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TOPIC HIGHLIGHT

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Helicobacter pylori infection in obesity and its clinical outcome after bariatric surgery

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Abstract

The present review summarizes the prevalence and active clinical problems in obese patients with *Helicobacter pylori* (*H. pylori*) infection, as well as the outcomes after bariatric surgery in this patient population. The involvement of *H. pylori* in the pathophysiology of obesity is still debated. It may be that the infection is protective against obesity, because of the gastritis-induced decrease in production and secretion of the orexigenic hormone ghrelin. However, recent epidemiological studies have failed to show an association between *H. pylori* infection and reduced body mass index. *H. pylori* infection might represent a limiting factor in the access to bariatric bypass surgery, even if high-quality evidence indicating the advantages of preoperative *H. pylori* screening and eradication is lacking. The clinical management of infection is complicated by the lower eradication rates with standard therapeutic regimens reported in obese patients than in the normal-weight population. Prospective clinical studies to ameliorate both *H. pylori* eradication rates and control the clinical outcomes of *H. pylori* infection after different bariatric procedures are warranted.

Key words: *Helicobacter pylori*; Obesity; Bariatric surgery; Ghrelin; Antibiotic resistance

Core tip: This review deals with the active clinical problems related to *Helicobacter pylori* (*H. pylori*) infection in obese patients. Even if still controversial, the infection might represent a confounding and limiting factor in bariatric surgery, due to the high incidence of postoperative foregut symptoms and/or lesions in non-eradicated patients. The controversies on preoperative *H. pylori* screening are highlighted, as well as those related to its clinical management, which is complicated by the low eradication rates in obesity. Finally, a revision of studies on the possible correlation between *H. pylori* and body mass index and its possible protective role in development of obesity is included.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most common human infections and it is estimated that more than half

of the world population is infected[1]. *H. pylori* is an ancient colonizer of the human stomach and represents the main etiological factor in the development of gastritis, peptic ulcer and gastric malignant lesions. The infection is still highly prevalent in developing countries but it is disappearing in the developed world (Table 1; modified from[2]). Indeed, epidemiological studies show that *H. pylori* infection still occurs more frequently in socioeconomically deprived populations living in crowded places with poor hygienic conditions, and conversely, has a lower frequency in people of high socioeconomic status[3]. The influence of these factors on *H. pylori* infection in obesity remains to be ascertained. A study on obese patients who were candidates for bariatric surgery[4] highlighted race as a risk factor for *H. pylori* infection, in that African-Americans and Hispanics had a higher probability than Caucasians of being infected, with significant odds ratios of 4.05 and 2.6, respectively. Interestingly, these two ethnic groups, at least in the United States, have the highest obesity rates[5].

Table 1 Prevalence of *Helicobacter pylori* infection in the general population worldwide

	Country	Prevalence (%)
North America	United States and Canada	30.0
	Canada	23.1
South America	Mexico	70-90
	Chile	70-90
	Brazil	82.0
Europe	Poland	84.2
	Albania	70.7
	Estonia	69.0
	Germany	48.8
	Czech Republic	42.1
	Iceland	36.0
	Switzerland	11.9
	Sweden	11.0
Middle East	Egypt	90.0
	Turkey	80.0
Asia	Bangladesh	> 90.0
	India	88.0
	Japan	55.4
	Taiwan	45.1
Africa	Ethiopia	> 95.0
	Nigeria	70-90
Australia		15.4

PREVALENCE OF *H. PYLORI* INFECTION IN OBESE PATIENTS

The prevalence of *H. pylori* infection in morbidly obese patients is still controversial. Candidates for bariatric surgery have a preoperative prevalence of *H. pylori* ranging from 8.7% in a German cohort[6] to 85.5% in a Saudi cohort[7], with other series showing intermediate values. Overall, available studies report a lower prevalence of *H. pylori* infection in obese patients than in the general population (Table 2). Nevertheless, the few studies that have compared simultaneously the prevalence between lean and obese patients are in disagreement, with half[3,4,8] showing a higher *H. pylori* prevalence in obese patients and the other half[18,23,27] an opposite trend. Discrepancies might be related to both small sample size and variability in diagnostic testing. Different methods are used to diagnose *H. pylori* infection. Serology was largely used in these studies but it has a low diagnostic accuracy of only 80%-84%, and is only useful to exclude *H. pylori* infection. Indeed, positive serology should be confirmed by a test for active infection, such as stool antigen assay or urea breath test (UBT). The former has a sensitivity of 94% and a specificity of 92%, whereas UBT has a sensitivity of 88%-95% and specificity of 95%-100%. Finally, histology has an excellent sensitivity and specificity, especially when specific immunostaining is used to detect *H. pylori* bacteria, and could be partially replaced by biopsy urease testing in patients who have discontinued treatment with proton pump inhibitors or antibiotics[1].

The majority of studies have used only one method to diagnose *H. pylori* infection. When more than one test was used, single tests were not compared with each other and used alternatively. The only study[14] that compared serology to histology found good accordance between the two methods. Testing for active infection has been rare. UBT and stool antigen assay have been used only in one study[12], without any comparison with histology. Even though antisecretory therapy affects diagnostic accuracy of most *H. pylori* diagnostic tests, patients with ongoing antisecretory treatment have been excluded only in one study[22].

H. pylori infection plays a special role in obesity for two main reasons: (1) its possible relationship with body mass index (BMI); and (2) it is a negative factor in limiting access to bariatric surgery.

H. PYLORI INFECTION AND PATHOPHYSIOLOGY OF OBESITY

Both environmental and host agents are involved in the pathophysiology of obesity, including diet, physical inactivity, and drug use, but also genetics and neurophysiological factors. However, an established factor in the development of obesity is dysregulation of the mechanisms that control food intake; mainly under the control of the hormones leptin and ghrelin that are secreted by the gastric mucosa. Leptin primarily suppresses food intake and therefore induces weight loss. Ghrelin increases abruptly before the onset of a meal and decreases rapidly after eating; it has orexigenic effects and inhibits the secretion of leptin. The relationship between ghrelin and *H. pylori* infection in obesity has received much attention in recent years because *H. pylori* gastric mucosal colonization may impair gastric ghrelin production, with subsequent reduction of hunger[28]. Consequently, it has been hypothesized that *H. pylori* infection might have a protective role against obesity.

Several studies[29-32] have investigated the relationship between *H. pylori*-related gastritis and ghrelin, by comparing *H. pylori*-positive with *H. pylori*-negative patients, or

Table 2 Prevalence of *Helicobacter pylori* infection in obese and normal weight patients worldwide

	n	% *H. pylori* + obese (*n*)	% *H. pylori* + control (*n*)	Country	*H. pylori* detection	Ref.
North America	202	6.9 (101)	4.9 (101)	United States	Histology	[8]
	611	23.7	ND		Histology	[9]
	169	30.1	ND		Histology	[10]
	74	24.0	ND		Urease test	[11]
	87	20.0	ND		Urease test	[12]
	58	12.0	ND		Mixed	[13]
	96	11.0	ND		Mixed	[14]
	2684	61.3 (240)	48.2 (2244)		Serology	[4]
	259	22.4	ND		Serology	[15]
South America	232	5.0	ND	Chile	Histology	[16]
	126	53.2	ND	Brazil	Histology	[17]
	83	50.0 (50)	66.6 (33)	Brazil	Histology	[18]
	42	50.0	ND	Brazil	Urease test	[19]
	533	52.5	ND	Chile	Urease test	[20]
	96	37.5	ND	Brazil	Mixed	[21]
Europe	319	39.0	ND	Switzerland	Urease test	[22]
	69	8.7	ND	Germany	Urease test	[6]
	224	23.0 (42)	77.0 (182)	Greece	Serology + histology	[23]
Middle East	656	7.3	ND	Kuwait	Histology	[24]
	62	85.5	ND	Saudi Arabia	Histology	[7]
	214	57.2 (103)	27.0 (111)	Turkey	Serology	[3]
Asia	152	41.4	ND	Taiwan	Histology	[25]
	156	39.7	ND		Histology	[26]
	1097	43.7 (414)	60.0 (683)		Serology	[27]

ND: Not defined; *H. pylori*: *Helicobacter pylori*.

patients before and after eradication treatment, analyzing circulating ghrelin levels, the number of ghrelin immunoreactive cells per cubic millimeter in gastric mucosa[33-35] and ghrelin mRNA expression[33,36,37]. The results of these studies have been conflicting, however, a recent systematic review[38] concluded that circulating ghrelin levels are lower in the presence of *H. pylori* infection. Moreover, studies dealing with morbidly obese patients who are candidates for bariatric surgery have shown discordant results with regard to the relationship between *H. pylori* and ghrelin. Obese patients have been reported to have a reduced[26] or increased[18] number of immunoreactive ghrelin cells, even if their number was lower in *H. pylori*-positive than -negative patients.

A possible explanation of these conflicting results can be ascribed to *H. pylori*-related gastritis patterns. The outcome of *H. pylori* infection differs according to gastritis extension, which generally starts with antritis subsequently progressing to pan-gastritis, which may be associated with atrophy. In the presence of atrophy, secretory activity decreases, which probably involves ghrelin production[39]. Upper gastrointestinal endoscopy with multiple mucosal sampling is required to define the pattern of *H. pylori*-related gastritis, even if an indirect non-invasive serological method is represented by the ratio between pepsinogen (PG) I and Ⅱ; a low PG Ⅰ / Ⅱ ratio being suggestive of the presence of atrophy[40]. By the use of PG Ⅰ / Ⅱ ratio, it has been shown that, within 1 year of *H. pylori* eradication, BMI increased only in the low PG Ⅰ / Ⅱ ratio group[41], suggesting that the sole presence of atrophy has a relevant role in influencing body weight. Indeed BMI, after adjusting for sex and age, was significantly lower in patients with atrophic gastritis than in those without atrophy[42]. Other factors can contribute to explain the controversial results about the relationship between *H. pylori* and ghrelin. First, the different time elapsing from eradication might have influenced the mucosal healing process and then restored normal secretory activity. Second, age might play a role because atrophy is more frequent in elderly patients. Finally, changes in plasma ghrelin concentrations are not strictly associated with gastric mucosal expression and this may be attributed to the presence of ghrelin isoforms with different biological activities[43].

H. PYLORI INFECTION AND BMI

Even if the significant increase in BMI observed after *H. pylori* eradication treatment highlights a possible inverse correlation between *H. pylori* infection and obesity, both in adults[44,45] and children[46], available data are controversial. Indeed, several studies did not find any influence of bacterial eradication on body weight[37,47]. Furthermore, epidemiological studies have failed to show any association between *H. pylori* infection and BMI, with a meta-analysis of 18 observational studies, including 10000 subjects, that reported a slightly higher BMI in *H. pylori*-positive patients[48].

Two theories emerge from these studies. Studies that observed a significant increase in BMI after successful *H. pylori* eradication support a protective role of infection towards obesity, which likely occurs through decreased production and secretion of the orexigenic hormone ghrelin[49]. Studies reporting a higher prevalence of infec-

tion in obese patients disclaim a protective role of *H. pylori* and support the increased incidence and severity of infection observed in obese patients[3]. Obesity can alter innate and adaptive immunity, with immunological impairment related to the grade of obesity, resulting in less maturation of monocytes into macrophages, reduced polymorphonuclear bactericidal capacity, and a significant decrease in NK cell activity[4].

However discrepancies among studies can be ascribed to other factors. As previously mentioned, a misleading factor is the frequent lack of classification of the patients according to their gastritis patterns, especially atrophy[49]. Furthermore, the relationship between *H. pylori* and BMI can be strongly influenced by the dietary change that can occur after eradication. Indeed, *H. pylori* eradication can ameliorate dyspeptic symptoms favoring dietary excess.

H. PYLORI AND BARIATRIC SURGERY

In the field of bariatric surgery, the American Association of Clinical Endocrinologists/The Obesity Society/American Society for Metabolic and Bariatric Surgery guidelines[50] do not provide clear indication about preoperative *H. pylori* screening and management. The document recommends *H. pylori* screening in patients belonging to high-prevalence areas and upper endoscopy in selected cases. Previous European guidelines[51] recommended upper gastrointestinal endoscopy before bariatric surgery in any symptomatic or asymptomatic patient in order to treat any lesions, including *H. pylori* infection, that may cause postoperative complications. The advantages of preoperative *H. pylori* screening and eradication are still controversial, mainly due to a lack of randomized control trials (RCTs). However, different attitudes might be influenced by the differences in health systems and access to upper gastrointestinal endoscopy.

Routine upper endoscopy studies, with concurrent *H. pylori* screening and biopsies to rule out pathological abnormalities (*e.g.*, esophagitis, polyps, hiatal hernia, gastritis, and duodenitis), have reported that abnormalities are present in up to 91% of bariatric candidates[12,16,22], with a higher incidence in patients with concomitant *H. pylori* infection[11,14,52]. Some of these alterations are expected to be cured by tailored bariatric surgery (*i.e.*, hiatal hernia and gastroesophageal reflux disease), even if the main concern is represented by postsurgical gastric malignancy, especially after bariatric procedures with gastric bypass. The majority of obese patients with upper gastrointestinal lesions at the time of routine preoperative endoscopy are asymptomatic[53], with only 20% of the obese patients with pathological findings presenting with upper gastrointestinal symptoms[6]. Also, esophageal dysmotility, frequently observed in these patients, occurs in the absence of symptoms[54]. The lack of visceral sensation in obese patients has been ascribed to alterations in the autonomic nervous system[55,56]. Thus, the decision to perform endoscopy before bariatric surgery on the basis of clinical presentation may be misleading.

Concerning the management of obese patients who are candidates for bariatric surgery, the main clinical issue is represented by *H. pylori* resistance to antibiotic eradication, which could delay access to bariatric surgery. Obese patients showed a significantly lower rate of eradication than controls, at least to the 7-d regimens[57], with BMI being an independent risk factor for eradication failure. Although the mechanisms by which obese patients have a poor eradication rate remain to be elucidated, it seems likely to be due to the following reasons leading to subtherapeutic drug concentrations. First, the physiological changes that occur in obesity, such as possible delayed gastric emptying[58], may lead to a decrease in the rate of drug absorption, regardless of the characteristics of the drug. Second, the volume of distribution of drugs may be altered in obese patients because the increased adipose tissue mass can influence medications with lipophilic properties[59,60]. Clearly, the need of a tailored eradication regimen for obese patients based on body weight arises, but no clinical trials have compared standard therapy versus weight-based regimens. An increase in the eradication treatment efficacy can be obtained by extending the treatment period[61]. A recent trial, aimed to compare 7- and 14-d first-line treatment with clarithromycin-based triple therapy in obese patients, showed that the latter is more effective[62].

EFFECT OF *H. PYLORI* INFECTION ON BARIATRIC SURGERY OUTCOMES

The majority of the studies, focused on standard laparoscopic Roux-en-Y gastric bypass (LRYGB) outcomes, have reported a reduced prevalence of postsurgical lesions after successful *H. pylori* eradication. After LRYGB, *H. pylori* eradicated patients present with a reduced incidence of viscus perforations[13] and of postoperative marginal ulcers[52]. In this latter retrospective study of 560 patients, the incidence of ulcers was 2.4% in patients that were tested and treated for *H. pylori* infection prior to surgery compared to 6.8% in those who did not undergo such screening. However, other authors have reported that, even though marginal ulcer rates following gastric bypass were higher in patients with *H. pylori*, the higher risk persisted even if the pathogen had been eradicated[63]. Indeed, after either LRYGB[64] or laparoscopic sleeve gastrectomy[65,66], postsurgical lesions, mainly concerning gastric ulcers, are attributed to surgical procedures, and not to *H. pylori* infection. Moreover a recent retrospective study did not show any effect of *H. pylori* status, whether preoperatively positive or persistently positive after treatment, on the rates of marginal ulcer or stomal stenosis in patients undergoing LRYGB[67]. So far, high-quality evidence indicating the advantages of preoperative *H. pylori* screening and eradication is lacking and prospective well-designed RCTs are necessary to establish the real clinical outcomes of *H. pylori*-positive and -negative patients after surgery. It should also be considered that the gastric environment for *H. pylori* colonization may dramatically

change after bariatric surgery[50] with possible spontaneous clearance of infection[68].

If the management of *H. pylori* infection in obese patients who are candidates for bariatric surgery is still controversial, there are plausible reasons to attempt eradication in *H. pylori*-positive patients, particularly in those undergoing LRYGB in whom a large part of the stomach is inaccessible to upper endoscopy after surgery. First, eradication should decrease the risk of gastroduodenal peptic lesions in the gastrojejunostomy site after gastric bypass, and thus decrease early as well as later ulcer-related postoperative symptoms and complications, which are higher in *H. pylori*-positive patients[69]. Second, there is evidence of a moderate benefit of *H. pylori* on symptomatic dyspepsia[70,71]. Third, *H. pylori* is a class I carcinogen in the development of gastric cancer with an odds ratio of 2.0-5.9[72]. A recent systematic review[73] on upper gastrointestinal malignancy after bariatric surgery concluded that, even if the incidence were rare, it is advisable to screen patients before surgery because adenocarcinoma, strictly related to *H. pylori* infection, was present in most cases. In addition, the coexistence of *H. pylori* infection with obesity can potentiate the cytokine-mediated crosstalk between inflamed gastric and adipose tissues, augmenting immune responses at both sites, and thereby contributing to a pro-tumorigenic gastric microenvironment[74].

CONCLUSION

Available data on *H. pylori* infection and obesity are still controversial. Current guidelines do not indicate clearly the management of *H. pylori* infection in obese patients who are candidates for bariatric surgery, and the need for *H. pylori* screening and eradication before surgery is still debated. The eradication treatment is often hampered by the low eradication rates obtained with first-line 7-d treatment. Prospective clinical studies aimed to ameliorate both *H. pylori* eradication rates and to evaluate the clinical outcomes of *H. pylori* infection after the different bariatric procedures are warranted.

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