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Is Diabetes Mellitus a Predisposing Factor for *Helicobacter pylori* Infections?

Om Saswat Sahoo[1] · Rhiti Mitra[1] · Arghyadeep Bhattacharjee[1,2] · Samarjit Kar[3] · Oindrilla Mukherjee[1]

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Abstract

Purpose of Review This review aims to analyse the consistency of reports suggesting the role of Diabetes Mellitus in the pathogenesis of *Helicobacter pylori* (*H. pylori*).

Recent Findings There have been numerous controversies citing the prevalence of *H. pylori* infections in patients suffering from type 2 diabetes mellitus (T2DM). This review investigates the possible crosstalk between *H. pylori* infections and T2DM and also designs a meta-analysis to quantify the association. Subgroup analyses have also been conducted to deduce factors like geography and testing techniques, in playing a role in stratification analysis.

Summary Based on a scientific literature survey and meta-analysis of databases from 1996 to 2022, a trend towards more frequent *H. pylori* infections in patients with diabetes mellitus was observed. The highly diversified nature of *H. pylori* infections across age, gender, and geographical regions requires large interventional studies to evaluate its long-term association with diabetes mellitus. Further possible linkage of the prevalence of diabetes mellitus concomitant with that of *H. pylori* infected patients has also been delineated in the review.

Keywords *Helicobacter pylori* · Diabetes mellitus · Meta-analysis

Abbreviations

BMI	Body mass index
CagA	Cytotoxin-associated gene A
CI	Confidence interval
DM	Diabetes mellitus
GI	Gastrointestinal
H. pylori	*Helicobacter pylori*
HbA1c	Glycated haemoglobin
OR	Odd ratio
T2DM	Type 2 diabetes mellitus
VacA	Vacuolating toxin A
WAT	White adipose tissue

Introduction

Diabetes, being one of the universal epidemic problems, has become the leading cause of a global burden with excessive impact on societies. Affecting nearly half a billion people worldwide, it is projected to increase by another 50% by the next decade [1]. However, emerging evidence states that morbidity and mortality due to diabetes have been associated with the gastrointestinal (GI) microbiota, thus shaping the balance between homeostasis and morbidity [2]. The involvement of the diabetic microbiota with the pathophysiology of gastrointestinal infections has been well defined and has been tried to get verified within the course of time. In fact, patients referred with diabetes often report significant GI symptoms, with the common ones being acid reflux, abdominal pain, nausea, dysphagia, diarrhoea etc. Further pieces of evidence state that diabetes is accompanied by *Helicobacter pylori* (*H. pylori*) infections, wherein chronic and insulin-affiliated inflammations escalate several gut-related hormones and inflammatory cytokines.

Apart from being the primary causative agent for gastric cancer, *H. pylori* plays a significant role in influencing GI microbiota composition, inducing inflammatory responses and stimulating a plethora of signalling cascades. Addressed

✉ Oindrilla Mukherjee
oindrilla.mukherjee@bt.nitdgp.ac.in

[1] Department of Biotechnology, National Institute of Technology Durgapur, Durgapur, West Bengal, India 713209

[2] Department of Microbiology, Kingston College of Science, Beruanpukuria, Barasat, West Bengal, India 700129

[3] Department of Mathematics, National Institute of Technology Durgapur, Durgapur, West Bengal, India 713209

with several virulence factors, *H. pylori* has been associated with higher risks of peptic ulcer diseases, gastric disorders and other extra-gastric diseases like cardiovascular, pulmonary, neurological and other endocrine disorders, thus establishing its confounding yet significant impact clinically [3]. Since 1989, the incidence of *H. pylori* in patients suffering from type II diabetes mellitus (T2DM) has also been established as a compounding factor in the colonization of the bacteria, leading to further altered glucose metabolism, impairment of cellular and humoral immunity and enhanced sensitivity towards pathogen colonization and infection [4]. In fact, several shreds of epidemiological evidence have been retrieved that *H. pylori* infection has been prevalent amidst diabetic patients, thus establishing a unique relationship between the bacteria and T2DM. This review aims to present the various bidirectional crosstalks concerning T2DM and *H. pylori* infection.

Clinical Relevance of *H. pylori* and Diabetes Mellitus

H. pylori is a Gram-negative microaerophilic bacterium that colonizes the intestinal cells of the gastric mucosa. Infecting more than 50% of the total world population, its prevalence has been ranging over the varied regions of the world. However, the occurrence of *H. pylori* is more prevalent in developing countries, in comparison to developed countries [5–7]. *H. pylori* infections are regarded as one of the primary etiological factors for the disruption of the Correa pathway and stimulation of GI disorders, like gastritis, gastric ulcer, intestinal metaplasia/dysplasia, etc. [8]. Though most of the cases of *H. pylori* infections are asymptomatic and are therefore passed over, there has been a strong linkage between *H. pylori* gastric infections and GI or MALT lymphoma and gastric cancers. However, the majority of the infected subjects just develop mild antrum gastritis allied with a variation of gastric homeostasis, characterized by hypergastrinemia and normal acid secretions [9]. Only a small proportion (10–15%) of infected individuals suffer from prolonged antrum gastritis, characterized by hypergastrinemia with increased acid secretions, thereby leading to ulcerations in the duodenum [10], and further lower strata of people develop multifocal atrophic gastritis with possible development of gastric cancers.

In regard to DM, T2DM has been turning to become endemic. Characterized by insufficient synthesis of insulin, secondary to insulin resistance, the incidence of T2DM can be coupled with obesity, lifestyle changes and aberrations of metabolic factors [11]. However, the multiple micro/macrovascular complications of DM account for most of the morbidity and mortality associated with the disease. Poor glycaemic control and prolonged duration of the illness further decide the variability of the complication. The microvascular complications, namely diabetic neuropathy, nephropathy, retinopathy and macrovascular complications like coronary heart diseases, peripheral vascular diseases, diabetic foot ulcers, are to be named among the many [12].

Shreds of evidence also state that DM, especially T2DM, many a time gets complemented by an *H. pylori* infection, which further complicates the existing T2DM. Though there has been no established confirmation for this relationship, there are some considerations which have been made for the last 3 decades. Diabetes being an illness affiliated with insulin resistance and chronic inflammation, impairs the cellular and humoral immunity, thereby making the subject much more susceptible to further infections like *H. pylori*. Secondly, the abridged secretion of gastric acids further facilitates bacterial colonization and infection [13], ultimately making diabetic patients more prone to such infections. In addition, diabetic patients also become more prone to infections owing to their routine check-ups at hospitals. However, the contention about the relationship between *H. pylori* infections and diabetes, as per some studies, remains at par with several prospective cohorts and meta-analysis, proving either of the case studies.

Epidemiological Surveys Supporting the Prevalence of *H. pylori* Infections in DM Patients

Even though there is no solid evidence which states that *H. pylori* infections are associated to patients suffering from DM, the possibility for this casual relationship which has been outreached by various cohorts and meta-analysis deserves a discussion. The relationship can also be dragged and correlated on the basis of dyspeptic symptoms [14], autonomic neuropathy [14, 15], gender [17], age [17], BMI [17], blood pressure [17], glycated haemoglobin (HbA1c) levels [16] etc. In particular, the prevalence of *H. pylori* infections was noted higher in female, obese, middle-aged patients with persistent DM [18]. Though many scientists referred this to be relative to gastric motility and peristaltic activity, several other factors were also reasoned out and put forward, which have been reviewed in the subsequent sections.

In the early twenty-first century, Marrollo et al. conducted a clinical case study with almost 200 patients to evaluate the prevalence of *H. pylori* in patients with DM. Endoscopic and histological analysis showed a prevalence rate of 65%, suggesting that *H. pylori* infections and lesions may be attributed to autonomic neuropathy, which is indirectly associated with DM [19]. Another study in 2002 confirmed a high incidence of gastroparesis and upper GI symptoms in patients suffering from DM, suggesting their association with *H. pylori* infections [20]. Gulcelik et al. also established the same, with an occurrence rate

of 75.6%; however, they ruled out the relation of *H. pylori* with other diabetic complications like nephropathy and retinopathy. Moreover, they suggested that eradication of *H. pylori* is essential to lower the risk of cardiovascular autonomic neuropathy in patients with DM [14]. In regard to the virulent strains of *H. pylori*, CagA was found to be correlated with poor glycaemic control and the development of microalbuminuria in T2DM patients [21]. A similar result was also observed by Abdollahi et al. with VacA, and they conferred that the simultaneous presence of both CagA and VacA increases the potential toxicity of microalbuminuria in T2DM patients [22].

A hospital-based case study conducted a stool antigen test on 148 subjects and suggested that diabetic patients are more prone to *H. pylori* infections in comparison to non-diabetic patients [23]. Two systematic meta-analyses of the association of T2DM with *H. pylori* infections were undertaken using electronic databases and journal references. A total of 41 and 37 case–control studies were observed, and the pooled data with a marked heterogeneity attributed that the risk of *H. pylori* infections was greatly high after the diagnosis of DM and suggested that sensitivity and specificity highly depend upon the geography of the area [24, 25]. Wang et al. also put forward a relationship of *H. pylori* infections with diabetic nephropathy and suggested that *H. pylori* infections, albeit associated with DM patients, but also might elevate the complications behind DM [25]. Several studies in China were conducted in virtue of the occurrence of *H. pylori* infections in DM patients. In summary, not just with T2DM, but *H. pylori* infection was also associated with high blood pressure, cholesterol disturbances and aberrant HbA1C expressions, which increase the chances of complications of DM [26, 27]. A Chinese study could also find the relationship between *H. pylori* infection with the occurrence of proteinuria in T2DM patients, and *H. pylori* eradication would help protect the kidney function in patients with T2DM [28]. Other prospective cohorts and meta-analysis studies also supported the fact that *H. pylori* infections were more associative towards DM patients, in comparison to patients without DM [4, 17, 31••, 32]. Indeed, several case studies also referred that eradication of *H. pylori* could improve glycaemic control in patients with T2DM, which indirectly establishes the relationship between *H. pylori* and T2DM [3, 33, 34]. A meta-analysis has been conducted to establish the understanding of whether people with DM are more prone to *H. pylori* infections, than those without.

Meta-Analysis of Studies Associating *H. pylori* Infections in DM Patients Compared to That with a Control Group

A literature survey was done in the scientific literature, using keywords like *H. pylori* and diabetes mellitus. Manual search was done to broaden the scope of the findings, and data was extracted on the basis of *H. pylori* positive patients in the diabetic and control group. A total of 20 studies, including several case studies and case controls, published between 1996 and 2022, were selected for the meta-analysis, which involved 35,224 individuals, with an infection rate of 50.58% (17,817/35,224). The cumulative diabetes group consisted of 8415 patients, out of whom 4518 patients were *H. pylori* positive (53.69%) and that in the sample size of the control group, 13,299 patients were *H. pylori* positive out of 26,809 patients (49.6%). Statistical analysis was performed in virtue of odd ratios (OR) with 95% confidence interval (CI). Two techniques, namely mucosal tissue biopsy and ELISA based serum analysis, were utilized to check the presence of *H. pylori* in all the tests of the sample. Stool antigen tests and urine analyses were disregarded in the sample, as they showed contentious results.

Results of the meta-analysis showed the prevalence of *H. pylori* infections in DM patients, when compared to that with the control group (53.69% vs 49.6%, OR = 1.178, 95% CI: 1.121–1.237, $p = 0.08$). Subgroup analyses further showed that mucosal tissue biopsy (61.37% vs 52.5%, OR = 1.437, 95% CI: 1.213–1.7, $p = 0.08$) showed more positive rate than ELISA-based serum analysis (52.8% vs 49.4%, OR = 1.14, 95% CI: 1.086–1.2, $p = 0.02$), suggesting that stratification analysis is not just biased with geography, age, BMI etc., but also with the technique incorporated to testify *H. pylori* positivity (Fig. 1; Table 1). Despite the technique used, potential increase in positivity was denoted in *H. pylori* infections in the diabetic group, when compared to that in the control group.

Mechanism of *H. pylori* Pathogenesis in T2DM Patients

There are numerous potential plausible explanations for the observed association of T2DM with the development of an *H. pylori* infection which have been explained in the following section of the review.

Role of Chronic Inflammation

Several shreds of evidence state that there remains an increased susceptibility of *H. pylori* infections in DM patients. As mentioned earlier, diabetes-induced insulin resistance and chronic inflammation impair the cellular and humoral immunity of the subject, thereby enhancing the individual's sensitivity to infection [46]. Chronic inflammation in T2DM occurs in response to hypoxia, which further triggers the inflammatory processes in the white adipose tissue (WAT) of the subject. Abdominal WAT, being

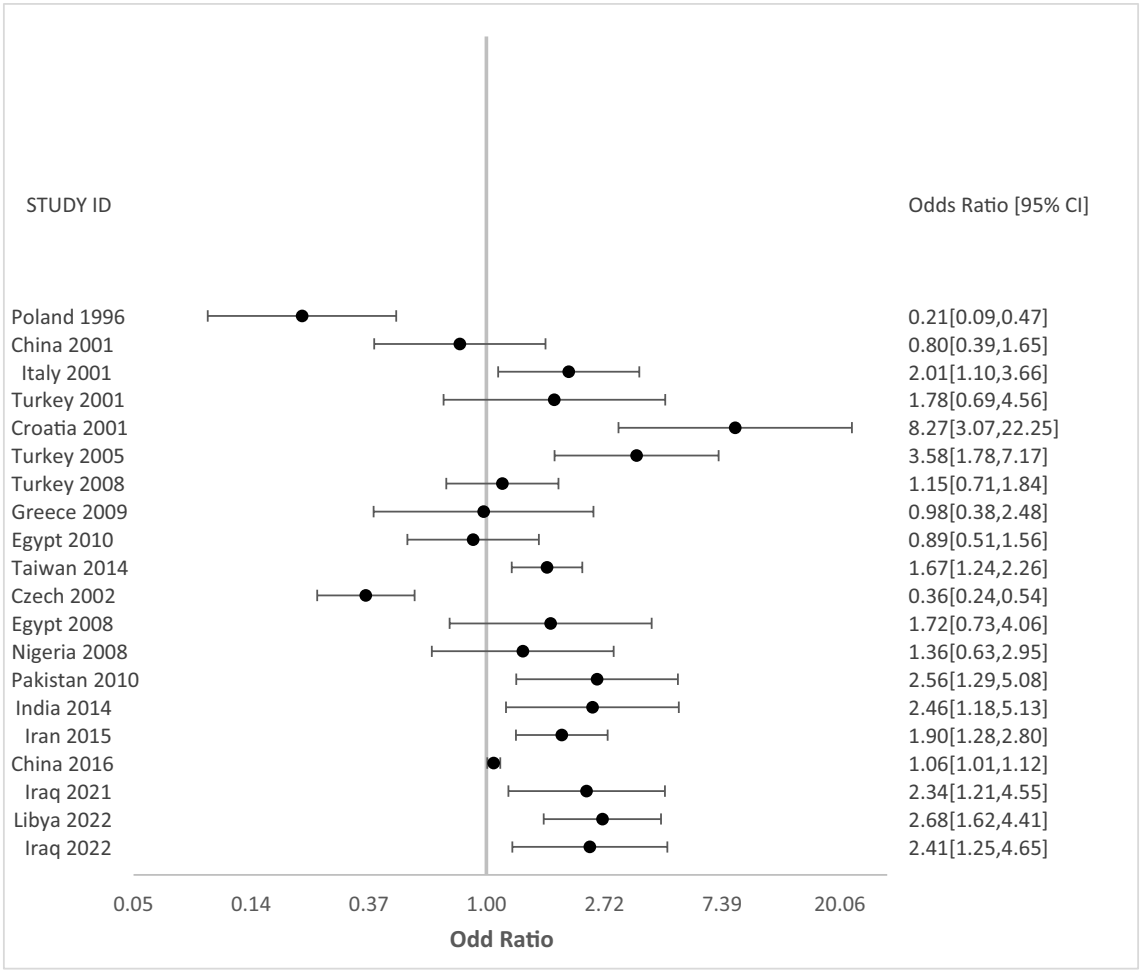

Fig. 1 Meta-analysis studies illustrating the prevalence of *H. pylori* infections in type 2 diabetes patients vs non-diabetes patients

the pioneer site for the production of cytokines and other bioactive substances like TNF-α, IL-1β, IL-6, adiponectin, resistin, leptin, monocyte chemoattractants, angiotensinogen, plasminogen activator inhibitor-1, retinol-binding protein-4, serum amyloid protein, vistafin etc. [46], characterizes the inflammation. Many of the proinflammatory stimuli in addition to the existing adiposity due to DM activates pathways like JNK, NF-κB and IKKβ, which further promotes oxidative stress and serine phosphorylation of varied receptor-substrate complexes [46]. Saturated fats, under cellular stress, promote the synthesis of ceramides, which accumulate in tissues and activate inflammatory pathways and other PKC isoforms [47]. Concordantly, insulin-resistant patients, in virtue of the activation of the various metabolic pathways like auto-oxidation of glucose, lipid peroxidation, polyol pathway etc., show overproduction of ROS, which contribute to damaging the DNA, further underwriting towards mutagenesis and carcinogenesis [48]. Several case–control studies and prospective cohorts have also shown that hyperglycaemia, a known symptom of T2DM, is associated with free radical formations, which leads to development of AGEs, which escalates inflammation [49]. Genes like PPAR-γ and KLF14, which are one of the forge regulators in adipose tissue biology and immune cell polarization, show aberrant expressions, thereby dysregulating PPAR-γ affiliated immunity. This increased rush of inflammatory cytokines, ROS, other mediators of these inflammatory pathways, like COX-2 and NF-κB, causes impairment in the absorption of nutrients and other medicinal drugs, facilitating the induction of infections.

Epidemiological studies state that this chronic inflammation of the gastric epithelium invites bacterial colonization by the infiltration of gastric submucosal monocytes and neutrophils, which further lead to damage in the gastric mucosa, epithelial remodelling and reduced gastric acid secretion inside the stomach. In fact, prevailing DM patients are also associated with impaired gastric secretions, gastrointestinal motor dysfunction and increased gastric mucosal atrophy [50, 51]. This impaired mucosal immunity [52] and the activation of the varied inflammatory pathways, in addition to

Table 1 Survey of *H. pylori* in type 2 diabetes patients and non-diabetes patients

Sl. No	Year	Country	Specimen	Study design	HP (+) in DM	HP (+) in controls	Ref
1	1996	Poland	Tissue	Case–control	12/39	68/100	[33]
2	2001	China	Tissue	Case–control	32/63	31/55	[34]
3	2001	Italy	Tissue	Case–control	48/74	56/117	[19]
4	2001	Turkey	Tissue	Case–control	59/67	58/72	[35]
5	2001	Croatia	Tissue	Case–control	31/46	8/40	[24]
7	2005	Turkey	Tissue	Cross-sectional study	59/78	33/71	[14]
8	2008	Turkey	Tissue	Case–control	87/141	83/142	[36]
11	2009	Greece	Tissue	Case–control	20/49	12/29	[39]
13	2010	Egypt	Tissue	Case–control	53/98	58/102	[21]
14	2014	Taiwan	Tissue	Cross-sectional study	147/238	358/729	[40]
6	2002	Czech	Serum	Case–control	53/195	110/216	[24]
9	2008	Egypt	Serum	Case–control	68/80	46/60	[37]
10	2008	Nigeria	Serum	Case–control	21/60	17/60	[38]
12	2010	Pakistan	Serum	Case–control	54/74	38/74	[23]
15	2014	India	Serum	Cross-sectional study	62/80	35/60	[41]
16	2015	Iran	Serum	Cross-sectional study	139/211	110/218	[42]
17	2016	China	Serum	Cross-sectional study	3254/6395	12,041/24415	[26]
18	2021	Iraq	Serum	Case–control	110/150	27/50	[43]
19	2022	Libya	Serum	Cross-sectional study	144/193	56/107	[44]
20	2022	Iraq	Serum	Case study	65/84	54/92	[45]

the damage in the gastric epithelium, provide an ambient environment for *H. pylori* to colonize the gastric epithelium, thus enhancing the susceptibility of infection.

Role of Hormones

Apart from the secretion of inflammatory cytokines, DM is majorly characterized by the dysregulation of several pancreatic and gut hormones. With reduced insulin secretion being one of the most chief pathophysiological defects in T2DM, several other gut-affiliated hormones also show elevated or suppressed release. The regulation of ghrelin and leptin that play a crucial role in energy homeostasis and are linearly responsible for obesity and insulin sensitivity is seen to be disturbed in DM [53–55]. Hypersecretion of somatostatin, a tetradecapeptide that regulates insulin and glucagon secretion, has also been documented in DM [56]. Moreover, hyperglycaemia, insulin resistance and hormonal disbalance can attenuate antioxidant enzyme activity which can, in turn, exacerbate oxidative stress and protein glycation in patients with DM [57]. Glutathione peroxidase (GPX), a selenium containing tetrameric enzyme, also known to reduce H_2O_2, organic hydroperoxides, and other lipoperoxides play a major role in the protection of the host against low levels of oxidative stress and GSH-dependent defence against peroxynitrite-mediated oxidations. However, the expression of GPX was significantly decreased in the diabetic group, thus inflaming the oxidative stress in DM patients [58]. Interestingly, insulin and insulin-like growth factor axis also ameliorate a varied number of signalling pathways, leading to phosphorylation of several adaptor proteins and activation of cell surface receptors. Being associated with several signalling pathways like Ras/Raf/MAPK and PI3K/mTOR [59], this insulin-IGF axis when dysregulated due to diabetes stimulates proliferation and protection from apoptotic stimuli and when linked with oxidative stress further leads to the pathophysiology of varied infections [60, 61], including *H. pylori* infection.

Other reasons

Another predisposing factor to *H. pylori* infections is the impaired gastrointestinal mobility in diabetic patients coupled with autonomic neuropathy. In a study by Feldman et al., long-standing diabetic patients secreted less gastric acid, in comparison to non-diabetic patients. The authors suggested this to be a vagal neuropathy or autovagotomy as diabetic patients in the long term have reduced responsiveness of parietal cells to endogenous gastrin [62]. In support, Marrollo et al. also discovered a higher rate of peptic lesions was found in patients with both diabetes and *H. pylori* infection, in comparison to those without the former. They postulated that this might be induced by hypergastrinemia, due to the hyperfunction of G cells [19]. Changes in the metabolism of glucose might also alter the production inside the gastric mucosa, thus preferring the colonization of more bacteria [13]. According to some studies, patients suffering from obesity or high BMI were

linked with an increased risk of *H. pylori* colonization, resulting from gastric motility [63].

Due to its established efficacy, metformin is currently one of the most widely prescribed oral-diabetic agents. However, the influence of metformin on serum vitamin B12 levels and other vitamin status-assessing biomarkers was reviewed, and it has been reported that metformin-treated patients suffer from vitamin B12 malabsorption [64]. Attributed to poor absorption and low dietary intake, conditions like pernicious anaemia, reduced gastric acid secretion and gastric dysfunction were observed in such patients. Stomach-related conditions like gastric atrophy and *H. pylori* persistent infections were also associated with the absorption of vitamin B12, thus leading to polyneuropathy, cognitive impairment, gastrointestinal dysfunction etc. [65, 66]. Intriguingly, B12 hypovitaminosis causes an imbalance in levels of homocysteine, a compound whose metabolism involves vitamin B12, which further leads to the release of an increased number of free radicals and generation of oxidative stress, thus responsible for vascularity damage, lipid peroxidation and infections (including *H. pylori* infection) [72].

Controversies Lying About the Association Between *H. pylori* and Diabetes Mellitus

However, on the other side of the coin, several statistics disprove the linkage between bacteria and diabetes. Xia et al. in their study showed that the seroprevalence of *H. pylori* infection was the same for both diabetic and non-diabetic patients [68]. They accounted immunocompromised state of diabetes and psychological distress to be the possible risk factors for upper GI symptoms in diabetic patients [68]. Similar results were also observed by others, where histological examination, mucosal biopsy and stool antigen tests supported the hypothesis that T2DM may not be a predisposing condition for *H. pylori* colonization [34, 69–71, 72]. In fact, Anastasios et al. further appended that the diminished secretion of hydrochloric acid, in diabetic patients (diabetes-induced achlorydria), might be harmful to *H. pylori*, thus establishing the predisposing condition of *H. pylori* colonization in DM patients [69]. Gentile et al. clarified that the coinciding GI symptoms observed in diabetic patients account for the consequence of the autonomic neuropathy with delayed gastric emptying, thus promoting the bacterial infection [15]. Aberrant glycaemic control was reasoned out to be gastric emptying where there is mismatch between absorption of carbohydrates and onset of insulin action [3]. Yet, another reason for the prevalence of *H. pylori* infections in diabetic patients accounts for their immunocompromised state. Both the cellular and humoral immunity in diabetic patients stay affected, with impairment in monocytes, natural killer cells and polymorphonuclear leukocytes; thus, they remain prone to exposure to bacterial subjects, leading to infections [15, 73].

Later in 2015, Tamura et al. also did not support the association of DM with *H. pylori* infections. Though they found a significantly higher prevalence ratio rate of DM in accordance to East Asia CagA-positive *H. pylori* infection in a general Japanese population, they claimed that people with old age strata tend to be diabetic and usually get infected with bacterial infections [74]. Analysis by Jafarzadeh et al. also led to the fact that anti-CagA IgG antibodies in diabetic patients were found to be the same as that in a healthy group from Iran, thus showing no association between CagA-positive strains of *H. pylori* and type II DM [75]. Large Korean cohort studies (serological and histological) by Pyo et al. also led to the same conclusion that *H. pylori* does not show any association with diabetes, impaired glucose tolerance, impaired glycaemic control or diabetic nephropathy [76]. Similar cross-sectional studies in 2020 were done in China, and no significant association was found between prevalent diabetes and *H. pylori* infections in males. However, the same study did find an association between DM and microbial exposures, including *H. pylori*-induced inflammation, in females only. The authors reasoned the same through sex-dimorphic hypothalamic insulin action, where *H. pylori* infection-induced hypothalamic inflammation disrupts insulin signalling more in females, in comparison to males, thus explaining the pronounced insulin resistance among females, thereby signifying the association of DM with *H. pylori* infection in females only [84••].

Or Is It the Other Way Round?

Influence of H. pylori in the Host Microbiota

Though there have been controversies that *H. pylori* is associated with diabetic patients, there have also been several research works disproving the same. Colonization with the *H. pylori* strains bearing the cagPAI (cytotoxin-associated gene pathogenicity island) influences the risk of several gastric infections. In the initial phase of the infection, *H. pylori* tries to neutralize the acidic environment of the stomach through the action of several enzymes, esp. urease. After modulating the pH, the pathogen continues to thrive by eliciting several cellular and humoral immune responses from the host. Apart from the cagPAI encoding the type IV secretion system (T4SS) that also mediates the interaction of *H. pylori* with the gastric epithelium, the bacterium also produces several virulence factors, namely cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), which have been seen to be implicated in the pathogenesis and in perturbing the host immunological responses [78,

79]. Known as a multi-functional toxin, VacA attributes to exert various side effects upon the host cell, i.e. disruption in the mitochondrial activity through downregulation of Bcl-2, mediation of apoptosis by the increased activation of caspase-9 and caspase-3 [80], blockage in T-cell proliferation and induction of programmed necrosis, thus dysregulating both the immunity and metabolism of the host cells [79].

Imbalance of Inflammatory Cytokines and Hormones

Gradually, *H. pylori* provokes the host organism by eliciting several inflammatory cytokines, namely IL-1, IL-6, IL-8, IL-17, IL-18, IL-21, IL-22, TGF-β, TNF-α and IFN-γ [81], which also get involved in the inflammatory state of the host. Apart from this, *H. pylori* has also been associated with deficiencies in iron, folate, vitamin B12, etc. [82]. When interacting with *H. pylori*, the gastric neuroendocrine cells secrete hormones like gastrin, leptin, somatostatin and ghrelin, which further influence the metabolic status of the host. *H. pylori*-infected mice studies have also shown decreased levels of blood plasma glucose level, enhanced leptin levels and increased glucose tolerance. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) were also found to be downregulated, post-colonization [83]. This perturbation of inflammatory cytokines, peptides and hormones further implicates aberrant metabolism, insulin resistance, lipotoxicity, glucose toxicity, cytokine dysregulation and hormonal imbalances, thereby causing severe outcomes, apart from GI problems, including DM. Recent findings have suggested the prevalence of *H. pylori* over other host–pathogen interactions, which thereby leads to numerous aberrant allergic, cardiovascular, dermatological, metabolic, ocular and neurological functions, thus influencing their respective organ systems [84••, 85, 86].

Dysregulation of Inflammatory and Endocrinal Pathways

However, the release of the above-mentioned inflammatory cytokines in the host, along with oxidative stress, activates the NF-κB pathway and also phosphorylates serine residues of the insulin receptor substrate, thereby causing insulin resistance [87, 88]. Numerous literature has shown that the inflammatory cytokines, especially TNF-α and IL-6, regulate the hepatic synthesis of C-reactive protein (CRP), which when conjugated with oxidative stress also leads to DM [89, 90]. Apart from the increased cytokine production, *H. pylori* in the gut microbiota also increase the production of lipopolysaccharides, a major constituent of the bacterial cell wall. These lipopolysaccharides activate several innate responses, thereby correlating with the degree of obesity and diabetes in *H. pylori* infective patients [91, 92]. Among the GI hormones, as mentioned above, the basal and stimulated secretion of gastrin reduces somatostatin secretion, thereby disrupting insulin homeostasis [85]. *H. pylori* also impairs insulin signalling by upregulating the suppressor of cytokine signalling 3 (SOCS3) and activating the c-Jun/miR-203/SOCS3 signalling pathway, thus giving possible explanations to aberrant glucose metabolism and insulin tolerance, contributing to the development of DM [93].

Chen and Blaser established a positive association between *H. pylori* and HbA1c levels, a potential biomarker for determining blood glucose levels. They argued that there might not be any mutual precursor reason underlying a patient suffering from both *H. pylori* positivity and glucose intolerance and referred that there must be a link between the increase in HbA1c levels in *H. pylori* patients, especially CagA-positive *H. pylori* patients [94]. Further studies in China and Taiwan showed that *H. pylori* infection was accompanied by an increased prevalence of HbA1c, decreased insulin secretion and a higher occurrence of DM [95, 96]. Intriguingly, a novel observation by Rahman et al. indicated that *H. pylori* subjects are more prone to being diabetic, with *H. pylori* (CagA)-positive subjects having significantly higher fasting glucose, as compared to negative controls, thereby ascertaining a link between CagA and insulin resistance [97]. Other cohort studies by Aydemir et al., Eshragian et al., Chen et al. and Kato et al. also were concordant with the hypothesis that there must be an association between *H. pylori* seropositivity and insulin resistance, thus concluding that *H. pylori* infections contribute either dependently or independently towards insulin dysregulation, thereby contributing towards DM [98–101].

However, an upregulation of peroxisome proliferator-activated receptor (PPAR-γ), an essential transcriptional factor that acts as a thermostat for inflammation and metabolism, was also observed in *H. pylori*-infected mice. In fact, PPAR-γ responsive genes (CD36 and FABP4) were also seen to be upregulated, suggesting an increased PPAR-γ activation in vivo. These in vivo findings illustrate that *H. pylori* infection, if modulated properly, might help in glucose homeostasis and provide partial protection against some metabolic disorders, including T2DM [102].

Conclusion

As mentioned above, *H. pylori* plays a critical role in the development and pathogenesis of various GI impairments like peptic lesions, MALT lymphoma, adenocarcinoma and gastric cancer. Besides, several other extra-gastric diseases like neurogenic, cardiovascular and endocrinal diseases also mediate the pathogenesis of such GI

injuries. Literature has suggested the inextricable linkage of GI impairments with diabetes mellitus. Albeit for the last several decades there has always been controversy regarding the association of diabetes mellitus and *H. pylori* infections, evidence concerning insulin resistance, chronic inflammation, hormonal misbalance, etc. implicates diabetes to be a predisposition for *H. pylori* infections. Though the pathophysiology of *H. pylori* infections is quite multifaceted and is of a multistep disease, which is very implausible to generate from a single cause, several risk factors contribute to the formation of *H. pylori* infection, out of which diabetes mellitus can play a major role. Large prospective cohorts have investigated the mediation of *H. pylori* infections in coordination with T2DM; however, several literatures ruled out stating *H. pylori* infections in diabetic patients have no scientific connections. *H. pylori* infections are quite geographical, age-, gender-, BMI-based infections; thus, they give unanimous results about the *H. pylori* strains in both diabetic and non-diabetic people and thus require large heterogeneous interventional studies to evaluate the long-term association of *H. pylori* and diabetes mellitus. In fact, several case studies have also been made on the inverse associations of the two illnesses, of whether diabetes mellitus is associated to pre-*H. pylori*-infected patients. Though there have been no established scientific reports, and since everything is based on meta-analysis, this area demands thorough research.

To this point, based on a systematic review and a meta-analysis of the currently available literature, we assume that *H. pylori* and diabetes mellitus have a strong linkage with each other. Data supporting the etiological role of diabetes mellitus in the development of *H. pylori* infections would specify precautionary measures, such as improved hygiene and treatments using gut-friendly antidiabetic drugs. In conclusion, the casual association of diabetes mellitus and *H. pylori* still stays contentious but is worthy of further investigation, since these two diseases affect people on a broad spectrum, both in the context of human health and health economics.

Author Contribution Om Saswat Sahoo: writing — original draft, review and figure preparation. Rhiti Mitra: writing — collection and analysis of data. Arghyadeep Bhattacharjee: writing — review and editing. Samarjit Kar: proofreading the manuscript and reviewing the statistical process. Oindrilla Mukherjee: idea development, manuscript preparation and manuscript revision. All the authors read and approved the final review draft.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Competing Interests The author declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as: •• Of major importance

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