A Review of *Helicobacter pylori* Infection in Patients with Diabetes Mellitus

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**Authors’ contributions**

This work was carried out in collaboration between both authors. Author MD designed the study. Authors MD and HSG wrote the first draft of the manuscript. Author HSG managed the literature searches. Both authors read and approved the final manuscript.

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**ABSTRACT**

Gastrointestinal symptoms, such as abdominal discomfort, chronic abdominal pain, dysphagia, heartburn, nausea, vomiting, diarrhea and constipation are more common in patients with Diabetes Mellitus (DM) than in the general population. Studies published in the past two decades have suggested a link between *Helicobacter pylori* (*H. pylori*) infection and DM in many aspects. These include; higher *H. pylori* infection prevalence however the data on the prevalence of *H. pylori* infection in patients with DM are scanty and contradictory, the eradication rate of *H. pylori* seems to be lower in DM patients than in non-diabetic controls, control of dyspeptic symptoms with eradication as well as association with late complications in DM patients. The aim of the present review is to gain a better understanding of *H. pylori* infection in DM patients.

**Keywords:** *Helicobacter pylori*; diabetes mellitus; eradication; late complications.

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1. INTRODUCTION

Gastrointestinal symptoms, such as abdominal discomfort, chronic abdominal pain, dysphagia, heartburn, nausea, vomiting, diarrhea and constipation are more common in patients with diabetes mellitus (DM) than in the general population [1-3]. The pathogenesis is unclear, but multiple factors like hyperglycemia, the motility disturbances resulting from diabetic neuropathy (including autonomic neuropathy and visceral sensory dysfunction), psychological factors and Helicobacter pylori (H. pylori) infection are probably responsible for these symptoms [4-8]. These symptoms can significantly reduce quality of life in patients with DM [9].

H. pylori are a gram-negative, spiral-shaped, microaerophilic bacterium. Approximately half of the world’s population is infected with H. pylori which is a major cause of chronic gastritis, peptic ulcer, gastric adenocarcinoma, and gastric lymphoma and is in relation with functional dyspepsia [10,11]. In the latest Maastricht IV consensus report H. pylori eradication therapy is recommended for patients with gastric and duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, patients who have undergone endoscopic resection of early gastric cancer. The benefit from eradication is less clear in functional dyspepsia patients [12].

Studies published in the past two decades have suggested a link between H. pylori infection and DM in many aspects. These include higher H. pylori infection prevalence, lower eradication rate, difficulty in the control of dyspeptic symptoms, association with late complications as well as increased gastric cancer risk in DM patients. Data have been accumulated recently about the relationship between gastric cancer and DM in the literature [13]. A recently published systematic review of randomised controlled trials reported a 35% reduction in the relative risk of developing gastric cancer with H. pylori eradication therapy, compared with placebo [14]. Therefore, both the identification and the treatment of H. pylori infection in DM patients are very important in this respect. The aim of the present review is to gain a better understanding of potential interactions of H. pylori infection and DM.

2. PREVALENCE OF H. pylori INFECTION IN DM

The data on the prevalence of H pylori infection in patients with DM are scanty and contradictory. H. pylori infection in patients with DM ranged between 30% and 80% in the previous reports [15-17]. Some previous reports, have found a high prevalence of H. pylori infection among diabetics as compared to the general population [18,19]. Some other studies did not detect a relationship between H. pylori infection prevalence and DM [20-22]. As shown in a previous study published by our group, the prevalence of H. pylori infection was not significantly different in patients with type 2 DM (T2DM) compared to non-diabetic controls (61.7% versus 58.5%, P>0.05) [23]. It has been suggested that the gold standard for the diagnosis of H. pylori infection in patients with T2DM should be regarded as 2 positive out of 5 different tests [24]. In our study, H. pylori status was evaluated by both rapid urease test and by histology with Giemsa stain. However, in our study a relatively low number of patients in a single center were studied and this was the major limitation of our study. These contradictory results may be related to the epidemiological distribution of infection (age and socioeconomic status), non-homogenous patient groups (diabetic status), and geographic region of study population, differences in sample size or the different methods used in the studies. A recent meta-analysis involving 14080 patients from 41 studies suggests that the prevalence of H. pylori infection in patients with with DM was higher than in control group (49.25% vs 38.92%, OR: 1.33, 95% CI: 1.08-1.64, p = 0.008). Subgroup analyses of different types of DM showed that 15 studies of T2DM revealed a higher rate of infection with H. pylori (p < 0.00001) but 15 studies with T1DM revealed no difference in rate of H. pylori infection rate between the T1DM patients and control group [25]. In conclusion, there is a trend toward a higher prevalence of H. pylori in DM than in non-DM controls and this trend is more significant in areas with higher prevalence of H. pylori infection.

3. PATHOGENIC MECHANISMS FOR INCREASED SUSCEPTIBILITY to H. pylori in DM PATIENTS

A complicated balance between predisposing and preventing factors determine the prevalence of H. pylori infection in DM. There are a many factors implicating the higher prevalence of
**H. pylori** infection in patients with DM. Delayed gastric emptying and reduction of acid secretion in patients with diabetic gastroparesis may predispose to bacterial overgrowth in the upper gastrointestinal tract and consequently this may be considered as a risk factor for **H. pylori** infection [26]. Impairment of cellular and humoral immunity by DM may enhance sensitivity to **H. pylori** infection [27]. Altered acid secretion may promote bacterial colonization and infection rate in the gut [28]. A growing body of evidence suggests that **H. pylori** itself might elicit a series of inflammatory changes in stomach and potentially affect the secretion of gastric related hormones, inflammatory cytokines. These chronic, low grade cytokine-mediated inflammatory state affects many tissues including adipocytes and inflammation of adipose tissue is an important factor in the pathogenesis of insulin resistance (IR) [29,30]. Furthermore, it has been suggested that altered glucose metabolism may lead to chemical changes in the gastric mucosa and these changes may provide a suitable media for **H. pylori** colonization [31]. On the other hand it is also very well known that patients with DM are more predisposed to infections and resultant increased antibiotic use may inhibit the colonization of **H. pylori** [32].

### 4. **H. pylori** ERADICATION IN DM

Ideal **H. pylori** treatment must be safe, inexpensive, easy and tolerable, with an eradication rate higher than 80% and it must have a low rate of antibiotic resistance [33]. The eradication rate of **H. pylori** seems to be lower in DM patients than in non-diabetic controls. The **H. pylori** eradication rate has been reported as being lower in patients with type 1 DM (T1DM) compared with non-diabetics (65% versus 92%) [34]. In a study performed on patients with T1DM, the eradication rate with different triple antibiotic regimens was 62%, and this rate increased to 88% with quadruple eradication regimens [35]. In a controlled prospective study, using standard 10-day regimens (clarithromycin 500 mg twice a day, amoxicillin 1 g twice a day, omeprazole 20 mg twice a day), the eradication rate was lower in patients with T2DM than it was in non-diabetics (50% versus 85%, respectively) [36]. Recently, Demir et al. [37] reported that the eradication rate (clarithromycin 500 mg twice daily, amoxicillin 1 gram twice daily and pantoprazole 40 mg twice daily, for 14 days) was significantly lower in DM than non-diabetic patients (%42.9 versus %79.3). We recently showed that the eradication rate of **H. pylori** with pantoprazole, clarithromycin, and amoxicillin (PCA) or ranitidine bismuth citrate, clarithromycin, and amoxicillin (RCA) for 14 days was significantly lower in patients with T2DM than in non-diabetics [38]. In this study, the **H. pylori** eradication rate with PCA regimen in patients with DM with both intention-to-treat (ITT) and per-protocol (PP) analysis was 48.9% and in non-DM patients was 75.9% with ITT and 77.2% with PP analysis. **H. pylori** eradication rates with RCA regimen in patients with DM were 45.9% with ITT and 45.8% with PP analysis, and in non-DM patients were 75.9% with ITT and 78.6% with PP analysis. Recent data showed that sequential therapy appears to be superior to standard triple therapy for eradication of **H. pylori** infection [39]. But we reported that the eradication rate of **H. pylori** with 14-day sequential therapy (pantoprazole 40 mg twice daily and amoxicillin 1000 mg twice daily for seven days, then pantoprazole 40 mg twice daily, metronidazole 500 mg twice daily and tetracycline 500 mg four daily for the remaining seven days) for the first-line treatment of **H. pylori** in patients with type 2 DM (T2DM) were disappointing (57.9% with ITT analysis, 59.5% with PP analysis) [40]. As shown in a previous study published by our group, bismuth-based quadruple eradication regimen (pantoprazole 40 mg b.i.d, bismuth citrate 400 mg b.i.d, tetracycline 500 mg q.i.d and metronidazole 500 mg b.i.d, for 14 days) as first-line therapy in patients with T2DM is much more effective than triple therapy and it is tolerable eradication regimen (85% versus 51%) [41]. Finally a recent meta-analysis which showed the higher risk of **H. pylori** eradication failure in individuals with DM compared with non-diabetic individuals suggests the necessity of prolonging treatment or developing a new regimen for **H. pylori** eradication in patients with DM [42].

### 5. THE POSSIBLE MECHANISMS UNDERLYING LOW ERADICATION RATES

Several mechanisms may play a role in the low eradication rate of **H. pylori** infection in DM patients. This may be explained by microcirculatory complications of DM in the gastric mucosa, impaired antibiotic absorption because of diabetic gastroparesis and reduced antibiotic binding to plasma proteins because of glycosylation [43,44]. Due to various impairments in the immune system of DM patients, the susceptibility to bacterial infection is increased, which may lead to frequent use of antibiotics and
to development of drug resistance [45]. Moreover, frequent antibiotic use owing to other infections might predispose patients to secondary H. pylori resistance [46]. Recent data suggest that clarithromycin resistance is a growing problem affecting the eradication rate of the H. pylori. The rate of resistance to clarithromycin has increased gradually in Turkey. Recently, a study on Turkish dyspeptic population revealed clarithromycin resistance of 40.2% by using PCR method [47]. We reported that clarithromycin resistance was significantly higher in T2DM patients than in non-diabetics (65% versus %35) [37]. These data suggest that clarithromycin resistance plays an important role in the decreased eradication rate in DM patients and macrolide antibiotics would not be a rational choice for eradication of H. pylori in DM patients. There are infrequent reports of H. pylori strains resistant to tetracycline [48,49]. However, no resistance to bismuth has been reported yet [50]. The issue of resistance primarily concerns the nitroimidazoles (metronidazole or tinidazole) and macrolides (clarithromycin). The rate of H. pylori resistance to metronidazole is approximately 25%. In vitro resistance to metronidazole is not always predictive of in vivo results, and increasing the dosage of metronidazole improves the results of therapy when treating metronidazole-resistant H. pylori strains [51,52]. These observations could explain the higher eradication rates with a bismuth-based quadruple eradication regimen in DM patients.

6. H. pylori ERADICATION AND DYSPEPTIC SYMPTOMS IN DM

Both DM and H. pylori are the important causes of dyspepsia. Factors most commonly implicated in the mechanisms of dyspepsia are hyperglycemia, the motility disturbances resulting from diabetic neuropathy (including autonomic neuropathy and visceral sensory dysfunction), psychological factors and H. pylori infection. Some authors have reported that large number of gastrointestinal lesions was found during endoscopy in H. pylori infected DM patients. In their study, H. pylori infection and dyspeptic symptoms were investigated in 71 consecutive patients with DM. Helicobacter pylori was present in 27 (77%) of 35 patients with DM with dyspeptic symptoms and in 22 (61%) of 36 patients without dyspeptic symptoms. Endoscopy revealed peptic ulcers in 13 of 23 patients [53]. Gasbarrini et al. [35] showed that H. pylori eradication significantly reduced the intensity of all the gastrointestinal symptoms except for the nausea in T1DM patients. In addition we reported in two studies that dyspeptic symptoms decreased significantly in patients with T2DM with successful eradication as compared with patients with eradication failure [38-40]. Successful eradication in patients with T2DM may have benefit on dyspeptic symptoms but there are only limited data from the literature available.

7. H. pylori ERADICATION AND GLYCEMIC CONTROL

There are conflicting and limited data regarding the effect of H. pylori eradication on the glycemic control in DM. It is well known that chronic infections such as tuberculosis may lead to difficulties in glycemic control [54]. A meta-analysis included 14 studies demonstrated that H. pylori was associated with poor glycemic control in patients with DM [55]. Zojaji et al. [56] reported that successful H. pylori eradication can improve the mean Hb1c and metabolic abnormalities in patients with T2DM. Dogan et al. [57] and Gen et al. [58] showed that successful H. pylori eradication significantly decreased fasting insulin and HOMAIR levels in non-diabetic patients. Nevertheless Candelli et al. [59] reported that successful H. pylori eradication did not improve metabolic control in a short-term follow-up in patients with T1DM. Similarly a recent study suggested that in patients with T2DM, successful H. pylori eradication has no role in the control of glycemia, the mean decrease in HbA1c and fasting plasma glucose levels in eradicated cases was similar to non-eradicated subjects three and six months after treatment [42]. Large, prospective studies are needed to evaluate the long-term benefit of H. pylori eradication on the glycemic control.

8. H. pylori ERADICATION AND LATE COMPLICATIONS OF DM

A growing body of evidence has linked late complications of DM (retinopathy, diabetic neuropathy and nephropathy) to H. pylori infection [17,60]. Malecki et al. [61] reported that H. pylori infection prevalence in DM patients with neuropathy was not significantly lower than in DM patients without neuropathy (29% versus 35%). In a report by Perisco et al. [62] no change in H. pylori infection prevalence was detected among neuropathic and non-neuropathic subjects. However in this study, a relatively low number of subjects without a control group were studied. In another study, H. pylori infection was detected in 94% of patients with autonomic
neuropathy but in only 34% of those without autonomic neuropathy [63]. Gulcelik et al. [17] also reported similar \textit{H. pylori} prevalence rates of 90.6% in DM patients with neuropathy versus 44% in DM patients without neuropathy. Delayed gastric emptying, as a result of diabetic autonomous neuropathy and bacterial overgrowth has been suggested as underlying reasons for high \textit{H. pylori} prevalence in DM patients. On the other hand, Kao \textit{et al} reported a similar \textit{H. pylori} prevalence among those with both delayed and normal gastric emptying times (62% versus 56%) [64]. We reported that peripheral neuropathy was more common among DM patients with \textit{H. pylori} regardless of glycemic control and duration of the DM [23]). Current literature suggests an association between \textit{H. pylori} and the autonomous neuropathy but the physio-pathological mechanism to explain this relationship is not clear yet. \textit{H. pylori} infection might be associated with deficiency of vitamin B12 (cobalamin) [65]. Not only atrophic gastritis secondary to \textit{H. pylori} infection but also the malabsorption of the cobalamin has been suggested as causative factor. The effect of \textit{H. pylori} eradication on the late complications of DM is not clear. \textit{H. pylori} infection has also been implicated in systemic inflammation, vascular endothelial damage and glomerular damage and resultant urinary albumin excretion in DM patients [66]. Recently, Yanik et al. [67] demonstrated that successful \textit{H. pylori} eradication has favorable effect on reducing microalbuminuria in DM patients. It has been suggested that DM together with \textit{H. pylori} decrease the prognosis of gastric cancer due to hypoalbuminemia [68]. However, considering the relatively very small population in these studies further studies with large populations are needed to verify this association.

9. CONCLUSION

In conclusion, dyspeptic symptoms are common among DM patients than in normal population and these symptoms may negatively affect the quality of life. The eradication of \textit{H. pylori} infection is more difficult among patients with DM than without DM. A bismuth-based quadruple regimen as a first-line \textit{H. pylori} treatment seems to be highly effective and reasonable in patients with DM. Although \textit{H. pylori} seems to have a role in the glycemic control in DM, the effect of \textit{H. pylori} eradication on the late complications of DM is not clear and eradication of \textit{H. pylori} does not benefit all DM patients. Reviewing the available data does not provide a clear answer to the debate about whether we need to extend the indications for \textit{H. pylori} eradications for DM patients. The scientific communities have not yet agreed about the \textit{H. pylori} in individuals with diabetes. This field requires studies with large populations needed to verify this association.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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