**Helicobacter pylori Infection and Circulating Ghrelin Levels- A Review**

Sakshi Bhutda a**, Yeshwant Lamture a, Meenakshi Yeola a, Pankaj Garde a and Tushar Nagtode a

a Department of Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, India.

**Authors’ contributions**

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

**Article Information**

DOI: 10.9734/JPRI/2021/v33i63B35906

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/81327

**ABSTRACT**

The correlation amidst Helicobacter pylori contamination & ghrelin levels flowing in the body is still an arguable subject. The enteric enteroendocrine system produces ghrelin, which is then octanoylated by, as of late, found ghrelin o-acyltransferase (GOAT) before being emitted into the circulatory system. Since ghrelin ties to the ghrelin neuroreceptor only after its acylation, this octanoylation is needed for a long time for ghrelin's natural components, like hunger incitement and calming characteristics (GHS-R). Given the site of ghrelin manufacture in the gut, it is expected that gastric mucosal injury impacts the flow of ghrelin levels among humans. H. pylori bacterium can contaminate > 50% of the world's citizens & can live for a lifetime once got rooted within the gastric mucosa. Chronic gastritis, stomach shrinkage, and ulceration, decreased appetite, and a decreased BMI are all connected to infection (BMI). The vast majority of research looking at flowing hunger hormone & ghrelin expression in the gut among patients with the contamination show that the bacteria inhibit ghrelin production and secretion. Ghrelin is restored once infection is eradicated, improving appetite and raising BMI. However, a causal association amidst H. pylori-related serum ghrelin reduction & edible consumption & fatness, and adiposity has yet to be shown in specific investigations. The majority of research looks at total ghrelin in the blood; however, the proportion of acyl/total hunger hormone may give a clear picture of how the acylated hunger hormone changes under the course of contamination & deterioration.

**Undergraduate Student;**  
**Dr.;**  
**Corresponding author: E-mail: Sakshibhutda0107@gmail.com;**
Keywords: Helicobacter pylori; ghrelin; gastritis; enteroreceptor.

1. INTRODUCTION

- **H. pylori: Bacterium**

H. pylori characteristics: GRAM -ve. Microaerophilic bacteria with helical structure. Natural colonization of the stomach lamina of individuals and nonhuman mammal. Not found in other animals. Prevalence – high; around 80% [1].

Studies show that the frequency of H. pylori +status depends on a variety of components, including aging, zone, lifestyle, the standard of living, and socioeconomic status [2]. The main route of H. pylori infection is speculated as oral-oral transmission. This helps to explain why the infection is so common among family members, such as parents and children. In this approach, it appears that sharing utensils during meals is vital for setting up an infection [3] Feco oral spread is a different way of contamination happens because of consume contaminated iterated water, primarily due to inadequate sanitation [4]. It’s also worth noting that rising socioeconomic position and bettering living conditions are both significant contributors to the decline in Helicobacter pylori contamination presence [5].

W. JR, M. B discovered Helicobacter pylori contamination in the abdomen, until then. Because of its high acidity, the gastrointestinal environment was thought to be germ-free [6,7,8].

The bacteria can use a variety of procedure to achieve successful colonization under such harsh conditions, including enhanced motility, a synthetic device that facilitates the development of a favorable environment during contamination maintenance as well as joining to epithelium [9,10,11]

Ghrelin is restored once infection is eradicated, improving appetite and raising BMI. However, a causal association amidst H. pylori-related serum ghrelin reduction & edible consumption & fatness, and adiposity has yet to be shown in certain investigations. The majority of research look at total ghrelin in the blood however, the proportion of acyl/total hunger hormone may give a clear picture of how the mechanism of acylated hunger hormone changes under course of contamination & deterioration.

Furthermore, body defense mechanism have an important part in the process of contamination and its progression, most likely through a T helper cell one feedback against the bacteria [12].

While almost Helicobacter pylori infections are not symptomatic, they increase the risk of developing illnesses such as peptic ulcers and stomach adenocarcinomas. As a result, competent clinical care, including a capable interpretation and successful treatment, are critical steps in improving a patient's clinical outcome [13,14].

Distinctive assortment of intrusive and non-obtrusive symptomatic techniques have been utilized to identify H. pylori and, in regards to treatment, bacterial obstruction addresses a significant test in contamination destruction [15].

- **Ghrelin**

LENOMORELIN, also known as hunger hormone is a twenty eight - amino corrosive gastric-obtained peptide. Ghrelin-delivering cells are a different gathering of endocrine cells found all through the gastric mucosa, as well as the small intestine and the endocrine pancreas to a lesser extent. Ghrelin levels in the blood increase during fasting and chronic calorific restriction to encourage food intake and fat storage while also preventing life-threatening blood glucose dips.

Ghrelin inhibits the proliferation of breast, lung, and thyroid cell lines, as well as protecting the gastric mucosa. Ghrelin accelerates stomach emptying and increases acid secretion in the gastrointestinal tract via vagal stimulation. Ghrelin levels fluctuate a lot depending on how much energy the body needs. Exogenous ghrelin has been shown to enormously decrease (NF)-B and plasma tumour necrosis factor activation [16].

- **The Gut- Brain Axis and Ghrelin**

The aquaphobic octanoyl moiety Esterhuysen to the 3rd serine remnant makes hunger hormone a twenty eight -aminoalkanoic -acid polypeptide autacoid. "Reverse pharmacology" was utilized to uncover ghrelin, which was previously thought to be an founding G protein-linked enteroreceptor but is now recognized as the
major ghrelin receptor, using the endogenous growth hormone secretagogue receptor (GHS-R). Following initiation of the GHS-R, it revealed that hunger hormone is a potent stimulant of GH production from mammalian somatotroph cells. It was discovered a fresh element of the somatotrophin for the first time. Phospholipase C, cAMP, and the nitric oxide/cGMP system are all involved in this activity.

The octanoylated mature hormone is released into the general body flow via the capillary networks of the gastric lamina propria. The stomach mucosa has the highest levels of ghrelin expression and secretion, whereas the pituitary and hypothalamus nuclei have the highest levels of GHS-R, leading to the theory that ghrelin and its receptor evolved to establish a connection.

The processes behind ghrelin's co- and post-translational alterations are only now beginning to be unraveled. The hydrophobicity imparted by acylation may allow ghrelin to pass the blood-brain barrier in both directions. This change also makes it easier for ghrelin to bind to the GHS-R, which is necessary for GHS-R-mediated ghrelin action. while the pancreatic may be the most prominent locus of expression in human tissues.

Moreover, it's tempting to think that paracrine GOAT expressing cells could acylate unacylated ghrelin produced from the stomach [17,18].

* Acylated Ghrelin is Not the Only Ghrelin

Several ghrelin isoforms, including the splice variant des-Gln14-ghrelin and the unmodified des-octanoyl or unacylated ghrelin, have been found ghrelin/GHS-R axis may be broadened to include them. Unacylated ghrelin cant join to & thus doesn't initiate the GHS-R, in spite among the majority of prevalent species of ghrelin in serum. Unacylated ghrelin, once assumed to be a by-product of bioactive ghrelin deterioration, speculated to be a vital hormone with a wide range of biological functions, including cardiovascular function, bone physiology, reproductive axis, and foetal growth [19]. These seemingly inverse biological features are most likely conclusion of alternate receptor activation, which supports the idea of anon-discovered non-GHS-R ghrelin receptor (s) [20,18].

* Ghrelin suppresses inflammation in rodent models of disease and in humans

Ghrelin and GHS-R are expressed in immune cells, and ghrelin/GHS-R activity and expression alter T cell function. Ghrelin antagonizes leptin in immune cells, just as it does in the hypothalamus. Human T cells activated by leptin produce more proinflammatory, anorectic cytokines like as IL-1, IL-6, and TNF, as well as enhanced GHS-R1a expression. In a dose-dependent manner, cotreatment with ghrelin suppresses leptin-induced cytokine levels. Ghrelin knockdown increases Th1 cytokine production and IL-17 secretion in primary human T cells, implying a function for autocrine/paracrine ghrelin in the endogenous control of pro-inflammatory cytokine production and secretion [21,22].

The number of studies confirming ghrelin's anti-inflammatory effect in vivo is quickly expanding, and includes animal models of pancreatitis and colitis. Downregulation of pro-inflammatory cytokines, inflammation-suppressing regulatory T cells, and elevated levels of the anti-inflammatory cytokine IL-10 have all been linked to ghrelin's therapeutic effect [23]. Ghrelin therapy also reduces pro-inflammatory cytokine production in brain and spinal cord resident macrophages (microglia), decreasing the severity of experimental autoimmune encephalomyelitis, a model of multiple sclerosis [24,18]. Ghrelin has been successfully used as an anti-inflammatory medication in cachexic individuals with persistent respiratory infection and inflammation in clinical trials. Ghrelin medication boosted body weight and dramatically reduced inflammation in the lungs in these individuals by decreasing neutrophil infiltration/accumulation and serum TNF-alpha [25].

* Synthesis of Data

The information gathered was divided in 3 categories:

1) Statistics analyzing flowing ghrelin concentrations in *H. pylori* +VE and -VE participants.
2) Statistics analyzing flowing ghrelin concentrations prior and post *H. pylori* removal.
3) Statistics evaluating among the gastric ghrelin characteristics.
Table 1. Research questions explored by the review

| Sr no. | Research questions : | Explanatory data : |
|--------|------------------------|--------------------|
| 1      | what is the link amidst helicobacter pylori & circulating ghrelin levels ? | Statistics analyzing flowing ghrelin concentrations in H. pylori +VE and -VE participants . |
| 2      | consequences of helicobacter elimination on flowing quantity of ghrelin in body ? | Statistics analyzing flowing ghrelin concentrations prior and post H. pylori removal . |
| 3      | what are consequences on gherlin levels in the gut due to helicobacter pylori infection ? | Data assessing any of the gastric ghrelin parameter |

2. DISCUSSION

- **Sources of Helicobacter Pylori and Ghrelin**

GHERLIN : Ghrelin is mostly generated by the stomach, with smaller amounts coming from the bowel, pituitary, kidney, placenta, hypothalamus, and pituitary, kidney, placenta, and hypothalamus [23,26].

The pancreatic islet's A-cells, the lung, and the kidney As a result, It's crucial to figure out which organ has the most influence variations in ghrelin levels in a variety of people illnesses. Despite the fact that the liver produces the majority of the circulating ghrelin. Additional sources of ghrelin secretion, such as those generated in the stomach, can enhance or reduce ghrelin secretion in a compensatory manner [27,28,29,30].

H. pylori infects more than half of the adult population on the planet. Atrophic gastritis and intestinal metaplasia are the earliest symptoms of H pylori infection, which can progress to dysplasia and gastric cancer. Thus, in case of H. pylori contagiousness influences gastric ghrelin synthesis & , as a result, plasma ghrelin collection is a fascinating subject [27].

- **Ghrelin and the Regulation of Glucose Homeostasis**

When injected into people, ghrelin causes an increment of plasma glucose & a decrement insulin levels. This coincided along the identification of the GHS-R in the pancreas islets . As a result, most research looking at the effects of ghrelin on GSIS have found that it inhibits it.

It's worth noting that the pancreas produces ghrelin, and ghrelin's influence on the endocrine pancreas could be via a paracrine mechanism. Endogenous ghrelin was found to increase insulin secretion when it was blocked, implying that ghrelin inhibits insulin production by acting directly on pancreatic -cells.

- **Relation Amidst BMI of Helicobacter pylori Infected Patients and Plasma Ghrelin Quantity**

Several investigations have demonstrated that flowing ghrelin is high among persons with anorexia nervosa. Decreased in adiposity, and normalized with increase in weight or decrease in weight , indicating that ghrelin has involvement in balance of energy on a long term basis . longitudinal and cross- sectional investigations of anorexia nervosa and obesity reveals strong link among flowing hunger hormone quantity in body and with body fat percentage, fat mass, BMI, body weight, insulin, leptin, and T3. The link amidst Body Mass Index & flowing ghrelin quantity in body was not strong in Helicobacter pylori contaminated participants. However this revealed that plasma ghrelin quantity is highly impacted by H. pylori infection [27,31,32,33,34,27,28,29].

- **Effects of the H. Pylori on Gastric Endocrine System**

Helicobacter pylori contamination is antrum predominant in the majority of infected people, and acidic content produced mainly by not affected corpus is increased, increasing the risk of duodenal ulcers. [35,29].

It was observed that Acid produced in the family members of patient with gastric cancer was lower in quantity compared to that of normal civilization , and that patients with antral predominant H. pylori infection and gastritis developed corpus predominant infection, the initial infection may start in the antrum and spread to the corpus among people in whom low basic acid is produced [36,37].
Hypochlorhydria allows other bacteria to infect you, which can increase the creation of carcinogenic (e.g. N-nitroso) chemicals [34]. Simultaneously, the amount of D cells making SST decrease in quantity. In the same way, some swine Helicobacter species change the no. of endocrine cells in the stomach lamina [40].

In chronic gastric inflammation and infection occurred due to Helicobacter pylori infection, have decreased control over the production of gastric juice, however the effect of helicobacter bacteria on endocrine system depends on the area of infection , or following influence of the endocrine system, like acid produced [38].

A few changes among these, such as an increment among no. of G cells, a decrement among no. of D cells, and specially an increment in the G/D cell proportion, have been linked to the formation of gastroesophageal ulcers in pigs [41].

**Consequences of Helicobacter pylori on Endocrine Cells**

Helicobacter pylori colonization causes dispersion of chemo attractants like IL-8, IL1, and TNF, which give signals to G cells, and the number of gastrin cells increases in Helicobacter pylori contaminated gastric lamina [39].

Because cells that produce hunger hormone are localized in stomach, it stands to reason that chronic gastritis and atrophy would impede hunger hormone manufacture , acylation, &/or emission , affecting hunger, weight, and BMI.

**Consequence of Helicobacter pylori on Circulating Ghrelin Levels**

Table 2. Total ghrelin levels

| Subject | Nationality | Sample type | Total Ghrelin in H. pylori patient | Reference |
|---------|-------------|-------------|-----------------------------------|-----------|
| 39 adults , F | Turkish | Plasma | INDISTINGUISHABLE | [43] |
| 256 adults , M | USA | Serum | INDISTINGUISHABLE | [44] |
| 85 children , F+ M | ITALIAN | Serum | INDISTINGUISHABLE | [45] |
| 196 adults , F | TAIWAIN | Plasma | INDISTINGUISHABLE | [46] |
| 63 adults , F+M | KOREAN | Plasma | INDISTINGUISHABLE | [47] |
| 41 adults , F+M | KOREAN | Plasma | INDISTINGUISHABLE | [48] |
| 50 adults , F+M | TURKISH | Plasma | INDISTINGUISHABLE | [49] |
| 110 adults , F+M | USA | Serum | INDISTINGUISHABLE | [50] |
| 24 adults , F+M | USA | Plasma | INDISTINGUISHABLE | [51] |
| 13 adults , F+M | _ | Serum | INDISTINGUISHABLE | [52] |
| 220 adults , F+M | Japanese | Plasma | DECREASED | [53] |
| 81 adults, F+M | Japanese | Plasma | DECREASED | [54] |
| 287 children , F+M | Poland | Serum | DECREASED | [55] |
| 160 adults , M | Japanese | Plasma | DECREASED | [56] |
| 145 adults , M | Taiwan | Plasma | DECREASED | [57] |
| 15 adults , F+M | Spain | Plasma | DECREASED | [58] |
| 62 adults , F+M | France | Plasma | DECREASED | [59] |
| 100 adults, F+M | Chinese | Plasma | DECREASED | [60] |
| 249 adults , F+M | Japanese | Plasma | DECREASED | [61] |
| 74 adults , F+M | Japanese | Plasma | DECREASED | [62] |
| 100 adult , F | Poland | Serum | DECREASED | [63] |
| 180 adult and children , F+M | Poland | Serum | DECREASED | [64] |
| 68 adults , F+M | Japanese | Plasma | DECREASED | [65] |
| 79 adults , F+M | Italian | Serum | DECREASED | [66] |
| 89 adults , F+M | Japanese | Plasma | DECREASED | [67] |
Table 3. Original studies measuring the effect of *H. Pylori* infection on plasma acyl and unacylated ghrelin levels

| Subjects | Nationality | Tissue | Acyl and total ghrelin in *H. pylori* infection or cure |
|----------|-------------|--------|--------------------------------------------------------|
| 69 adults F+M | Japanese | P | Decreased acyl ghrl in atrophy only [66] |
| 50 Adults F+M | Italian | P | Increased acyl ghrl and acyl/total ratio in atrophy cf. Healthy controls [67] |
| 220 Adults F+M | Japanese | P | Decreased acyl ghrl associated with atrophy and increased after cure [68] |

Some of the discrepancies in the literature about the effect of *H. pylori* infection on circulating ghrelin levels could be because of difference among people and civilization, illness severity (for ex, presence or absence of atrophy), and *Helicobacter pylori* strain dissimilarity [68]. This is further exacerbated by the fact that ghrelin is measured using a variety of immunoassays and that acylated ghrelin is not stable and deteriorate fast to unacylated ghrelin [42].

The best way to assess plasma ghrelin is a debated topic; some researchers believe that measuring total ghrelin accurately reflects activated ghrelin quantity & is an appropriate method. The majority of studies looking into the effects of *H. pylori* have only looked at total ghrelin levels, and the majority of these studies found that infection lowers plasma ghrelin levels. [Table 2 ].

However, a common thread running across these research is that abdominal epithelial cells degradation can lead to reduction in total plasma ghrelin & there is a negative link amidst plasma ghrelin quantity & atrophic seriousness and intensity in a subset of these investigations was found [52,67s].

Because acyl- and unacylated ghrelin have potentially different, even inverse biological effects, therefore proportion of changed to unchanged hunger hormone is critical. Few studies have taken this under notice in the background of *Helicobacter pylori* contamination , and those that have found inconsistent results. [Table 3 ].

The acylated ghrelin/total ghrelin proportion along with plasma acyl ghrelin levels are DECREASED in Japanese adults, whereas there is a notable rise in acyl ghrelin & the proportion of acylated ghrelin/total ghrelin in Western males, which the authors postulate may be because of an autogenous, balancing increase in the acylation mechanism as a result to a loss The degree of articulation and function of GOAT while *Helicobacter pylori* contamination, gastric infection and inflammation since long time, & degeneration of its mucosa would be a logical expansion of this research [67,66,69-70]

3. CONCLUSION

According to existing research, the concentration of circulating ghrelin in patients contaminated with *Helicobacter pylori* is DECREASED compared to those that are not contaminated with bacteria . Although , a more complicated connection between the amount of flow of ghrelin in the body and helicobacter elimination. The strain of infecting H pylori, the length of follow-up, the amount of H pylori-induced gastritis, and other underlying disease may all influence this connection. There is requirement of research is needed to fully understand the influence of Helicobacter. pylori eradication on circulating ghrelin levels.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Clyne M, Dolan B, Reeves EP. Bacterial factors that mediate colonization of the stomach and virulence of Helicobacter pylori. FEMS Microbiol Lett. 2007;268(2):135–43.

2. Prevalence of Helicobacter pylori infection worldwide: A systematic review of studies with national coverage- PubMed [Internet]. [Cited 2021 Aug 19]. Available: https://pubmed.ncbi.nlm.nih.gov/24563236/.

3. Role of infected grandmothers in transmission of Helicobacter pylori to children in a Japanese rural town- PubMed [Internet]. [Cited 2021 Aug 19]. Available: https://pubmed.ncbi.nlm.nih.gov/23560808/.

4. Goh KL, Chan WK, Shiot S, Yamaoka Y. Epidemiology of Helicobacter pylori infection and public health implications. Helicobacter. 2011;16 Suppl 1:1–9.

5. WL, FL, BI. Seroprevalence of Helicobacter pylori infection in Polish children and adults depending on socioeconomic status and living conditions. Advances in medical sciences [Internet]: 2014;59(1). [Cited 2021 Aug 19]. Available: https://pubmed.ncbi.nlm.nih.gov/24797992/.

6. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983;1(8336):1273–5.

7. Wroblewski LE, Peek RM. Helicobacter pylori, Cancer, and the Gastric Microbiota. Adv Exp Med Biol. 2016;908:393–408.

8. Boquet P, Ricci V. Intoxication strategy of Helicobacter pylori VacA toxin. Trends Microbiol. 2012;20(4):165–74.

9. Eaton KA, Morgan DR, Krakowska S. Motility as a factor in the colonisation of gnotobiotic piglets by Helicobacter pylori. J Med Microbiol. 1992;37(2):123–7.

10. Aim RA, Bina J, Andrews BM, Doig P, Hancock RE, Trust TJ. Comparative genomics of Helicobacter pylori: Analysis of the outer membrane protein families. Infect Immun. 2000;68(7):4155–68.

11. Camilo V, Sugiyama T, Touati E. Pathogenesis of Helicobacter pylori infection. Helicobacter. 2017;22 Suppl 1.

12. Bamford KB, Fan X, Crowe SE, Leary JF, Gourley WK, Luthra GK, et al. Lymphocytes in the human gastric mucosa during Helicobacter pylori have a T helper cell 1 phenotype. Gastroenterology. 1998;114(3):482–92.

13. Malfertheiner P, Venerito M, Schulz C. Helicobacter pylori infection: New facts in clinical management. Curr Treat Options Gastroenterol. 2018;16(4):605–15.

14. Abadi ATB, Kusters JG. Management of Helicobacter pylori infections. BMC Gastroenterol. 2016;16(1):94.

15. Safavi M, Sabourian R, Foroumadi A. Treatment of Helicobacter pylori infection: Current and future insights. World J Clin Cases. 2016;4(1):5–19.

16. Stec-Michalska K, Malicki S, Michalski B, Peczek L, Wisniewska-Jarosinska M, Nawrot B. Gastric ghrelin in relation to gender, stomach topography and Helicobacter pylori in dyspeptic patients. World J Gastroenterol. 2009;15(43):5409–17.

17. Kojima M, Kangawa K. Ghrelin: Structure and function. Physiol Rev. 2005;85(2):495–522.

18. Jeffery PL, McGuckin MA, Linden SK. Endocrine impact of Helicobacter pylori: Focus on ghrelin and ghrelin o-acyltransferase. World J Gastroenterol. 2011;17(10):1249–60.

19. Soares JB, Leite-Moreira AF. Ghrelin, des-acyl ghrelin and obestatin: Three pieces of the same puzzle. Peptides. 2008;29(7):1255–70.

20. Chen CY, Chao Y, Chang FY, Chien EJ, Lee SD, Doong ML. Intracisternal des-acyl ghrelin inhibits food intake and non-nutrient gastric emptying in conscious rats. Int J Mol Med. 2005;16(4):695–9.

21. Dixit VD, Schaaffer EM, Pyle RS, Collins GD, Sakhthivel SK, Palaniappan R, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest. 2004;114(1):57–66.

22. Dixit VD, Yang H, Cooper-Jenkins A, Giri BB, Patel K, Taub DD. Reduction of T cell-derived ghrelin enhances proinflammatory cytokine expression: Implications for age-associated increases in inflammation. Blood. 2009;113(21):5202–5.
23. Gonzalez-Rey E, Chorny A, Delgado M. Therapeutic action of ghrelin in a mouse model of colitis. Gastroenterology. 2006;130(6):1707–20.

24. Theil M-M, Miyake S, Mizuno M, Tomi C, Croxford JL, Hosoda H, et al. Suppression of experimental autoimmune encephalomyelitis by ghrelin. J Immunol. 2009;183(4):2859–66.

25. Kodama T, Ashitani J-I, Matsumoto N, Kangawa K, Nakazato M. Ghrelin treatment suppresses neutrophil-dominant inflammation in airways of patients with chronic respiratory infection. Pulm Pharmacol Ther. 2008;21(5):774–9.

26. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402(6762):656–60.

27. Osaka H. Ghrelin and Helicobacter pylori infection. World J Gastroenterol. 2008;14(41):6327–33.

28. Marshall BJ, Goodwin CS, Warren JR, Murray R, Blincow ED, Blackburn SJ, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of Campylobacter pylori. Lancet. 1988;2(8626–8627):1437–42.

29. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345(11):784–9.

30. Wotherspoon AC, Dogliani C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet. 1993;342(8871):575–7.

31. Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal MS, Tanaka M, et al. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab. 2002;87(1):240–4.

32. Tolle V, Kadem M, Bluet-Pajot M-T, Frere D, Foulon C, Bossu C, et al. Balance in ghrelin and leptin plasma levels in anorexia nervosa patients and constitutionally thin women. J Clin Endocrinol Metab. 2003;88(1):109–16.

33. Wu MS, Lee WJ, Wang HH, Huang SP, Lin JT. A case-control study of association of Helicobacter pylori infection with morbid obesity in Taiwan. Arch Intern Med. 2005;165(13):1552–5.

34. Furuta T, Shirai N, Xiao F, Takashima M, Hanai H. Effect of Helicobacter pylori infection and its eradication on nutrition. Aliment Pharmacol Ther. 2002;16(4):799–806.

35. Vakil N, Talley NJ, Stolte M, Sundin M, Junghard O, Bolling-Sternevald E. Patterns of gastritis and the effect of eradicating Helicobacter pylori on gastro-oesophageal reflux disease in Western patients with non-ulcer dyspepsia. Aliment Pharmacol Ther. 2006;24(1):55–63.

36. Imagawa S, Yoshihara M, Ito M, Yoshida S, Wada Y, Tatsugami M, et al. Evaluation of gastric cancer risk using topography of histological gastritis: A large-scaled cross-sectional study. Dig Dis Sci. 2008;53(7):1818–23.

37. Bordi C, Ravazzola M. Endocrine cells in the intestinal metaplasia of gastric mucosa. Am J Pathol. 1979;96(2):391–8.

38. Maciorowska E, Panasiuk A, Kondej-Muszyńska K, Kaczmarski M, Kemona A. Mucosal gastrin cells and serum gastrin levels in children with Helicobacter pylori infection. Adv Med Sci. 2006;51:137–41.

39. Dzierzanowska-Fangrat K, Michalkiewicz J, Cielecka-Kuszyk J, Nowak M, Celinska-Cedro D, Rozynek E, et al. Enhanced gastric IL-18 mRNA expression in Helicobacter pylori-infected children is associated with macrophage infiltration, IL-8, and IL-1 beta mRNA expression. Eur J Gastroenterol Hepatol. 2008;20(4):314–9.

40. Sapierzyński R, Fabisiak M, Kizerwetter-Swida M, Cywińska A. Effect of Helicobacter sp. infection on the number of antral gastric endocrine cells in swine. Pol J Vet Sci. 2007;10(2):65–70.

41. Xia F, Takashima M, Hanai H. Effect of Helicobacter pylori infection and its eradication on nutrition. Aliment Pharmacol Ther. 2002;16(4):799–806.
43. Gokcel A, Gumurdulu Y, Kayaselcuk F, Serin E, Ozer B, Ozsahin AK, et al. *Helicobacter pylori* has no effect on plasma ghrelin levels. *Eur J Endocrinol.* 2003;148(4):423–6.

44. Roper J, Francois F, Shue PL, Mourad MS, Pei Z, Olivaress de Perez AZ, et al. Leptin and ghrelin in relation to *Helicobacter pylori* status in adult males. *J Clin Endocrinol Metab.* 2008;93(6):2350–7.

45. Pacifio L, Anania C, Osborn JF, Ferrara E, Schiavo E, Bonamico M, et al. Long-term effects of *Helicobacter pylori* eradication on circulating ghrelin and leptin concentrations and body composition in prepubertal children. *Eur J Endocrinol.* 2008;158(3):323–32.

46. Chuang CH, Sheu BS, Yang HB, Lee SC, Kao AW, Cheng HC, et al. Gender difference of circulating ghrelin and leptin concentrations in chronic *Helicobacter pylori* infection. *Helicobacter.* 2009;14(1):54–60.

47. Jun DW, Lee OY, Lee YY, Choi HS, Kim TH, Yoon BC. Correlation between gastrointestinal symptoms and gastric leptin and ghrelin expression in patients with gastritis. *Dig Dis Sci.* 2007;52(10):2866–72.

48. Cindoruk M, Yetkin I, Deger SM, Karakan T, Kan E, Unal S. Influence of *H. pylori* on plasma ghrelin in patients without atrophic gastritis. *World J Gastroenterol.* 2007;13(10):1595–8.

49. de Martel C, Haggerty TD, Corley DA, Vogelman JH, Orentreich N, Parsonnet J. Serum ghrelin levels and risk of subsequent adenocarcinoma of the esophagus. *Am J Gastroenterol.* 2007;102(6):1166–72.

50. Shak JR, Roper J, Perez-Perez GI, Tseng C, Francois F, Gamagaris Z, et al. The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinoergic, and digestive hormones. *Obes Surg.* 2008;18(9):1089–96.

51. Uzzan B, Catheline J-M, Lagorce C, Airinei G, Bon C, Cohen R, et al. Expression of ghrelin in fundus is increased after gastric banding in morbidly obese patients. *Obes Surg.* 2007;17(9):1159–64.

52. Kawashima J, Ohno S, Sakurada T, Takabayashi H, Kudo M, Ro S, et al. Circulating acylated ghrelin level decreases in accordance with the extent of atrophic gastritis. *J Gastroenterol.* 2009;44(10):1046–54.

53. Isomoto H, Ueno H, Saenko VA, Mondal MS, Nishi Y, Kawano N, et al. Impact of *Helicobacter pylori* infection on gastric and plasma ghrelin dynamics in humans. *Am J Gastroenterol.* 2005 Aug;100(8):1711–20.

54. Plonka M, Bielanski W, Konturek SJ, Targosz A, Siwowski Z, Dobrzan ska M, et al. *Helicobacter pylori* infection and serum gastrin, ghrelin and leptin in children of Polish shepherds. *Dig Liver Dis.* 2006;38(2):91–7.

55. Osawa H, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, et al. Impaired production of gastric ghrelin in chronic gastritis associated with *Helicobacter pylori*. *J Clin Endocrinol Metab.* 2005;90(1):10–6.

56. Alonso N, Granada ML, Salinas I, Reverter JL, Flores L, Ojajunen I, et al. Plasma ghrelin concentrations in type 1 diabetic patients with autoimmune atrophic gastritis. *Eur J Endocrinol.* 2007;157(6):763–9.

57. Salles N, Ménard A, Georges A, Salzmann M, de Ledinghen V, de Mascarel A, et al. Effects of *Helicobacter pylori* infection on gut appetite peptide (leptin, ghrelin) expression in elderly inpatients. *J Gerontol A Biol Sci Med Sci.* 2005;60(11):A16180662/Available: https://pubmed.ncbi.nlm.nih.gov/16180662/[Cited 2021 Aug 29].

58. Isomoto H, Nishi Y, Ohnita K, Mizuta Y, Kohno S, Ueno H, et al. The Relationship between plasma and gastric ghrelin levels and strain diversity in *Helicobacter pylori* virulence. *Am J Gastroenterol.* 2005;100(6):1425–7.

59. *Helicobacter pylori* infected gastric mucosa--inflammation, atrophy and carcinogenesis - *PubMed* [Internet]. [Cited 2021 Aug 29]. Available: https://pubmed.ncbi.nlm.nih.gov/16180662/.

60. Czesnikiewicz-Guzik M, Bielanski W, Guzik TJ, Los ter B, Konturek SJ. *Helicobacter pylori* in the oral cavity and its implications for gastric infection, periodontal health, immunology and dyspepsia. *J Physiol Pharmacol.* 2005;56 Suppl 6:77–89.

61. Konturek PC, Czesnikiewicz-Guzik M, Bielanski W, Konturek SJ. Involvement of *Helicobacter pylori* infection in neuro-
hormonal control of food intake. J Physiol Pharmacol. 2006;57 Suppl 5:67–81.

63. Isoimoto H, Nakazato M, Ueno H, Date Y, Nishi Y, Mukae H, et al. Low plasma ghrelin levels in patients with Helicobacter pylori-associated gastritis. Am J Med. 2004;117(6):429–32.

64. D’Onghia V, Leoncini R, Carli R, Santoro A, Giglioni S, Sorbellini F, et al. Circulating gastrin and ghrelin levels in patients with colorectal cancer: Correlation with tumour stage, Helicobacter pylori infection and BMI. Biomed Pharmacother. 2007;61(2–3):137–41.

65. Isoimoto H, Ueno H, Nishi Y, Wen C-Y, Nakazato M, Kohno S. Impact of Helicobacter pylori infection on ghrelin and various neuroendocrine hormones in plasma. World J Gastroenterol. 2005;11(11):1644–8.

66. Suzuki H, Masaoka T, Hosoda H, Nomura S, Ohara T, Kangawa K, et al. Plasma ghrelin concentration correlates with the levels of serum pepsinogen I and pepsinogen I/II ratio—a possible novel and non-invasive marker for gastric atrophy. Hepatogastroenterology. 2004;51(59):1249–54.

67. Campana D, Nori F, Pagotto U, De Iasio R, Morselli-Labate AM, Pasquali R, et al. Plasma acylated ghrelin levels are higher in patients with chronic atrophic gastritis. Clin Endocrinol (Oxf). 2007;67(5):761–6.

68. Bajwa MA, Idrees M, Maheshwari PK. Association of dupA, iceA, homB genes of Helicobacter pylori with gastritis, peptic ulcer disease and gastric cancer. Journal of Pharmaceutical Research International. 2020;32(25):1-6. DOI: 10.9734/jpri/2020/v32i2530818

69. Khatib, Mahalaqua Nazli, Abhay Gaidhane, Shilpa Gaidhane, Zahiruddin Quazi Syed. Ghrelin as a promising therapeutic option for cancer cachexia. Cellular Physiology and Biochemistry 48, no. 2018;5:2172–88. Available:https://doi.org/10.1159/000492559

70. Khatib, Mahalaqua Nazli, Anuraj H Shankar, Richard Kirubakaran, Abhay Gaidhane, Shilpa Gaidhane, Padam Simkhada, Zahiruddin Quazi Syed. Ghrelin for the management of cachexia associated with cancer. Cochrane Database of Systematic Reviews. 2018;2. Available:https://doi.org/10.1002/14651858.CD012229.pub2