



Helicobacter Pylori Infection and its Relation to Bariatric Surgery Outcome among Slovenian Candidates for Bariatric Surgery

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Abstract

H. pylori infection represents a limiting factor in the access to bariatric surgery irrespective to the type of surgical procedure. Preoperative *H. pylori* screening and eradication is recommended to improve outcomes after bariatric surgery and to cure *H. pylori* related disease (gastric and extra gastric manifestations) and long term sequences of the infection. The impact of *H. pylori* in the pathophysiology of obesity, the role of infection in production and secretion of the orexigenic hormone ghrelin and subsequent clinical manifestations of *H. pylori* infection in obese population is still debated. Lower eradication rates with standard therapeutic regimens reported in obese patients than in the normal-weight population postpone bariatric surgery and related complications and is also to worse long term results. Improvement of eradication strategies and clinical approach is needed improve short and long term outcomes in bariatric surgery patients. Tailored regimen with dose adjustment to BMI might offer a proper clinical approach as presented in small retrospective clinical study.

Keywords: Obesity; Helicobacter pylori; Eradication

Introduction

Helicobacter pylori (*H. pylori*) (*HP*) is one of the most common human infections and it is estimated that more than half of the world population is infected [1]. Epidemiological studies show that *HP* 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 [2]. In low-income countries obesity is generally more prevalent among the better-off [3]; therefore clarifying the impact of these factors on *HP* infection in obesity remains to be elucidated.

The prevalence of *HP* infection in morbidly obese patients is still controversial. Candidates for bariatric surgery have a preoperative prevalence of *HP* ranging from 8.7% in a German cohort [4] to 85.5% in a Saudi cohort [5], with other series showing intermediate values [6]. *HP* is clearly associated with peptic ulcers; gastric mucosa-associated lymphoid tissue (MALT) and gastric cancer (GC) [7]. There have also been few

reported studies that have tried to link sleeve gastrectomy postoperative complications with *HP* infection [8,9]. Because of all these potential consequences, some experts recommend routinely checking for the bacteria and eradicating the infection before performance of bariatric surgery [10-12].

However, there is no clear indication about the preoperative *HP* screening and management in candidates for bariatric surgery. Therefore, the study's aims were

- To evaluate the prevalence of *HP* infection and the eradication rates,
- To evaluate clinical outcomes and postoperative complications regardless the type of Bariatric procedure used and
- To evaluate any influence of bacterial eradication on body weight among Slovenian candidates for bariatric surgery.

Materials and Methods

Participants

In our retrospective study from January 2014 to September 2015, 96 morbidly obese males (n=12) and female (n=84) with mean BMI of 46kg/m², aged from 28 to 57 years, preparing for bariatric surgery were reviewed. Exclusion criteria were: the use of drugs (non-steroidal anti-inflammatory (NSAIDs), anti-thrombogenic, prior proton pump inhibitor), patients with a history of gastric surgery, hemorrhagic disease, liver cirrhosis, end-stage renal disease requiring dialysis, severe heart failure with any symptoms and early or advanced gastric cancer, because these conditions can affect the mucosal appearance of the stomach [13-16]. Exclusion criteria were also BMI<35, upper gastrointestinal symptoms (dyspepsia, gastroesophageal reflux, dysphagia, melena or hematemesis), a history of *HP* infection and *HP* eradication therapy as well as allergy to esomeprazole, amoxicillin or metronidazole.

Basic demographic data, co-morbidities, medication taken, endoscopic, histopathologic and microbiologic findings of upper gastrointestinal endoscopy, length of hospitalization, operative complications (peri- and post) and percent excess weight loss (% EWL) one year after the procedure were obtained from the electronic medical records at the Clinical department of abdominal surgery. National cohort data of *Helicobacter pylori* infection prevalence in Slovenian population was used to compare bariatric patients group.

Preoperatively, patient's general status, mental condition and dietary habits were carried out by bariatrician, psychologist and dietitian; BIA was used to characterise Patients body composition, dietary counseling and OSA detection was mandatory for the cohort of patients included. Study design was explained to each patient before the initial assessment and written informed consent was given prior to participation. The trial protocol was approved by The National Medical Ethics Committee of the Republic of Slovenia.

Anthropometry and biochemical measurements Basic anthropometric characteristics

Were obtained using standardized techniques and equipment. Body mass index (BMI) was calculated as BW/BH² and classified as normal weight within 18.5 - 24.9 according to World Health Organisation recommendations for adults [17]. Following an overnight fast, venepuncture from the antecubital vein was drawn for analysing blood glucose and lipoprotein levels using standard methods.

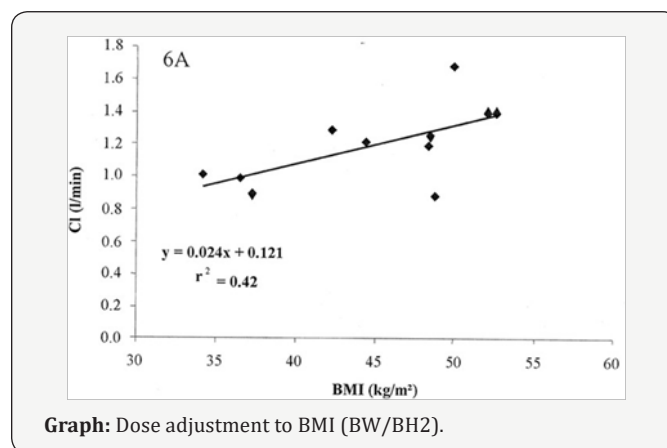
Diagnosis of *H. pylori* infection

Indication for upper gastrointestinal endoscopy was pre-bariatric surgery evaluation. Endoscopic assessment was performed by well-trained endoscopist using a high resolution video endoscope (Olympus, Optera gastrointestinal video scope). Each patient had three biopses taken; two from the antrum and

one from the gastric body for. All endoscopic data were saved into electronic endoscopic database. One biopsy of each patient was used for identifying the presence of urease enzyme in or on the gastric mucosa with rapid urease test (RUT, 65% sensitivity), while the other two were processed for hematoxylin-eosin and modified Giemsa staining and histopathologically examined for the presence of *HP* by an experienced pathologist (100% sensitivity). Positive endoscopically obtained biopsies were culture for *HP* bacteria and antibiotic susceptibility. All patients with a positive RUT received standard 7d treatment protocol just after EGDS with dose adjustment to BMI (esomeprazole 40mg mg every 12 hours, amoxicillin 1300mg every 12 hours and metronidazole 750mg every 12 hours) and RUT negative patients, positive in histology, 2 weeks later. Antibiotic schema prescription based to local antibiotic sensitivity to *HP*. Antibiotic dosage correction (adjustment) to BMI was used. Routine repeated upper gastrointestinal endoscopy was performed in all *HP* positive patients after 1 month free interval of standard 7d treatment protocol.

Dose adjustment to BMI (BW/BH²)

Standard antibiotic dose prescription was corrected to individual BMI (BW/BH²) based on Creatinin Clereance (CI) (l/min) in relation to BMI. One third elevation dose (30%) was prescribed to every 73 histologically positive Giemsa patients, of them to RUT positive patients in the 24 hours period and the next 3 late RUT positive patients in 48 hours period. To RUT negative and histology positive patients antibiotic prescription scheme was given in the period of two weeks followed EGDS (Graph 1).



Statistical Analysis

In total, 96 morbidly obese male (n=12) and female (n=84), mean age 36 years and mean BMI of 46 +/- 8,3kg/m² were enrolled. 87,5% of them were female and 12,5% were male. Histology as seen by positive Giemsa staining was positive in 76% of patients included (73 out of 96 patients). RUT turned positive within 10 minutes in 63% of all histology positive patients (60 out of 73 patients) and in the 24 hours period in 65% (63 out of 73) patients. All 73 (76%) of patients received

standard 7d treatment protocol (esomeprazole, amoxicillin and metronidazole) for *HP* eradication. In 2 of 96 patients (2,1%) *H. pylori* repeated, representing 2,7% of all *HP* positive patients. Antibiotic dosage correction to BMI was used, representing 30% elevation standard dose of antibiotic and same dose esomeprazole. Cultured biopsies due to the rapid emergence of antibiotic resistant strains of *H. Pylori* were performed due to constantly evolving process of antibiotic resistance presented in numerous studies. Data showed standard antibiotic susceptibility of *H. pylori* comparing to National Registry with data no positive for amoxicillin resistency and metronidazole in acceptable range of 29%. Same antibiotic treatment schema to non obese patients was prescribed in augmented dose to BMI.

Data analyses were conducted using SPSS Statistics showed higher incidence of *H. pylori* colonisation in observed morbidly obese patients compared to same aged slovenian population group (20y -49y) (73% vs. 29,5%, $p < 0,001$). Data also showed no any different susceptibility of *H. pylori* to antibiotic in observed group of morbidly obese patient to National data ($p < 0,0001$). Statistically important higher levels of lipoprotein level (dyslipidemia) in observed morbidly obese patients (19% vs 10%, $p < 0,0001$) compared to non obese population; all patients were negative to medication with tiazide diuretics, corticosteroids and beta blockers and comorbidity affecting lipoprotein level. Higher levels of blood sugar ranged from higher basal glicemia to type II diabetes mellitus were detected in morbidly obese patients group (35% vs. 6% in aged group from 20-79 y, respectively). Same aged group population have the incidence of class I obesity in the range of 40% population. Patient interview prior of the introduction of treatment scheme showed no data positive to appetite change, epigastric pain, reflux episodes, nausea, vomiting, feeling bloated and unexplained weight change in all patients. BIA revealed normal ranged lean body mass and elevated levels of fatty mass and water retention in observed group of morbidly obese patients ($p < 0,0001$) compared to general population.

Fatty mass distribution was positive to abdominal free fatty mass, abdominal wall deposits of fat and abdominal organ deposition. OSA was detected in 54, 7% of *H. pylori* positive patients, represented 41,6% of observed group of morbidly obese patients ($p < 0,0001$). Eradication rate was positive in 92% of patients with tailored protocol treatment with augmented doses to BMI (92% vs. 84,3% to standard dose protocol). Statistically important weight loss was observed in patient cohort prior bariatric surgery ranged between 8 -15 EWL%, statistically equal to *H. pylori* negative patients. Impotrant weight loss was observed after *H. pylori* eradication in observed group of patients. Excellent EWL% was observed ranged from 68 -88 % in one year period after bariatric procedure, equal to *H. pylori* negative patients. Comorbidities were improved in all patients ($p < 0,0001$) and improvement of basal glycemia was present in all patients with higher preoperative weight loss just before

surgery. In observed group of patients 2 early postoperative infection complications were treated with prolonged antibiotic profilaxis scheme (Cefamezine 3g each application per 8 hours). In prior preoperative *H. pylori* positive patient 2 postoperative complications were observed: in sleeve gastrectomy female, polimorbid patient, double protocol for *H. pylori* eradication Resection line leak day 16 postoperatively, treated conservatively with OVESCO clip placement and percutaneous drain positioning; and one-anastomosis by-pass female patient marginal ulcer perforation 7 mounth after surgery, treated with laparoscopic suturing and omentoplasty. Both patients were standardly treated for medical circumstances. At the time of postoperative complication both patients were *H. pylori* negative based on blood and stool antigen (Hp SA test). In 8 of 96 patients (8,3%) late moderate anemia was present despite feral supplementation (7 sleeve gastrectomy patient and on single anastomosis by-pass patient).

Discussion

Helicobacter pylori is the main cause of gastric cancer and MALT lymphoma in patients with genetic predisposition and therefore international treatment recommendations include gastric cancer 7, 23 (with an odds ratio of 2.0-5.9) prevention guidelines. In the field of bariatric and metabolic surgery exclusion surgical procedures might be a crucial factor in the prevalence of *H. pylori* related diseases and should be a leading factor to clarify indication about preoperative *H. pylori* screening and management.

European guidelines following Maastricht IV/ Florence Consensus Report 1, recommend 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 even more, postsurgical gastric malignancy, especially after bariatric procedures with gastric bypass. Routine upper endoscopy studies, to rule out pathological abnormalities (e.g., esophagitis, polyps, hiatal hernia, gastritis, and duodenitis), in concomitant to *H. pylori* colonisation rewall the incidence of 91%, higher that in conjunction to colonisation.

The majority of obese patients with upper gastrointestinal lesions at the time of routine preoperative endoscopy are asymptomatic, with only 20% of the obese patients with pathological findings presenting with upper gastrointestinal symptoms. On the other hand, alterations of the autonomic system leak visceral sensation in obese patients and those explain asymptomatic pathological situations might be misleading. Several studies also found a correlation with *H. pylori* and extra gastric manifestations [17], also positive in the population of obese and morbidly obese patients pre and post surgery [18] with clinical pathology of idiopathic trombocitopenic purpura, CagA-positive *H. pylori* infection in iron-deficiency anemia and ischemic heart disease. Data accumulating from epidemic studies

are also positive about the correlation to chronic idiopathic urticaria. *H. pylori* infection affects atherosclerosis and is associated with ischemic heart disease and stroke, reported by de Korwin [19] and this is also the priority investigation field. The ghrelin production in *H. pylori* positive patients is impaired but the correlation of hunger in these circumstances is not clear. Extragastric diseases in *H. pylori* positive patients remain controversial about the possible association: *H. pylori* infection may trigger direct extra gastric manifestations or indirectly. Various mechanisms might play a role, of them the release of inflammatory mediators, molecular mimicry including systemic immune response and atrophic gastritis [20]. Anti-*H. pylori* therapy improves iron- deficiency anemia, idiopathic thrombocytopenic purpura (significant increase of platelet count), and chronic urticaria (30% remission rate) [19]. There are limitations concerning the impact of eradication therapy to extra gastric manifestations and it would be of high importance to do randomized controlled trials to confirm these positive effects [19]. Even in obese patients who are candidates for bariatric surgery *H. pylori* resistance to antibiotic eradication, showed a significantly lower rate of eradication than controls, at least to the 7-d regimens. Delayed access to bariatric surgery can represent an important entity also to late postoperative results. Among possible factors influencing eradication risks BMI and sub therapeutic drug concentration are important. Higher BMI per se trigger delayed gastric emptying for physiological accommodation and also delay drug absorption that in correlation to higher adipose tissue accumulation trigger different volume drug distribution. Adipose tissue endocrine regulation might also alter mechanisms of drug distribution via cytokine release and augment local inflammatory response. The results of our study strongly suggest the tailored regimen for *H. pylori* eradication with respect to the correlation of creatinine clearance and BMI that suggest 30% antibiotic dose adjustment with eradication rate of 92%, statistically higher than non-tailored protocols. The adipose body was clearly presented in BIA, with average elevation between 65-72% to non obese population. Different fatty mass distribution in observed group was statistically important and also distribution pattern is associated to the incidence of OSA in patients with abdominal and thoracic wall distribution.

The next entity of adipose body load is also a pro-tumorigenic gastric microenvironment [21,22]. Also, fluid retention in obese, clearly presented by any type of technique for body composition calculation, affect drug volume distribution and subsequent dose inefficacy. Clearly, the need of tailored *H. pylori* eradication regimen for candidates of any bariatric surgery is important to reduce the prevalence of postsurgical lesions. The literature report clear evidence of reduced incidence of visceral perforation and marginal ulcer in patients being eradicated of *H. pylori* prior bariatric surgery to non-eradicated group [18,23]. Data also present higher risk persistency even that the *H. pylori* eradication protocol was performed preoperatively

[24] but to clarify the impact and correlation between *H. pylori* and a type of postoperative complications well- designed RCTs are obligatory. Low incidence of postoperative complications in our patient cohort with a complication rate of 2,2% related to sleeve gastrectomy leak and one- anastomosis gastric bypass perforation evidenced also the impact of other factors might be included not also active *H. pylori* colonization. The free period after treatment eradication protocol allow tissue regeneration and local environment improvement might be an important factor to reduce the rate of postoperative complications. Preoperative protocols also suggest a certain EWL% to improve metabolic improvement in order to glycemia, non-specific hyperlipidemia and glycemic control that all affect the incidence of postoperative complications, also being presented with the results of our study.

Conclusion

Our study evidenced the importance of tailored *H. pylori* eradication protocol prior bariatric and metabolic surgery procedures to improve eradication rate and to reduce the incidence of postoperative complication rate in mostly asymptomatic *H. pylori* positive candidates. Dose augmentation might be based to the relation of (BMIkg/m²) and creatinine clearance (l/min) as efficient in our study with high incidence of *H. pylori* candidates for bariatric surgery. A small cohort of observed patients suggests well-designed RCTs to validate the suggested approach and the impact to postoperative complication rate and improvement of strategies in bariatric candidates [25].

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Ethical Approval

Ethical standards of the institutional and/or national research committee were in accordance with the 1964 Helsinki declaration and its later amendments or comparable in all procedures performed in studies involving human participants. The study was approved by National Ethical Committee and Ethical Committee UMC Ljubljana.

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