscopic findings			
Gastroesophageal junction from the incisor teeth (centimeters)	39±2	39±1.8	-
Esophagus			
Normal	97 (66)	91 (65)	Chi-square test
Lower 1/3rd erosive esophagitis	50 (34)	49 (35)	0.8605 (NS)
Stomach			
Normal	14 (9.52)	58 (41.43)	Chi-square test <0.0001 (S)
Pan gastritis	6 (4.08)	2 (1.43)	
Antral gastritis	129 (87.75)	80 (57.14)	
Duodenum			
Normal	77 (52.38)	88 (62.86)	Chi-square test
Duodenitis	70 (47.62)	52 (37.14)	0.0727 (NS)
HP detected by rapid urease test	82 (55.78)	33 (23.57)	Chi-square test <0.00001
Histopathology			
Esophagus			
Erosive esophagitis	42 (28.57)	30 (21.43)	Chi-square test
Barrett's esophagus	5 (3.40)	0 (0)	0.62942 (NS)
Normal	100 (68.03)	110 (78.57)	
Stomach			
Gastritis of fundus/body	90 (61.22)	33 (23.57)	<0.00001 (S)
Gastritis of antrum	113 (76.87)	89 (63.57)	0.013638 (S)
Normal	12 (8.16)	36 (25.71)	
Duodenitis	75 (51.02)	47 (33.57)	0.0028
HP detected	65 (44.21)	27 (19.29)	<0.00001 (S)

DM=Diabetes mellitus, BMI=Body mass index, OHA=Oral hypoglycemic agents, FBS=Fasting blood sugar, PPBS=Postprandial blood sugar, HbA1c=Glycosylated hemoglobin, HP=*Helicobacter pylori*, N/A=Not available, NS=Not significant, S=Significant

dyspeptic symptoms, gross GI findings showed that 99 (34.5%) had erosive esophagitis (50 patients with diabetes and 49 nondiabetics) and 217 (75.08%) had antral gastritis (135 patients with diabetes and 82 nondiabetics). HPE confirmed erosive esophagitis in 72 (25.08%) patients, Barrett's esophagitis in 5 (1.74%), and antral gastritis in 202 patients (70.38%). A total of 122 (42.50%) patients had duodenitis (70 patients with diabetes and 52 nondiabetics on gross examination and 72 patients with diabetes and 47 nondiabetics on HPE). Gross as well as histologically proven antral gastritis was associated with T2DM in a statistically significant manner when compared to nondiabetic controls. Our gross and HPE findings matched for esophagus and

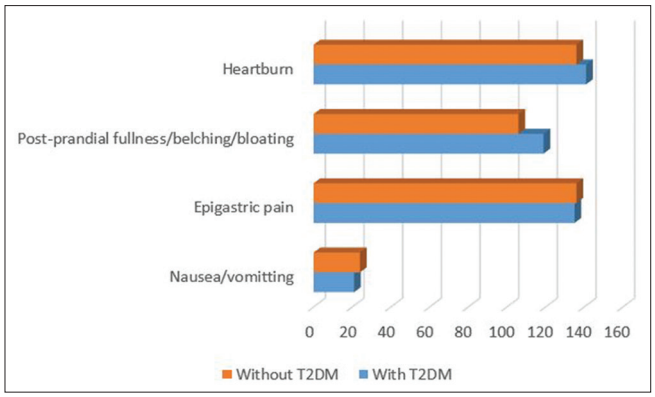

Figure 1: Symptoms of dyspepsia in the study population. There was no statistically significant difference in various dyspeptic symptoms among patients with diabetes and non-diabetics (Chi-square and Fisher's exact test applied $P > 0.05$ for all symptoms)

stomach for diabetics as well as nondiabetics, but there was a disparity in findings of duodenitis. There was no significant difference between patients with diabetes and nondiabetics in the gross finding of duodenitis, but HPE-proven duodenitis was associated with T2DM in a statistically significant manner when compared to nondiabetics.

A total of 115 (40.07%) patients tested positive for HP by RUT (82 were diabetics). Of these, 92 (32.05%) patients also tested positive for HP by HPE of biopsy samples (65 were patients with diabetes). The sensitivity of RUT was 100% (96.07%–100.00% at 95% confidence interval [CI]), specificity was 89.45% (84.59%–93.19% at 95% CI), positive predictive value was 80% (73.10%–85.48% at 95% CI), and negative predictive value was 100% with accuracy of 92.58% (89.08%–95.24% at 95% CI).

HP infection (detected by RUT as well as by histopathology) was associated with T2DM in a highly statistically significant manner as compared to nondiabetics ($P < 0.00001$).

Table 2 compares different clinical and endoscopic parameters between HP-positive and HP-negative T2DM patients. There was no statistically significant difference between any of the clinical parameters in HP-positive and HP-negative patients with diabetes including HbA1c levels and duration of T2DM.

Discussion

Dyspepsia is a common complaint in general as well as in diabetic population. Dyspepsia accounts for 8.3% of all physician referrals and incurs huge economic burden on the patients.[7] Functional dyspepsia (FD) which includes epigastric pain syndrome and postprandial distress syndrome (PDS) without evidence of structural disease on endoscopy (as per Rome IV criteria) and gastroesophageal reflux disease (GERD) account for majority of dyspeptic symptoms.[8] The definition of GERD became more restrictive in the Rome IV report which proposed that hypersensitive esophagus should be separated from GERD and should be classified within the realm of functional esophageal disorders along with, but separate from functional heartburn.[9] There is no gold standard for diagnosis of GERD and UGIE often shows no visible mucosal lesions.[10] A 24-h pH monitoring is required to objectively document GERD. The total percentage of time with pH <4.0 (acid exposure time [AET]) is calculated and when abnormal values are found GERD is confirmed.[9]

An estimated 422 million adults were living with diabetes in 2014 globally. Its prevalence has nearly doubled since 1980, increasing from 4.7% to 8.5% in the adult population of the world. The last decade saw fast rise in the prevalence of diabetes in low- and middle-income countries.[11] There were over 72 million cases of diabetes in India in 2017.[12] Etiology of dyspepsia in T2DM is multifactorial. Autonomic neuropathy, delayed gastric emptying, HP infection, poor glycemic control, etc., are few of the factors which are thought to cause dyspepsia in patients with diabetes.[13,14]

In our study, dyspepsia was more prevalent in older age patients with diabetes as compared to nondiabetics (56.0 ± 8.44 years vs. 42.81 ± 12.12 years; $P < 0.05$). Similar were the findings in few other studies where dyspepsia among patients with diabets was more common in the age group of 51–60 years.[15,16]

Male preponderance was observed among all dyspeptic patients in our study which was similar to other studies from India and Pakistan.[15,17] Postmenopausal females with long-standing T2DM had higher prevalence of dyspepsia than younger females in our study. A review article by Ahlawat *et al*. summarized the available prevalence data of dyspepsia in males and females and found strikingly inconsistent prevalence rates.[18] For example, Talebi-Taher *et al*., Ford *et al*., and Dawod and Emara in their studies found higher prevalence of dyspepsia in females than males.[16,19,20] In a Norwegian study of over 14,000 people, Johnsen *et al*. found a significantly higher rate of FD in men compared with women (22.6 vs. 18.1%; $P < 0.05$).[21] A review done to study the epidemiology of uninvestigated FD in Asians revealed that there is no gender predilection. However, cultural differences do exist in reporting of symptoms of dyspepsia.[22] A meta-analysis concluded that female gender, smoking, HP positivity, NSAID use, etc., results in a significantly higher prevalence of unexplained dyspepsia.[19]

Table 2: Comparison of laboratory parameters in dyspeptic diabetic patients according to their *Helicobacter pylori* infection status

Patients with T2DM (*n*=147)	HP		Statistical test
	Positive on histopathological examination (*n*=65)	Negative by histopathological examination (*n*=82)	
Age (years)	55.65±8.28	56.84±8.58	Student's *t*-test *P*=0.3955 (NS)
Gender (%)	Males: 34 (52.3) Females: 31 (47.7)	Males: 57 (69.5) Females: 25 (30.5)	N/A
BMI	26.1±3.4	25.7±3.9	Student's *t*-test *P*=0.7691 (NS)
FBS (mg/dl)	142±29.92	146±28.86	Student's *t*-test *P*=0.7282 (NS)
PPBS (mg/dl)	249±46.92	251.78±42.78	Student's *t*-test *P*=0.7351 (NS)
HbA1c (%)	8.25±0.91	8.42±1.07	Student's *t*-test *P*=0.3177 (NS)
Duration of T2DM (years)	8.4±5.9	7.0±4.9	Student's *t*-test *P*=0.1077 (NS)
Treatment taken			
OHA	56	70	N/A
Insulin	8	10	
Both	1	2	
Duration of dyspepsia (months)	8.67±5.20	7.49±6.00	Student's *t*-test *P*=0.2135 (NS)
Symptoms			Chi-square/Fisher's exact test
Heartburn	64	77	*P*=0.2282 (NS)
Regurgitation	57	62	*P*=0.0639 (NS)
Indigestion	60	75	*P*=1.0000 (NS)
Nausea/vomiting	08	13	*P*=0.5417 (NS)
Tobacco addiction	41	60	
Duration of addiction (years)	15.89±5.09	16.51±3.91	

DM=Diabetes mellitus, BMI=Body mass index, OHA=Oral hypoglycemic agents, FBS=Fasting blood sugar, PPBS=Postprandial blood sugar, HbA1c=Glycosylated hemoglobin, HP=*Helicobacter pylori*, N/A=Not available, NS=Not significant

In our study, 60.62% patients were tobacco users. Wildner–Christensen *et al*. did a survey of 5749 individuals for the risk factors of dyspepsia and they too found tobacco use to be a risk factor for it.[23] Among the tobacco users, 56.9% were patients with diabetes and had addiction since many years (16.25 ± 4.41 years).

Most of the dyspeptic T2DM patients had uncontrolled diabetes (mean FBS of 145.85 ± 29.24 mg/dl, PPBS of 251 ± 44.51 mg/dl and HbA1c of 8.4 ± 1.0) with majority being on oral antidiabetic drugs. A study by Tseng *et al*. too concluded that patients with diabetes with dyspeptic GI symptoms had uncontrolled mean fasting and postprandial blood sugar levels (131.6 + 34.4 mg/dl and 209.9 + 72.6 mg/dl, respectively) and high HbA1c (7.0% +1.3%).[24] A total of 67% dyspeptic diabetics had poorly controlled T2DM in another study by Khoshbaten *et al*.[25] Postprandial fullness, heartburn, and epigastric pain were the common dyspeptic symptoms in patients with diabetes as well as nondiabetics. The results matched with that of the study by Wafula *et al*.[26]

In this study, a total of 42 (28.57%) patients with diabetes had histologically proven erosive esophagitis. Thus, GERD may be responsible for their dyspeptic symptoms. The remaining 105 dyspeptic diabetes patients with normal esophageal histology were classified as having FD or endoscopy-negative reflux disease (ENRD). The definitive diagnosis of the cause of dyspepsia in these patients requires 24-h esophageal pH studies, but that too has significant limitations of being less sensitive, expensive, inconvenient, inaccessible, and uncomfortable.[27] FD and ENRD are the two conditions which are linked and are most likely the components in the spectrum of the same disease entity, with regard to both symptoms and pathophysiology. Proposed theories for their occurrence are abnormal acid exposure, visceral hypersensitivity, HP infection, lax GE junction, and delayed gastric emptying.[28] ENRD, like FD, by

definition, requires normal UGIE. ENRD predominantly presents with classic symptom of heartburn and FD often presents with EPS or PDS, but this difference is often blurred and patients frequently present with overlapping symptoms. As per the Montreal classification, ENRD is defined as the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy.[29] It is of three subtypes based on 24-h pH monitoring into (a) with abnormal acid exposure time but with normal endoscopy, (b) sensitive esophagus with acid hypersensitivity, and (c) Functional heartburn where there is no correlation between symptoms and acid exposure.[29] FD is defined as recurrent and/or persistent pain/discomfort in the upper abdomen, without evidence of organic disease that is likely to explain the symptoms.[30] In T2DM patients, we found changes of gastritis in 76.87% of the antral biopsies and duodenitis in 51.02% of duodenal biopsies. A study done in 2007 by Boehme *et al*. found that T2DM patients had highly active gastric inflammation including gastritis, erosions, and gastric ulcers with little or no dyspeptic symptoms.[31] The cause of these mucosal changes may be due to poor glycemic control and diabetic gastroparesis.[6,14] HP was found in 55.78% diabetics by RUT which was confirmed by histopathology in 44.21% patients with diabetes. Taking histopathological finding of HP as the gold standard for diagnosing HP infection, RUT was highly sensitive (100%) and specific test (79.27%) for HP detection with accuracy of 88.44%. In another study, sensitivity and specificity of different tests used for HP detection were as follows: culture, 98.4 and 100%; polymerase chain reaction, 96.7 and 100%; histological examination (antrum), 96 and 98.8%; histological examination (antrum + corpus), 98.4 and 98.8%; RUT, 90.2 and 100%; C-urea breath test, 100 and 100%; and serological examination, 98.4 and 88.4%.[32] Like many other studies done till date, we too conclude that RUT is a good initial test as it is rapid, cheap, and easily available as compared to other HP detection tests.[33-35]

We found that HP infection was more prevalent in T2DM than in nondiabetics ($P < 0.00001$). Several other studies too found that diabetes patients had higher prevalence of HP infection.[15,16,20] However, Demir *et al*. and Anastasios *et al*. did not support an association between HP infection and diabetes.[4,36] The prevalence of HP infection in patients with diabetes and nondiabetics was 37.3% and 35.2% ($P = 0.78$) in the study by Anastasios *et al*. and it was 61.7% and 58.5%, respectively, in the study by Demir *et al*.

We found that there was no statistically significant association between HP infection and HbA1c or duration of diabetes. Hsieh *et al*. and Bajaj *et al*. found an association between high HbA1c and HP infection which is in contrast to our findings ([8.2 ± 1.2% and 6.9 ± 0.8%, respectively, for patients with diabetes and nondiabetics [$t = 4.39$; $P = 0.0001$] and [5.78% vs. 5.69%, $P = 0.01$]).[37,38] The Third National Health and Nutrition Examination Survey done in 2004 on American men aged 40–74 years did not find consistent association of HP infection with diabetes prevalence or HbA1c.[39]

The causal relationship and the temporal association between HP infection and T2DM is difficult to ascertain. One hypothesis is that since HP infection is mostly acquired in childhood[40] and T2DM later in life, HP may directly or indirectly (through increased inflammatory mediators such as interleukin-6 and tumor necrosis factor-α) increase the HbA1c levels. Another hypothesis is that the association could be related to the reduced gastric motility observed in both HP infection and T2DM, and chemical changes occurring in the gastric mucosa following nonenzymatic glycosylation end products.[41]

A combination of genetic, environmental, and lifestyle factors play a role in the pathogenesis of T2DM with the end result being absolute or relative insulin deficiency and rise in blood sugar levels.[42] Identifying the treatable causes of diabetes will help develop strategies to delay/prevent its occurrence or slow its progression. Recent studies have suggested a possible role of inflammation in T2DM,[43] hence there is a renewed interest in the study of its association with HP infection which causes a persistent low-grade gastric mucosal inflammation and which is easily treatable.

Grading of esophagitis and gastritis in patients with diabetes was not done in the current study. HP eradication and treatment follow-up was not studied so whether the UGI endoscopic changes and histological lesions disappeared after HP treatment is not known.

Conclusion

To conclude, dyspepsia is common in T2DM patients. Majority of the patients with diabetes in the present study were male in 5th and 6th decade of life. Diabetes and nondiabetes patients had similar spectrum of dyspeptic symptoms without any gender difference. Heartburn and indigestion were the common symptoms. Among patients with diabetes, gross endoscopic and histologically proven gastritis of the antrum was common followed by duodenitis and esophagitis. HP infection was associated with type 2 diabetes in a statistically significant manner when detected by RUT as well as HPE examination. However, there was no

association between the HP infection and HbA1c as well as duration of T2DM. RUT proved to be a highly sensitive and specific test for HP detection in patients with diabetes. Further studies after eradication of HP can be done to corroborate the temporal association between T2D and HP infection.

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Conflicts of interest

There are no conflicts of interest.

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