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TOPIC HIGHLIGHT

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Helicobacter pylori and functional dyspepsia: An unsolved issue?

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Abstract

Patients with *Helicobacter pylori* (*H. pylori*) infection may complain of dyspeptic symptoms without presence of macroscopic lesions on gastroduodenal mucosa. Such a condition is usually recognized as functional dyspepsia, and different pathogenetic mechanisms are involved. The role of *H. pylori* in these patients is controversial. Several trials assessed the potential role of *H. pylori* eradication in improving dyspeptic symptoms, and data of some meta-analyses demonstrated that cure of infection is associated with a small (10%), but significant therapeutic gain as compared to placebo. The reason for which dyspeptic symptoms regress in some patients following bacterial eradication, but persist in others remains unclear. Regrettably, trials included in the meta-analyses are somewhat different for study design, definition of symptoms, assessment of symptoms changes, and some may be flawed by potential pitfalls. Consequently, the information could be not consistent. We critically reviewed the main available trials, attempting to address future research in this field

Key words: *Helicobacter pylori*; Dyspepsia; Symptoms; Therapy; Pathogenesis

Core tip: The role of *Helicobacter pylori* infection in functional dyspesia is still controversial. Some meta-analyses indicated the infection eradication is associated with a significant therapeutic gain as compared to placebo. However, the considered trials differ for study design, definition of symptoms, assessment of symptoms changes, and some may be flawed by potential pitfalls. Therefore, further studies are needed.

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INTRODUCTION

Functional dyspepsia (FD) is classically defined as continuous or frequently recurring epigastric pain or discomfort centred in upper abdomen for which no organic

cause can be determined[1]. It includes a heterogeneous and broad range of chronic upper abdominal symptoms which are widely shared with different gastrointestinal disorders, including reflux disease, irritable bowel disease, gallbladder and pancreatic dysfunction, and celiac disease. Therefore, FD is generally diagnosed when other frequent gastrointestinal diseases are excluded, and upper endoscopy ruled out macroscopic lesions - *i.e.*, investigated dyspepsia. Such a condition is frequently encountered in clinical practice, its prevalence being close to 20%-30% in the general population. Of note, dyspeptic symptoms persist over the long-term in the majority of patients, despite periods of remission may occur, so that several FD patients recurrently require medical consultations and therapies[2]. Consequently, the management of FD patients has a relevant economic impact, and it involves both general practitioners and gastroenterologists. Regrettably, the aetiology of FD remains largely unknown - different factors being presumably involved - and no definite and effective treatment is currently available for all these patients.

The discovery of *Helicobacter pylori* (*H. pylori*) in the '80[thies] triggered the expectation that dyspeptic symptoms could be caused by such a persistent infection in the stomach, which invariably causes chronic active gastritis. Starting at the end of '90[thies], several studies have been performed to assess the potential role of *H. pylori* eradication on FD, and a Cochrane meta-analysis including data of 12 trials involving 2541 patients was published on 2003[3]. It was calculated that *H. pylori* eradication had a small (37% *vs* 29%; 8%), but statistically significant effect (RR = 0.91; 95%CI: 0.86-0.95) in reducing dyspepsia symptoms as compared to placebo at 12 mo follow-up, with a number need to treat (NNT) of 15. An update of data including 17 trials with 3,566 patients showed that there was a 10% (95%CI: 6-14) relative risk reduction of dyspepsia following *H. pylori* eradication as compared to placebo, with a NNT of 14 (95%CI: 10-25)[4]. The last Consensus of an International panel of clinical investigators on gastroduodenal functional disorders (Rome Ⅲ) recommended *H. pylori* eradication in all infected patients with non-ulcer dyspepsia diagnosed at upper endoscopy, also suggesting non-invasive testing followed by *H. pylori* eradication ("test and treat") in those patients with no alarm features, although many infected patients with FD may not gain symptomatic benefit[2].

Can we therefore conclude that everything is clear on this issue? Unfortunately, results of different studies are conflicting, so that no definitive information emerges from the available data. This could depend on different factors, such as the study design, definition of symptoms, assessment of symptoms changes, and potential pitfalls. The knowledge of these limitations could add "a further light at the end on the tunnel" of FD.

H. PYLORI AND FD PATHOGENESIS

The pathogenesis of FD still remains unrevealed, and several alterations have been invoked as putative mechanisms responsible of dyspeptic symptoms. These include altered gastric emptying (delayed or accelerated), impaired accommodation of proximal stomach, and sensory abnormalities (gastroduodenal hypersensitivity)[2]. However, the underlying causes of these alterations are unknown. To date, no conclusive data have been reported on the role of *H. pylori* infection on these dysfunctions. Indeed, disturbances of either motor or sensory function in the gastroduodenal tract of patients with *H. pylori* are not consistent[5,6]. Some studies found that *H. pylori* infection delays gastric emptying, it is associated with a loss of gastric phase Ⅲ of the migrating motor complex, and its eradication significantly improves gastric emptying. However, other studies failed to confirm these observations[7].

Nevertheless, at least in theory, *H. pylori* infection may cause dyspeptic symptoms through other mechanisms such as: (1) alterations of gastric acid secretion; (2) persistent and active inflammation of gastric mucosa; and (3) post-infective changes in gastroduodenal mucosa.

It has been found that gastrin releasing peptide-stimulated maximal acid output (MAO) is 3-fold increased in dyspeptic patients with *H. pylori* infection as compared to uninfected controls[8], and approximately 50% of the non-ulcer dyspepsia infected patients had a similarly stimulated MAO when compared with duodenal ulcer patients[9]. Indeed, *H. pylori* alters production of both gastrin (increased) and somatostatin (decreased) in gastric mucosa, as well as of ghrelin which is involved in acid secretion, hunger sensations, and gastrointestinal motility[10]. Noteworthy, these alterations of gastric acid secretion normalize 6-12 mo following a successful *H. pylori* eradication[10]. Therefore, it is expected that at least some dyspeptic symptoms probably linked to acid hypersecretion, such as epigastric pain, could regress 1 year after the cure of infection. Although the level of stimulated gastric acid secretion at entry was not a predictive factor of FD improvement following *H. pylori* therapy[11], no study assessed the relationship between gastric acid output levels and dyspeptic symptoms 1 year following a successful *H. pylori* eradication.

As far as gastritis is concerned, no consistent data demonstrated that such an inflammatory status of gastric mucosa may be associated with dyspeptic symptoms. A certain genetic predisposition to develop dyspeptic symptoms in patients with *H. pylori*-associated gastritis has been suggested[12]. Indeed, more than half of the patients with *H. pylori* infection are asymptomatic, despite the infection invariably causes a chronic active gastritis. However, it has been widely reported that the active component of gastritis - *i.e.*, polymorphonuclear infiltration - quickly and completely recovers following bacterial eradication, whilst the presence of lymphocytic infiltrate in gastric mucosa may persist several months or years[13]. It has been speculated that these cells may cause alterations of gastric mucosa function by producing different cytokines, similarly to what it is accepted for irritable bowel disease (IBS)[14,15]. Therefore, to correlate dyspeptic symptoms modification and gastritis grade (*i.e.*, lymphocytic infil-

trate) 1 year following a successful bacterial eradication would be an ideal clinical situation to unravel such an issue. Indeed, at least in theory, a total recovery of gastric function should be expected only in those patients in whom both the infection is cured and the inflammation disappeared - *i.e.*, grade 0 gastritis according to the update Sydney System classification[13]. Of note, a trial found that FD symptoms disappeared after curing *H. pylori* infection more frequently in patients with gastritis grade score 0-1 than in those with grade 2-3 (32% *vs* 17%, $P = 0.008$)[16].

Similarly to IBS in which the role for an acute gastrointestinal infection is recognized as a trigger of symptoms in a subset of patients, some studies suggest that dyspeptic symptoms may develop following an infection[17]. A study found that the risk of dyspepsia is 5.2-fold (95%CI: 2.7-9.8) increased 1 year following an acute *Salmonella*-associated gastroenteritis[18]. Similarly, another study found that the risk of hunger pain was 5.77-fold (95%CI: 1.3-25.7) increased 1 year after a water-borne viral gastroenteritis with Norovirus[19]. As for IBS, an increased infiltration of both enterochromaffin cells (EC) and mast cells in gastroduodenal mucosa in post-infectious FD patients has been recently reported[20]. In addition, a role for eosinophils, inflammatory cells, and neuroendocrine cells (*i.e.*, serotonin) infiltration in duodenal mucosa in post-infectious FD patients has been suggested[21]. Since it is widely recognized that *H. pylori* initiates as an acute infection with dyspeptic symptoms, it would appear worthy to assess whether dyspeptic symptoms persist following *H. pylori* eradication in a subset of patients due to a persistence of these cells in gastroduodenal mucosa.

CONCERNS ON *H. PYLORI* ERADICATION TRIALS IN FD PATIENTS

Several trials on the role of *H. pylori* eradication in FD patients are now available, and data of the majority of these studies have been pooled in some meta-analyses[3,4,22]. However, it is remarkable to note that the evaluation of symptoms at entry as well as the assessment of their modifications following bacterial eradication is not the same among different studies. In detail, type and number of symptoms evaluated at entry are not the same, and the definition of symptoms regression or improvement are somewhat different.

By taking into account only double-blind, placebo-controlled trials with at least 50 patients for arms followed for 6-12 mo, in which the final evaluation of *H. pylori* status was performed by means of either upper endoscopy with biopsies or a ^{13}C-urea breath test, we identified 12 studies (Table 1)[11,16,23-32]. Noteworthy, the number and type of symptoms evaluated at entry, the score used to evaluate symptoms modifications, and the period considered for final symptoms assessment are very different among studies. In addition, the use of non-steroid anti-inflammatory drugs (NSAIDs), and the presence of gastric erosions at endoscopy were considered as exclusion criteria in some, but not in other studies. Symptoms modification was evaluated by assessing the score of symptoms present in the last 1-7 d preceding the end of follow-up in some studies and in the last 1-6 mo in others. Furthermore, some trials considered symptomatic improvement following the eradication therapy, irrespectively of whether the patients were actually eradicated or not. Unfortunately, only few studies correlated the symptoms modifications and gastritis score at the end of follow-up, in order to assess whether a complete gastritis regression was also associated with symptom resolution[16]. Similarly, no study tested the potential correlation between gastric acid secretion normalization and symptom disappearance following a successful bacterial eradication. Finally, in different multicenter trials, several participating centres enrolled less than 5-10 patients - with only 1 patient included in a centre[16] - so that a β-type error in patients enrolment cannot be ruled out. Based on all these observations, it remains unclear whether it is appropriate to pool data of these heterogeneous trials, and how robust the final data interpretation may actually be.

Another aspect deserving consideration is that *H. pylori* eradication observed in the placebo group would appear unexpectedly high in some of these trials, with cure rates approaching 6.3%, 6.6%, 7.4%, 8%, and 12%[23,26,28,29,31], whilst the cure rate was reasonably low (0%-2%) in others studies[24,27,32]. *H. pylori* infection virtually persists long-life whether not opportunely treated, and spontaneous disappearance is considered as an infrequent event[33].

Unexpectedly, in a trial[11], comparison of symptom modification was performed between patients receiving eradication therapy and those receiving placebo, rather than between patients cured from *H. pylori* and those with persistent infection. To establish whether *H. pylori* infection really impacts on FD symptoms, the comparison should be between patients definitely cured and those not cured. Indeed, the eradication rate following the triple therapy used is distinctly lower than 100% and, most likely, as many as 15%-20% of patients computed in the eradication therapy group probably remained infected. Both patients and physicians would know whether FD symptoms disappear by really eliminating *H. pylori* infection, rather than following a potentially eradicating therapy.

In the majority of studies (Table 1), assessment of symptom modification was based on the overall score, instead of evaluation of each independent symptom. This would consider FD as a well-definite disease, rather than a combination of symptoms, most likely depending on different pathogenetic mechanisms[34,35]. Intuitively, it would appear at least implausible to expect that *H. pylori* eradication would improve some symptoms - such as abdominal pain, flatulence, diarrhoea, constipation, bloating - which are generally attributed to large bowel[36].

It is widely recognized that NSAIDs - including low-dose aspirin - may cause dyspeptic symptoms, irrespective of onset of either gastroduodenal ulcers or erosions[37].

Table 1 Double-blind, placebo-controlled trials on *Helicobacter pylori* eradication in functional dyspepsia patients

Patients (follow-up)	Low-dose aspirin	Gastric erosions	Symptoms evaluated	Score used (period)	Primary end-point	Comment	Ref.
Therapy = 160 Placebo = 158 (12 mo)	No	NA	Pain or discomfort; heartburn; nausea; postprandial fullness	GDSS: 0-20 (the last 6 mo)	Therapy better than placebo	Evaluation according to the final *H. pylori* status was lacking	[11]
Therapy = 170 Placebo = 167 (12 mo)	Yes	< 5	Ulcer-like; motility-like; reflux-like	GSRS: 0-6 (the last 7 d)	No difference	Rate of family history of ulcers (34% *vs* 23%) and caffeine use (82% *vs* 73%) were significantly higher in therapy group than placebo. Distribution of low-dose aspirin use was lacking. The rate of "indeterminate" UBT result was unexpectedly high (16%)	[16]
Therapy = 129 Placebo = 124 (12 mo)	No	No	Epigastric pain; nausea; abdominal distension; eructation; vomiting; early satiety; regurgitation; retrosternal burning	Likert score: 0-5 (the last 7 d)	Therapy better than placebo	Difference remained significant when symptoms resolution was assessed according to final *H. pylori* status	[23]
Therapy = 81 Placebo = 80 (12 mo)	No	NA	Epigastric pain; burning; postprandial fullness; nausea; vomiting	Score: 0-3 (the last 1 d)	No difference	No difference was observed when symptoms resolution was assessed according to final *H. pylori* status	[24]
Therapy = 135 Placebo = 143 (12 mo)	NA	< 5	Ulcer-like; motility-like; reflux-like	GSRS: 1-7 (the last 7 d)	No difference	No difference according to final *H. pylori* status. A significant difference was observed between patients with persistent gastritis and those with gastritis healing	[25]
Therapy = 135 Placebo = 143 (6 mo)	No	< 10	Epigastric pain or burning; epigastric fullness; heartburn, regurgitation; nausea vomiting, abdominal pain; flatulence; diarrhoea; constipation	Likert score: 0-3 (the last 7 d)	No difference	No difference was observed when symptoms resolution was assessed according to final *H. pylori* status	[26]
Therapy = 71 Placebo = 65 (12 mo)	Yes	No	Epigastric pain; nausea; bloating; heartburn early satiety; vomiting; regurgitation; hunger pain	Score: 0-16 (the last 1 d)	No difference	No difference was observed according to final *H. pylori* status. Both patient groups received omeprazole therapy during the first 3 mo	[27]
Therapy = 201 Placebo = 203 (12 mo)	Yes	Yes	Rome Ⅲ criteria	PADYQ: 0-44 (the last 30 d)	Therapy better than placebo	Therapy success occurred for "postprandial distress syndrome" but not for "epigastric pain syndrome"	[28]
Therapy = 75 Placebo =82 (12 mo)	Yes	< 5	Epigastric pain; belching; heartburn, bloating; flatulence; sour taste; nausea; halitosis	DSS likert score: 1-5	No difference	No difference was observed when symptoms resolution was assessed according to final *H. pylori* status	[29]
Therapy = 50 Placebo = 50 (12 mo)	No	No	Ulcer-like; motility-like; reflux-like; unspecified	Score for severity: 0-2 Score for frequency: 0-3	Therapy better than placebo	Difference was based on the reduction on mean score. Difference remained significant according to final *H. pylori* status. The rate of asymptomatic patients was lacking	[30]
Therapy = 50 Placebo = 50 (12 mo)	NA	NA	Abdominal fullness; early satiety; bloating; nausea (Rome Ⅱ criteria)	Likert score: 0-6	No difference	No difference was observed when symptoms resolution was assessed according to final *H. pylori* status	[31]
Therapy = 164 Placebo = 164 (12 mo)	NA	< 5	Indigestion; diarrhoea constipation; reflux; abdominal pain	GSRS: 1-7 (the last 7 d)	No difference	No difference was observed when symptoms resolution was assessed according to final *H. pylori* status	[32]

GSRS: Gastrointestinal symptoms rating score; GDSS: Glasgow dyspepsia severity score; PADYQ: Porto Alegre dyspeptic symptoms questionnaire; DSS: Dyspepsia summary score; NA: Not available.

Therefore, inclusion of patients taking these drugs in trials aimed to assess an independent role of *H. pylori* in FD should be regarded as confounding. Regrettably, in a trial[16], the rate of low-dose aspirin users in either therapy and placebo arm was lacking, so that a different distribution between the two groups cannot be ruled out.

The potential role of gastroduodenal erosions in dyspeptic patients remains largely unclear. Indeed, gastroduodenal erosions may be encountered in asymptomatic patients. However, at least in theory, the presence of breaks on gastric mucosa - irrespective of diameter - may favour a H^+ back diffusion and, consequently, stimulation of visceral nerve terminations with epigastric pain. In the considered trials (Table 1), patients with gastroduodenal erosions were excluded in some studies, whilst enrolled in others when erosions were either < 5 or < 10. However, no data on erosions resolution at the end follow-up were provided, and their potential association with symptom modification was not assessed. Some data would suggest that gastric erosions did not regress following *H. pylori* eradication[38].

CONCLUSION

The most definite information currently available on the role of *H. pylori* eradication in FD patients arises from two meta-analyses where trials with a follow-up of 6-12 mo were included[3,4,22]. Basically, it has been calculated that *H. pylori* eradication is associated with a 10% (95%CI: 6-14) therapeutic gain as compared to placebo, with a NNT of 14 (95%CI: 10-25), and that symptoms improvement ultimately occurs in nearly 40% of eradicated patients[4]. Another meta-analysis, including data more recent studies (overall 14 trials with 2993 patients), confirmed that improvement of dyspepsia symptoms occurs more frequently after *H. pylori* therapy than placebo (OR = 1.38, 95%CI: 1.18-1.62, $P < 0.0001$), without differences among Europe, United States and Asia[22]. However, as we discussed, criteria adopted regarding type of symptoms at entry, evaluation of symptoms modification at follow-up, and clinical characteristics of enrolled patients (gastroduodenal erosions, use of NSAIDs, *etc.*) frequently varied among these studies. In addition, the role of dietary and lifestyle factors was not considered[39]. These factors could affect symptoms evaluation, particularly when only 1 d - or few days - recording is used, as occurred in several trials. On the other hand, some alterations induced by *H. pylori* infection - *i.e.*, low-grade chronic inflammation, gastric acid out-put perturbation, EC and mast cells infiltration, *etc.* - with a putative role in FD symptoms were not opportunely assessed following a successful cure of infection. Unfortunately, despite several trials with some thousands of patients, no clear predictive factors of FD regression after bacterial eradiation have been identified. During the last decades, progressive attempts aimed to unify different dyspeptic symptoms in few, well-structured categories were performed. The latter functional disorders classification (Rome Ⅲ) proposed two main type of FD, there is postprandial distress syndrome (postprandial fullness and early satiation) and epigastric pain syndrome (EPS: pain or burning localized to the epigastrium, not generalized or localized to other abdominal or chest regions, not relieved by defecation or passage of flatus, not fulfilling criteria for gallbladder and sphincter of oddi disorders). For both conditions, criteria should fulfilled for the last 3 mo with symptom onset at least 6 mo before diagnosis. This could reduce the confusion in FD definition in future studies, allowing a more reliable comparison among therapeutic trials. Regrettably, a recent Korean trial showed that application of these Rome Ⅲ criteria to FD is very difficult, and only 4 patients fulfilling these criteria were identified by gastroenterologists at 11 tertiary referral hospitals during 1 year[40]. In addition, the observation that EPS frequently overlaps with non-erosive reflux disease - which is not associated with *H. pylori* infection[41] - further puzzles data interpretation[42]. Therefore, the saga continues.

While waiting to understand what subset of FD patients may actually benefit of *H. pylori* eradication, it should be considered that bacterial eradication in dyspeptic patients significantly reduces the number of upper endoscopies[43], medical visits[44], and the use of drugs[45], so that it is cost-effective at long-term follow-up[46]. Prevention of peptic ulcer onset, and reduction of both cancer and lymphoma development in the stomach are other remarkable gains favouring *H. pylori* eradication in symptomatic patients[47].

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