Ghrelin, *Helicobacter pylori* and Body Mass: Is There an Association?

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ABSTRACT: Eradication of *Helicobacter pylori* is accompanied by an array of metabolic and hormonal changes in the host. Weight gain following *H. pylori* eradication is a poorly understood phenomenon and probably results from an interaction between multiple factors. Ghrelin, a peptide hormone secreted by the stomach, is involved in the regulation of food intake and appetite and may account for some of these changes. Although several observational studies have demonstrated that *H. pylori* infection suppresses circulating ghrelin levels, it has yet to be proven that ghrelin levels increase following eradication. On the other hand, gastric expression of ghrelin, also suppressed by *H. pylori*, clearly increases following eradication. The determinants of plasma ghrelin levels remain elusive, as do the effects of eradication on these levels. Weight gain following *H. pylori* eradication may be attributable to changes in plasma and gastric ghrelin; however, this hypothesis needs to be further investigated.

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KEY WORDS: ghrelin, *Helicobacter pylori*, obesity, body mass index, eradication

Eradication of *Helicobacter pylori* has been associated with metabolic disturbances including weight gain [1-3]. Although *H. pylori* eradication increases gastric secretion of ghrelin [4], its precise effect on circulating ghrelin levels is not straightforward. Furthermore, a causal link between increased ghrelin and weight gain following *H. pylori* eradication is unproven.

ROLE OF GHRELIN IN ENDOCRINE DISORDERS AND OBESITY

Ghrelin is a 28-amino acid peptide produced primarily by the P/D1 cells of the gastric fundus. Its main target is the growth hormone secretagogue receptor. Ghrelin is central to energy balance and metabolism. Plasma ghrelin levels increase prior to meals and in the setting of starvation or cachexia. Ghrelin levels are reduced post-prandially and in subjects with obesity or insulin resistance [5]. Following gastric bypass the pre-prandial peak in ghrelin levels is not observed, probably a factor in aiding weight loss [6]. On the other hand, exogenous ghrelin administration causes increased growth hormone secretion and obesity [7]. Genomic variants of ghrelin and *GHSR* genes have been implicated in the pathophysiology of obesity. Altered ghrelin levels have been observed in Cushing's syndrome and thyroid disease probably due to the secondary insulin resistance in these subjects [8].

Weight gain following *H. pylori* eradication is a well-described phenomenon whose mechanism is poorly understood

EFFECT OF *H. PYLORI* ON BODY WEIGHT AND METABOLISM INDICES

A meta-analysis of 18 observational studies including 10,000 subjects found a higher body mass index among *H. pylori*-positive subjects compared with *H. pylori*-negative subjects. There are, however, no significant differences regarding other coronary risk facts, except, perhaps, high density lipoprotein, which is lower in infected subjects [9]. In a recent large randomized controlled study, Lane and co-workers [1] found a significant increase in body mass following eradication of *H. pylori* in a European population, a phenomenon previously observed in Asian populations [2,3]. Here, weight gain was largely attributed to the resolution of dyspepsia. Hyperlipidemia has also been shown to worsen following eradication of *H. pylori* [2,10].

EFFECT OF *H. PYLORI* INFECTION ON CIRCULATING GHRELIN LEVEL

Some 26 studies have compared plasma ghrelin levels between *H. pylori*-infected and non-infected subjects, with inconsistent results. A meta-analysis performed by Nweneka and Prentice [11] concluded that circulating ghrelin is significantly lower in *H. pylori*-positive subjects. Nevertheless, *H. pylori*-associated gastric ulcer is associated with high serum ghrelin [12]. Lowest plasma ghrelin levels are seen in gastric atrophy [13].

EFFECT OF *H. PYLORI* INFECTION OF GASTRIC GHRELIN ASSAYS

In addition to circulating plasma ghrelin, gastric ghrelin secretion may be quantified using various techniques. Direct assays of ghrelin levels in gastric fluid samples from *H. pylori*-infected and non-infected subjects have been compared, with highly variable results [14-18]. Similarly, comparisons of ghrelin radioimmunoassay in gastric biopsies from infected and non-infected subjects are inconsistent [15,19]. Ghrelin mRNA expression may be a more reliable method for assessment of gas-

tric ghrelin. In most studies, mRNA expression is lower among *H. pylori*-positive subjects [19-22]. Quantitative assessment of ghrelin immunoreactive cells consistently shows fewer ghrelin-producing cells in *H. pylori*-positive subjects [19,22-25], thus indicating that *H. pylori* infection suppresses ghrelin expression in the stomach. The number of ghrelin-producing cells in the stomach decreases proportionally to the severity of *H. pylori* gastritis [14,23,25].

EFFECT OF ERADICATION OF CIRCULATING GHRELIN AND GASTRIC SECRETION

Nwokolo et al. [26], in their study of 12 healthy subjects, were the first to observe a rise in circulating plasma ghrelin levels following eradication of *H. pylori*. Gokcel et al. [27] found no change in ghrelin levels in a larger study. Inconsistent results of subsequent in vivo and in vitro studies have added to the confusion in the field. Here, too, Nweneka and Prentice [11] performed a meta-analysis (n=592) that ultimately showed that *H. pylori* eradication does not have an effect on circulating ghrelin levels. Nevertheless, pre-eradication elevation of ghrelin may be a predictor of a fall in plasma levels post-eradication [11,22].

Ghrelin, a peptide hormone involved in the regulation of food intake, is suppressed by *H. pylori* infection. Following eradication therapy gastric secretion of ghrelin increases

Gastric ghrelin parameters have also been examined before and after eradication. Two studies demonstrated that *H. pylori* eradication increases ghrelin mRNA (including one randomized controlled study in which a control group did not receive eradication) [4,22]. Ghrelin immunoreactive cells also increase in number following *H. pylori* eradication [24]. Only radioimmunoassay of biopsy specimens failed to demonstrate a change in ghrelin expression following eradication [15].

The above discrepancy between circulating and gastric ghrelin levels may reflect the fact that the region of the stomach biopsied influences results. Following eradication, both fundic and corpus ghrelin may increase, while antral ghrelin probably decreases or remains unchanged [11]. Another possible explanation may be related to differing *H. pylori* strains. Patients with CagA+/VacA+ strains have lower circulating ghrelin levels compared to patients with less virulent *H. pylori* strains [28].

H. PYLORI ERADICATION, PLASMA GHRELIN, GASTRIC GHRELIN AND BODY MASS: A COMPLEX INTERACTION

It has been speculated that following *H. pylori* eradication, an increase in gastric ghrelin secretion leads to increased plasma ghrelin levels, resulting in obesity [24,26]. However, only one study has measured BMI, plasma ghrelin and gastric ghrelin expression before and after *H. pylori* eradication [29]. Here, mean plasma ghrelin levels *fell* following eradication therapy and were inversely correlated with body weight gain. Gastric ghrelin expression increased following eradication but did not correlate with BMI. This suggests that plasma ghrelin concentration more strongly influences body weight change than increases in gastric ghrelin, and that increased expression of preproghrelin mRNA in the stomach does not directly influence the total plasma ghrelin level. The discrepancy between gastric ghrelin expression and plasma ghrelin concentration may be reconciled by the presence of ghrelin isoforms which affect growth hormone secretagogue receptors differently [30]. Nevertheless, the regulation of gastric ghrelin secretion and the determinants of plasma ghrelin levels have yet to be elucidated.

OBESTATIN – A NOVEL HORMONE

Obestatin and ghrelin are derived from a common precursor, preproghrelin, yet obestatin exhibits opposite effects to those of ghrelin [31]. Obestatin antagonizes growth hormone secretion and reduces food intake. Its discovery in 2005 brought an additional layer of complexity to the understanding of the function of ghrelin. The ghrelin/obestatin balance may be a key factor determining an individual's response to *H. pylori* infection and weight gain following *H. pylori* eradication.

CONCLUSIONS

Although weight gain following *H. pylori* eradication has been demonstrated in numerous studies, the role of ghrelin in regulating this process is unclear. More studies are required to elucidate the determinants of plasma ghrelin levels and the complex interaction between factors that mediate weight gain following *H. pylori* eradication.

BMI = body mass index

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Capsule

Antibody based protection against HIV infection by vectored immunoprophylaxis

Despite tremendous efforts, development of an effective vaccine against human immunodeficiency virus (HIV) has proved an elusive goal. Recently, however, numerous antibodies have been identified that are capable of neutralizing most circulating HIV strains. These antibodies all exhibit an unusually high level of somatic mutation, presumably owing to extensive affinity maturation over the course of continuous exposure to an evolving antigen. Although substantial effort has focused on the design of immunogens capable of eliciting antibodies *de novo* that would target similar epitopes, it remains uncertain whether a conventional vaccine will be able to elicit analogues of the existing broadly neutralizing antibodies. As an alternative to immunization, vector-mediated gene transfer could be used to engineer secretion of the existing broadly neutralizing antibodies into the circulation. Balazs et al. describe a practical implementation of this approach, that they call vectored immunoprophylaxis (VIP), which in mice induces lifelong expression of these monoclonal antibodies at high concentrations from a single intramuscular injection. This is achieved using a specialized adeno-associated virus vector optimized for the production of full-length antibody from muscle tissue. The authors show that humanized mice receiving VIP appear to be fully protected from HIV infection, even when challenged intravenously with very high doses of replication-competent virus. These results suggest that successful translation of this approach to humans may produce effective prophylaxis against HIV.

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Eitan Israeli

"There is no exception to the rule that every rule has an exception"

James Thurber (1894-1961), American writer and cartoonist