Netherlands
The Journal of Medicine

REVIEW

Helicobacter pylori, obesity and gastro-oesophageal reflux disease

Is there a relation? A personal view

R.J.L.F. Loffeld

Department of Internal Medicine, Zaans Medical Centre, PO Box 210, 1500 EE Zaandam, the Netherlands, tel.: +31 (0)75-650 27 79, fax: +31 (0)75-650 23 79, e-mail: r.loffeld@chello.nl

ABSTRACT

The incidence and prevalence of gastro-oesophageal reflux disease is rising. Changing dietary habits and increasing body weight can be held responsible. In several studies a close relation was found between body weight and the occurrence of reflux disease. It may be concluded that there is a definite relation between body mass index and the occurrence of reflux disease. *H. pylori* probably also plays a role. *H. pylori* causes changes in fundic leptin levels and plasma levels of ghrelin. Eradication of *H. pylori* infection can increase appetite leading to a rise in body mass index due to a higher caloric intake. *H. pylori* can be a 'protective' factor against the development of overweight. Since only a minority of overweight or obese patients with gastro-oesophageal reflux disease will lose weight successfully, medical treatment with effective acid suppression will be the mainstay of the treatment of reflux disease in patients with a high body mass index.

KEYWORDS

Gastro-oesophageal reflux disease, ghrelin, *H. pylori*, leptin, obesity

INTRODUCTION

Gastro-oesophageal reflux disease is caused by reflux of stomach and duodenal contents into the oesophagus. Reflux can be the result of failure of the natural antireflux barrier between the gastric cardia and the oesophagus. The most important pathophysiological mechanism causing reflux is long-lasting spontaneous relaxation of the lower oesophageal sphincter (LOS) or low pressure in the LOS. A hiatus hernia is an additional risk factor. The incidence and prevalence of gastro-oesophageal reflux disease is rising, at least in the Western world. This will be accompanied by an increasing incidence of the complications of gastro-oesophageal reflux.[1,2]

The incidence of overweight and obesity has also been reported to be rising. It can be expected that complications due to overweight will also rise. Changing dietary habits and the increasing body weight may possibly induce reflux disease.

And finally, the incidence of *H. pylori* infection in the Western world has been decreasing for almost forty years. It has been reported that following eradication of *H. pylori*, reflux disease and/or an increase in body weight can develop. In the present paper the possible relations between *H. pylori*, obesity and reflux disease are discussed.

REFLUX DISEASE

Gastro-oesophageal reflux disease can present clinically in several ways. In most studies, patients are included who have reflux oesophagitis with or without symptoms, patients with an abnormal pH recording in the distal part of the oesophagus, or patients with symptoms without ever undergoing endoscopy. In addition, *H. pylori*-positive as well as *H. pylori*-negative patients, and patients who have had undergone successful anti-*H. pylori* therapy are included. Studies including only patients who have never had *H. pylori* are sparse.[3] Not every patient with the typical reflux symptoms actually suffers from reflux oesophagitis nor does every patient with reflux oesophagitis have reflux. In daily practice, the majority of patients with

more severe forms of reflux oesophagitis do not have reflux symptoms but merely complain of dysphagia.[4]

GASTRO-OESOPHAGEAL REFLUX DISEASE AND OBESITY

Increased intra-abdominal pressure plays an important role in the mechanism of reflux.[5] In several studies no relation was found between body weight and the occurrence of gastro-oesophageal reflux disease.[6,7] However, in recent years several studies have been published which show different results. Overweight and obesity go along with an important increase in the occurrence of gastro-oesophageal reflux.[8-10] Patients with overweight or obesity suffered more often from gastro-oesophageal reflux than controls with a normal body weight. The pressure in the LOS also appeared to be lower in patients with a higher body mass index.[11] Wilson and co-workers studied the relation of body mass index and the presence of a hiatus hernia and reflux oesophagitis.[12] A total of 1389 consecutive patients were studied. Oesophagitis was seen in 189 patients; the remainder were used as control group. Patients were divided in three groups according to body mass index: normal weight (BMI 20 to 25), overweight (BMI 25 to 30), and obesity (BMI >30). Reflux oesophagitis was more often present with a hiatus hernia and/or a higher body mass index. There was no difference between men and women or race. Body mass index was also an independent risk factor for development of a hiatus hernia.[12] A dose-effect relation was detected.[13] Murray and co-workers studied the relation of body weight and reflux symptoms in the Bristol *Helicobacter pylori* Project. Overweight was a risk factor for developing reflux, but obesity was an even higher risk. The severity of reflux symptoms correlated significantly with body weight.[14] The relation of body mass index and reflux was stronger in women, especially in premenopausal women.[13-15] Population-based studies showed that a higher body mass index is not only a risk factor for gastro-oesophageal reflux disease, but also for development of an adenocarcinoma in the oesophagus.[16,17] This relation is also present with carcinomas of the gastric cardia but not with squamous cell carcinoma of the oesophagus. El-Seraq and co-workers carried out logistic regression analysis in order to identify risk factors.[3] Overweight and obesity were independent risk factors for the more severe forms of reflux oesophagitis according to the Los Angeles classification.[3] The pressure in the LOS can be lower in patients with a higher body mass index, but there is no difference in manometric findings in the body of the oesophagus compared with patients with a normal body weight. Oesophageal peristalsis is normal.[18] Patients with gastro-oesophageal reflux disease often have intolerance for certain kinds of food. They tend to avoid these foods. Ingestion of food with excess in fat, especially animal fat and cholesterol, increase the risk for gastro-oesophageal reflux disease.[16] Food low in fat and high in fibre appears to have a protective effect. Obviously, a high body mass index is the result of a feeding pattern in which the intake of calories exceeds the daily needs. Despite this observation, fat and a high body mass index are independent risk factors for development of gastro-oesophageal reflux disease.[16]

H. PYLORI AND REFLUX DISEASE

Despite the fact that there is an ongoing discussion in the literature as to whether or not *H. pylori* protects against development of reflux disease and eradication causes reflux disease,[19-22] it is clear that *H. pylori* has definite effects on gastric acid production.[23,24] The effect depends on the distribution of the *H. pylori*-associated gastritis. Patients with an antral predominant gastritis have an elevated maximal stimulated acid production. Patients with a corpus predominant gastritis or a pangastritis have a lower acid production. With effective acid suppressive therapy a shift occurs from antral predominant gastritis to corpus predominant gastritis or pangastritis.[25,26] Patients included in clinical trials are not allowed to take acid suppressive drugs prior to inclusion. But the majority had already been treated with acid suppressive drugs in the past; naive patients are seldom included in trials. One can assume that the effects of acid suppressive therapy on the *H. pylori*-associated gastritis will not subside in a short period of time. Hence presence or absence of *H. pylori* can have a major effect on the results of studies evaluating gastro-oesophageal reflux disease. In duodenal ulcer disease, if *H. pylori* has been successfully eradicated, reflux oesophagitis has been reported to occur.[27] The patients who actually developed reflux oesophagitis also had a significant increase in body weight. The dietary habits must have changed, otherwise this weight gain would not have occurred!

H. PYLORI AND OBESITY

Recent research can explain the effect of *H. pylori* eradication on body weight.

Identification of ghrelin has revealed complex interactions in regulation of food intake.[28] Ghrelin is an important factor in appetite and satiety. Plasma ghrelin concentrations, gastric ghrelin mRNA, and ghrelin positive cell numbers in gastric mucosa are significantly lower in *H. pylori*-positive subjects.[29,30] However, this finding has not been invariably confirmed.[31] After successful eradication of *H. pylori* the number of ghrelin positive cells increases significantly irrespective of the presence of gastric atrophy.[30] This could lead to increased appetite and weight gain. Also, in an experimental study in which *H. pylori*

infection was induced, significant decrease in ghrelin mRNA levels and plasma ghrelin levels occurred.[32] Not only ghrelin levels increase after eradication, intra gastric acidity also increased by 14%.[33] This possible mechanism links *H. pylori*, obesity and reflux disease.

Leptin is another important hormone. Fasting and starvation decrease gastric leptin mRNA and protein level, and this fall produces a signal to eat. Hence, increased leptin signalling leads to decreased food intake and, in addition, to increased energy expenditure and increased thermogenesis.[34] Leptin is produced in the fundus of the stomach. Stretching of the fundus due to food intake probably leads to a decrease in fundic leptin, an increase in plasma level of leptin, and to a feeling of satiety. *H. pylori* infection significantly increases gastric leptin expression.[35] Eradication of *H. pylori* decreases gastric leptin expression. The plasma leptin levels do not change, but there is a significant decrease in immunoreactivity of leptin in mucosa of the fundus.[35] This decrease was accompanied by an increase in body mass index in the studied patients. Because the serum levels of leptin did not change, this weight gain must be due to a local effect in the fundus. The effects of *H. pylori* on ghrelin and leptin strongly suggest that the bacterium 'protects' against obesity. The decreasing incidence of this infection may be contributing to an increase in appetite and food intake.

CONCLUSION

From the presented data it can be appreciated that there is a certain relation between body mass index and reflux disease, *H. pylori* and reflux disease, and *H. pylori* and obesity. The exact relation and the consequences are not yet entirely clear. The primary cause of the rising body weight is the changes in lifestyle, at least in the Western world. The intake of fat and carbohydrates increases, while physical activity clearly decreases. It can be postulated that body weight can increase after eradication of the bacterium, and that reflux disease can develop in patients who had a *H. pylori*-associated pangastritis due to acid suppressive therapy. It can be postulated that *H. pylori* infection due to effects on leptin and ghrelin protects against intake of large amount of calories in these patients.

The prevalence of *H. pylori* infection is decreasing, possibly leading to a loss of this 'protective' factor. Young people in the Netherlands no longer acquire *H. pylori*. Is obesity in the youngsters in part caused by the lack of this 'protective' factor? Should *H. pylori* not be eradicated? Should the stomach be colonised by *H. pylori*? The bacterium is absolutely the cause of major morbidity. Weight gain, due to normalisation of ghrelin and leptin, after successful eradication can be controlled by dietary measures. Even if reflux disease does develop, than treatment with acid suppressive therapy is generally available.

The increasing body weight can be held responsible for at least a major part of the rising incidence of gastro-oesophageal reflux disease. Whether all these assumptions are true should be the goal of future studies.

REFERENCES

1. El-Serag HB. The epidemic of esophageal adenocarcinoma. Gastroenterol Clin North Am 2002;31:421-40.
2. Sonnenberg A. El-Serag HB. Clinical epidemiology and natural history of gastroesophageal reflux disease. Yale J Biol Med 1999;72:81-92.
3. El-Seraq HB, Johanson JF. Risk factors for the severity of erosive esophagitis in Helicobacter pylori-negative patients with gastroesophageal reflux disease. Scand J Gastroenterol 2002;37:899-904.
4. Werdmuller B, van der Putten ABMM, Loffeld RJLF. The presentation of gastroesophageal reflux disease: a prospective clinical and endoscopic study. Dis of the Esophagus 1996;9:285-9.
5. Sugerman HJ. Effects of increased intra-abdominal pressure in severe obesity. Surg Clin North Am 2001;81:1063-75.
6. Lundell L, Ruth M, Sandberg N, Bove-Nielson M. Does massive obesity promote abnormal gastroesophageal reflux? Dig Dis Sci 1995;40:1632-5.
7. Madisch A, Weihs C, Schlaud M, Heimann D, Meyer H, Hotz J. The body mass index (BMI) has no impact on the frequency of typical reflux symptoms- results of a nationwide telephone-based informing campaign in Germany. Zentrallbl Chir 2002;127:1064-7.
8. Fisher BL, Pennathur A, Mutnick JL, Little AG. Obesity correlates with gastroesophageal reflux. Dig Dis Sci 1999;44:2290-4.
9. Ruhl CE, Everhart JE. Overweight, but not high dietary fat intake, increases risk of gastroesophageal reflux disease hospitalization: the NHANES I epidemiologic follow-up study first national health and nutrition examination survey. Ann Epidemiol 1999;9:424-35.
10. Foster A, Richards WO, McDowell J, Laws HL, Clements RH. Gastrointestinal symptoms are more intense in morbidly obese patients. Surg Endosc 2003;19:23-6.
11. Iovino P, Agrisani L, Tremolatteria I, Nirchio E, Ciarella M, Borrelli V, Sabbatini F, Mazzzacca G, Ciacci C. Abnormal esophageal acid exposure is common in morbidly obese patients and improves after successful Lap-ban system implantation. Surg Endosc 2002;16:1631-5.
12. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol 1999; 94:2840-4.
13. Nilsson M, Johnson R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA 2003;290:66-72.
14. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. Int J Epidemiol 2003;32:645-50.
15. Nilsson M, Lundegardh G, Carling L, Ye W, Lagergren J. Body mass and reflux oesophagitis: an estrogen-dependent association? Scand J Gastroenterol 2002;37:626-30.
16. Mayne ST. Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinoma of esophagus and gastric cardia in humans. J Nutr 2002;132(11 suppl):3467-70.
17. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883-90.

18. Wajed SA, Streets CG, Bremner CG, DeMeester TR. Elevated body mass disrupts the barrier to gastroesophageal reflux. Arch Surg 2001;136:1014-8.
19. Loffeld RJ, van der Hulst RW. Helicobacter pylori and gastro-oesophageal reflux disease: association and clinical implications. To treat or not to treat with anti-H. pylori therapy. Scand J Gastroenterol suppl 2002;236:15-8.
20. Graham DY. Helicobacter pylori is not and never was 'protective' against anything, including GERD. Dig Dis Sci 2003;48:629-30.
21. Zentilin P, Liritano E, Vignale C et al. Helicobacter infection is not involved in the pathogenesis of either erosive or non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003;17:1057-64.
22. Cremonini F, Di Caro S, Delgado-Aros S et al. Meta-analysis: the relationship between Helicobacter pylori infection and gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003;18:279-899.
23. Moss SF, Calam J. Acid secretion and sensitivity to gastrin in patients with duodenal ulcer: effect of eradication of Helicobacter pylori. Gut 1993;34:888-92.
24. El-Omar E, Penman I, Darrion CA, Ardhill JS, McColl KEL. Eradicating Helicobacter pylori infection lowers gastrin mediated acid secretion by two thirds in patients with duodenal ulcer. Gut 1993;34:1060-5.
25. Sharma P. Helicobacter pylori: a debated factor in gastroesophageal reflux disease. Dig Dis 2001;19:127-33.
26. Sharma P, Vakil N. Review article: Helicobacter pylori and reflux disease. Aliment Pharmacol Ther 2003;17:297-305.
27. Labenz J, Blum AL, Bayerdorfer E, Meining A, Stolte M, Borsch G. Curing Helicobacter pylori infection in patients with duodenal ulcer may provoke reflux esophagitis. Gastroenterology 1997;112:1442-7.
28. Kojima M, Hosoda H, Kangawa K. Ghrelin, a novel growth-hormone-releasing and appetite-stimulating peptide hormone from stomach. Best Pract Clin Endocrinol Metab 2004;18:517-30.
29. Osawa H, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, Shiiya T, Satoh K, Ishino Y, Sugano K. Impaired production of gastric ghrelin an chronic gastritis associated with Helicobacter pylori. J Clin Endocrinol Metab 2005; 90(1):10-6.
30. Tatsuguchi A, Miyake K, Gudis K, Futagami S, Tsukiu T, Wada K, Fukuda Y, Sugisaki Y, Sakamoto C. Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. Am J Gastroenterol 2004;99:2121-7.
31. Gokcel A, Gumurdulu Y, Kayaselcuk F, Serin E, Ozer B, Ozsahin AK, Guvener N. Helicobacter pylori has no effect on plasma ghrelin levels. Eur J Endocrinol 2003;148:423-6.
32. Suzuki H, Masaoke T, Hosoda H, Ota T, Minegishi Y, Nomura S, Kangawa K, Ishii H. Helicobacter pylori infection modifies gastric and plasma ghrelin dynamics in Mongolian gerbils. Gut 2004;53:187-94.
33. Nwokolo U, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of Helicobacter pylori. Gut 2003;52:637-40.
34. Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. Neth J Med 2003;61:194-212.
35. Azuma T, Suto H, Oti Y, Ohtani M, Dojo M, Kuriyama M, Kato T. Gastric leptin and Helicobacter pylori infection. Gut 2001;49:324-9.