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doi:10.3748/wjg.14.6327

World J Gastroenterol 2008 November 7; 14(41): 6327-6333
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

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Ghrelin and *Helicobacter pylori* infection

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Author contributions: Osawa H contributed to this work. Osawa H wrote the paper based on results of his own experience and recent literature sources (PubMed, ISI Web of Science) on ICP.
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Received: October 15, 2008 Revised: October 28, 2008
Accepted: November 2, 2008
Published online: November 7, 2008

Abstract

Ghrelin is primarily secreted from the stomach and has been implicated in the coordination of eating behavior and weight regulation. Ghrelin also plays an essential role in the mechanism of gastric mucosal defense. Thus, it is important to clarify which diseases primarily influence changes in plasma ghrelin concentrations. *Helicobacter pylori* (*H pylori*) infection is involved in the pathogenesis of gastritis, gastric and duodenal ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma. *H pylori* eradication is related to body weight change. Compared, *H pylori* infected and negative subjects with normal body mass index, plasma ghrelin concentration, gastric ghrelin mRNA, and the number of ghrelin producing cells in gastric mucosa are significantly lower in *H pylori* infected subjects than in *H pylori*-negative controls. Plasma ghrelin concentration decreases with the progression of gastric atrophy. Impaired gastric ghrelin production in association with atrophic gastritis induced by *H pylori* infection accounts for the decrease in plasma ghrelin concentration. However, the ratio of plasma acylated ghrelin to total ghrelin levels is higher in patients with chronic atrophic gastritis than in healthy subjects. This may result from the compensatory increase in plasma active ghrelin concentration in response to gastric atrophy. After *H pylori* eradication, gastric preproghrelin mRNA expression is increased nearly 4-fold in most cases. However, changes in plasma ghrelin concentrations before and after *H pylori* cure are not associated with the gastric ghrelin production. Plasma ghrelin changes are inversely correlated with both body weight change and initial plasma ghrelin levels.

Key words: Ghrelin; *Helicobacter pylori*; Eradication; Body weight; Leptin

Osawa H. Ghrelin and *Helicobacter pylori* infection. *World J Gastroenterol* 2008; 14(41): 6327-6333 Available from: URL: http://www.wjgnet.com/1007-9327/14/6327.asp DOI: http://dx.doi.org/10.3748/wjg.14.6327

INTRODUCTION

Ghrelin, a 28 amino acid peptide isolated from rat and human stomach, possesses strong growth hormone-releasing activity and plays central as well as peripheral roles in food intake, gastric motility, and acid secretion[1-3]. Ghrelin has been shown to evoke weight gain by actions in the hypothalamus[3]. Plasma ghrelin concentrations rise before meals and fall after meals. This peptide also contributes to the regulation of both somatic growth and adipose tissue mass, and is therefore, a short-term, meal-related orexigen as well as a long-term regulator of body weight[4,5]. Circulating ghrelin concentrations in newborns are not associated with gender, body weight, or hormonal parameter[6]. In children and adults, however, plasma ghrelin concentrations are lower in obese subjects compared with those with normal body weight and lean subjects[7]. The decrease of plasma ghrelin concentrations appears to compensate for the positive energy balance in obese individuals[7].

SOURCES OF GHRELIN AND *HELICOBACTER PYLORI* (*H PYLORI*) INFECTION

Ghrelin is predominantly produced by the stomach[8], whereas substantially lower amounts are derived from bowel[9], pituitary, kidney, placenta, hypothalamus[8], lung, kidney, and A-cells of the pancreatic islet. Thus, it is important to clarify which organ primarily influences changes in plasma ghrelin concentrations in various diseases. Although the majority of circulating ghrelin is produced in the stomach, other sources may increase or decrease ghrelin secretion in a compensatory manner. After gastrectomy, for example, plasma ghrelin level is

surprisingly reduced only by 65%[5].

The gastric ghrelin is produced in X/A like-cells of enteroendocrine cells/oxyntic glands in the mammalian gastric mucosa[9]. Thus, there exists the possibility that chronic persistent damage of the gastric mucosa, such as chronic gastritis, might affect ghrelin production, leading to changes in food intake and body weight. *H pylori* is a gram-negative bacterium that colonizes the stomach. *H pylori* infection is involved in the pathogenesis of gastritis, gastric and duodenal ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma[10-12]. More than 50% of the adult population is infected with *H pylori* worldwide. *H pylori* infection first leads to atrophic gastritis and intestinal metaplasia, which may further lead to dysplasia and gastric carcinoma. Thus, it is an intriguing question whether *H pylori* infection affects gastric ghrelin production and consequently alters plasma ghrelin concentration.

RELATIONSHIP BETWEEN PLASMA GHRELIN LEVELS AND BODY MASS INDEX IN *H PYLORI* INFECTED PATIENTS

In determining whether ghrelin is involved in long-term energy homeostasis, several studies have found that circulating ghrelin is elevated in individuals with anorexia nervosa[7], reduced in obesity[7,13,14] and normalized with weight gain[13] or weight loss. Circulating ghrelin levels are negatively correlated with the percentage of body fat, fat mass, body mass index (BMI), body weight, insulin, leptin, and T3 in cross-sectional and longitudinal studies examining anorexia nervosa and obesity. In *H pylori*-infected subjects, however, the correlation between BMI and circulating ghrelin levels was weak[15,16]. This suggested that *H pylori* infection could affect plasma ghrelin levels strongly.

EFFECT OF *H PYLORI* INFECTION ON PLASMA GHRELIN LEVELS

Several investigators reported the relationship between plasma ghrelin levels and *H pylori* infection. Nwokolo *et al*[17] reported that plasma ghrelin concentrations increased after the eradication of *H pylori*. On the contrary, Gokcel *et al*[18] reported that *H pylori* infection has no effect on plasma ghrelin levels. Although the relationship between *H pylori* infection and plasma ghrelin concentrations had been still controversial in Western countries, Japanese investigators revealed the effects of *H pylori* infection on plasma ghrelin concentrations[17,18]. The direct relationship between *H pylori* infection and gastric ghrelin production, which could influence plasma ghrelin concentrations, have been demonstrated. Osawa *et al*[19] and Tatsuguchi *et al*[16] investigated the association of *H pylori* infection with gastric ghrelin production in the human stomach concomitantly examining plasma ghrelin concentrations.

PLASMA GHRELIN CONCENTRATIONS ARE LOWER IN *H PYLORI*-POSITIVE SUBJECTS

Several investigators clarified the effect of *H pylori* infection on plasma ghrelin levels. Plasma ghrelin concentrations were significantly lower in *H pylori*-positive patients than in *H pylori*-negative controls[15,16,19]. Its level is obviously independent of sex and BMI and varied among *H pylori* infected subjects even with same BMI[15]. Mean plasma ghrelin levels in *H pylori*-positive subjects remain two-third of those of *H pylori*-negative subjects[19]. In addition to several clinical factors including BMI, food intake, and serum insulin levels[7,20], *H pylori* infection is also another determinant of plasma ghrelin levels as well as body mass index.

EXPRESSION LEVELS OF GASTRIC GHRELIN ARE LOWER IN *H PYLORI*-POSITIVE SUBJECTS

It is important to focus on the gastric mucosa in order to better understand the effects of *H pylori* infection on the alteration of ghrelin expression. Gastric ghrelin mRNA levels were much lower in *H pylori*-positive patients than in *H pylori*-negative controls using real-time quantitative RT-PCR[16,19]. The median of gastric ghrelin mRNA expression levels in *H pylori*-positive subjects was less than one 45th of that in *H pylori*-negative controls[19]. Moreover, plasma ghrelin concentrations were in parallel with the gastric ghrelin mRNA expression levels in *H pylori*-positive patients. Therefore, the attenuation of the ghrelin production in the gastric mucosa accounts for the decrease in the plasma ghrelin concentrations in *H pylori*-positive individuals[19].

GHRELIN-PRODUCING CELLS IN THE GASTRIC MUCOSA ARE FEWER IN *H PYLORI*-POSITIVE SUBJECTS

Ghrelin immuno-reactive cells are seen in the lower half of fundic epithelial glands[9]. Immunoreactivity is concentrated in the basal cytoplasm of the positive cells. The number of ghrelin-positive cells in the gastric mucosa of *H pylori*-positive individuals was significantly lower than those of *H pylori*-negative individuals[19]. Furthermore, the numbers of ghrelin-positive cells in the gastric mucosa fell significantly in accompaniment to the decrease in plasma ghrelin concentrations in *H pylori*-positive subjects[16,19]. These results reinforce the fact that the attenuation of the gastric ghrelin production caused by *H pylori* infection accounts for the decrease in the plasma ghrelin concentrations in *H pylori*-positive individuals.

PLASMA GHRELIN CONCENTRATIONS ARE ASSOCIATED WITH THE DEGREE OF GASTRIC ATROPHY IN *H PYLORI*-POSITIVE SUBJECTS

Since *H pylori* infection first induces gastric atrophy in its pathological course, it is important to clarify the association between plasma ghrelin concentration and degree of gastric atrophy in *H pylori*-positive patients. Several reports revealed that groups of *H pylori*-positive subjects with higher degrees of gastric atrophy tended to have lower plasma ghrelin concentrations, leading to a negative association between plasma ghrelin concentration and gastric atrophy grade[15,16,19]. Moreover, activity and topography of gastritis affects circulating ghrelin levels[21]. Histological severity of mononuclear cell infiltration and glandular atrophy of the corpus significantly influenced the expression levels of ghrelin mRNA, its peptide contents and the density of immunoreactive cells, indicating that gastric ghrelin biosynthesis seems to be affected by chronic mucosal inflammation and/or atrophy in association with *H pylori* infection. In addition, plasma ghrelin concentrations in *H pylori*-positive patients correlated with serum pepsinogen I concentration as well as pepsinogen I / Ⅱ ratio. Pepsinogen I and pepsinogen Ⅱ differ in their location in the stomach. Both are located in the chief and mucous neck cells of the oxyntic gland mucosa in the gastric corpus but only pepsinogen Ⅱ is present in the gastric antrum. A pepsinogen I / Ⅱ ratio < 3 is considered to be a reliable marker for severe atrophic gastritis[22]. Serum levels of pepsinogen I as well as the ratio of pepsinogen I / Ⅱ fell significantly as plasma ghrelin concentrations decreased, indicating the positive association between plasma ghrelin and pepsinogen I concentrations as well as pepsinogen I / Ⅱ ratios in *H pylori*-positive patients[19]. Collectively, these results reveal that plasma ghrelin concentrations are associated with the progression of gastric atrophy. Although geographical differences in the prevalence of atrophic gastritis in Asians and Westerners would require additional consideration, these findings strongly suggest that the reduction of ghrelin-producing cells in the gastric mucosa by *H pylori* infection results in the lower plasma ghrelin concentration in *H pylori*-positive patients.

Checchi *et al*[23] reported that serum ghrelin levels are negatively affected by autoimmune gastritis as well as by *H pylori* associated gastritis, and represent the most sensitive and specific noninvasive markers for selecting those patients at high risk for having gastric damage. Of particular interest is the fact that the measurement of serum ghrelin levels is superior to that of pepsinogen I / Ⅱ ratio and serum gastrin to predict gastric damage.

STOMACH REGULATES ENERGY BALANCE *VIA* ACYLATED GHRELIN AND DESACYLATED GHRELIN

It is known that ghrelin circulates in two different forms: the so-called acylated ghrelin, octanoylated, in serine 3, and the so-called desacylated, without the octanoyl group[24]. This latter form is dramatically less potent on the GHS-receptor than the acylated form[25]. Acylated ghrelin is involved in the regulation of GH secretion, energy balance, gastrointestinal motility, cardiac performance, and anxiety[8]. Administered acylated ghrelin induces body weight gain and adiposity by promoting food intake and decreasing fat use or energy expenditure[26]. In contrast to acylated ghrelin, desacylated ghrelin induces a negative energy balance by decreasing food intake and delaying gastric emptying[27]. The effect is mediated *via* the hypothalamus. Although derived from the same precursor, the inverse effects of these two peptides suggest that the stomach might be involved as an endocrine organ in the regulation of the energy balance.

PLASMA ACYLATED GHRELIN LEVELS ARE HIGHER IN PATIENTS WITH CHRONIC ATROPHIC GASTRITIS

Total plasma ghrelin concentrations decrease in patients with gastric atrophy secondary to *H pylori* infection, and the levels are related to the degree of atrophy. These finding might be explained by the loss of ghrelin-producing cells caused by inflammatory and/or atrophic changes. Campana *et al*[28] reported that plasma acylated ghrelin levels were higher in patients with chronic atrophic gastritis than in healthy subjects. This opposite tendency compared to total plasma ghrelin concentration may result from the compensatory increase in plasma active ghrelin concentration in response to gastric atrophy. This hypothesis seems to be supported by a recent report showing that a significant decrease in gastric pH was found after injection of exogenous ghrelin. Gastric atrophy causes an increase gastric pH, leading to an increase in serum gastrin levels. Both the increase in acylated ghrelin and gastrin could represent a compensatory mechanism to stimulate gastric acid production.

GHRELIN HAS A PROTECTIVE EFFECT AGAINST MUCOSAL INJURY OF STOMACH

H pylori infection induces gastric mucosal damage including gastric ulcer and chronic gastritis. It is an intriguing question whether lower plasma ghrelin level in *H pylori*-infected patients affects gastric mucosa. Sibilia *et al*[29] reported that ghrelin protects against ethanol-induced gastric ulcers in rats. Similarly, Konturek *et al*[30] reported that ghrelin expression of gastric mucosa is enhanced after exposure to ethanol, and ghrelin exhibits a strong gastroprotection due to its anti-inflammatory action mediated by prostaglandins. The gastroprotective effect of ghrelin is accompanied by a significant rise in the gastric blood flow, which is known to play an essential role in the mechanism of gastric mucosal defense. This ghrelin-induced hyperemia could be prob-

ably attributed to the direct vasodilatory effect of this peptide.

PLASMA GHRELIN LEVEL AND BODY WEIGHT

Eradication of *H pylori* has been a standard therapy for peptic ulcer disease[10,11] and improves gastritis[10]. Much attention has recently been directed to the relationship between obesity and *H pylori* infection. Several studies showed that *H pylori* infection is inversely related to obesity. For example, Wu *et al*[31] reported that the seropositivity of *H pylori* infection was significantly lower in morbid obesity patients. Furuta *et al*[32] showed the body weight gain after *H pylori* cure. As ghrelin is mainly synthesized and secreted by gastric mucosa, it has been assumed that the inverse effect of *H pylori* infection on body weight may attribute to the difference of plasma ghrelin concentrations in patients with or without *H pylori* infection[33]. This hypothesis states that an increase of gastric ghrelin production after *H pylori* cure may elevate plasma ghrelin concentration resulting in body weight gain.

PLASMA GHRELIN LEVELS AND BODY WEIGHT GAIN AFTER *H PYLORI* ERADICATION

Do plasma ghrelin levels affect body weight gain after *H pylori* eradication, or body weight gain affect plasma ghrelin levels? Gastric ghrelin production is decreased by *H pylori* infection and increased by eradication therapy[19]. As ghrelin is a body weight regulating peptide, much attention has been paid to the nutritional status and the dynamics of gastric and plasma ghrelin in response to *H pylori* infection[31,32]. In this respect, Nwokolo *et al*[17] reported that plasma ghrelin levels increased at 6 wk after *H pylori* cure in 10 patients in UK. Because plasma ghrelin levels increased significantly by 75%, they proposed that increased ghrelin following *H pylori* eradication may play a role in obesity. This could lead to increased appetite and weight gain, and contribute to the increasing obesity seen in Western populations where *H pylori* prevalence is low. Also, Czesnikiewicz-Guzik *et al*[34] reported that plasma ghrelin levels increased significantly to two-fold levels at 4 wk after *H pylori* cure in 41 patients in Poland. After Nwokolo's report, it has been believed that plasma ghrelin concentrations will increase after *H pylori* cure due to the increase of gastric ghrelin production, leading to body weight gain[16]. However, their reports suggested that plasma ghrelin levels increased, but did not reveal a changes of plasma ghrelin levels in patients with body weight gain after *H pylori* cure. Plasma ghrelin levels decrease as a compensatory effect in obesity patients who has positive energy balance. Therefore, it is questionable whether plasma ghrelin levels increase in a condition of body weight gain after eradication. Another study found that plasma ghrelin levels were unaffected[35]. In fact, plasma ghrelin concentration is not simply regulated by the levels of gastric ghrelin production. Even in healthy humans, plasma ghrelin concentration is tightly correlated with body weight[7]. Therefore, it has been proposed[36] that it should be re-examined whether the rise in plasma ghrelin following *H pylori* eradication exists and whether it can be an important determinant of body weight increase. It is possible that only a subpopulation of infected patients may show a rise in ghrelin following eradication.

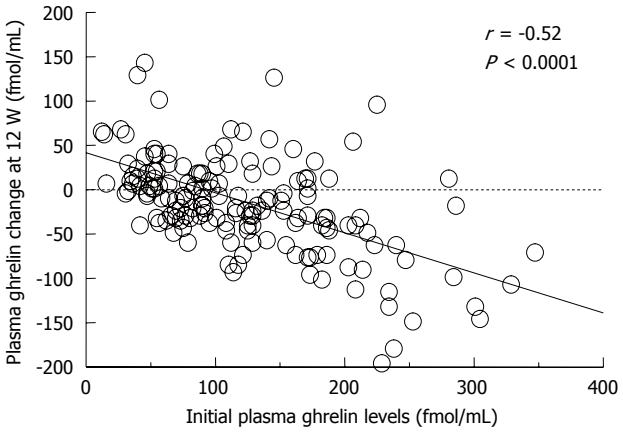

Figure 1 The relationship between the initial plasma ghrelin levels and the change in plasma ghrelin levels at 12 wk after *H pylori* cure. The change was obtained by subtracting the levels before the treatment from the levels at 12 wk after. The change in 12 wk correlated inversely with initial plasma ghrelin levels. This figure is cited from *J Gastroenterol* 2006; 41: 954.

DISPARATE CHANGES IN PLASMA GHRELIN AFTER *H PYLORI* CURE

The effect of *H pylori* eradication on plasma ghrelin concentration was reported in 134 Japanese patients[37]. Interestingly, mean plasma ghrelin concentrations decreased significantly from 120 fmol/mL before *H pylori* eradication to 103 fmol/mL at 12 wk after *H pylori* eradication. However, its levels after treatment changed diversely among enrolled patients. In fact, levels increased in 50 patients and decreased in 84 patients. There are some potential mechanisms leading to disparate changes in plasma ghrelin levels after *H pylori* eradication. The relationship between the initial plasma ghrelin levels and their changes were analyzed after *H pylori* cure. Figure 1 shows the relationship between the initial plasma ghrelin levels, and the changes in plasma ghrelin concentration at 12 wk after *H pylori* cure. Interestingly, higher initial plasma ghrelin levels decreased after the cure, but lower initial plasma ghrelin levels did not change significantly. The change of plasma ghrelin concentration after 12 wk was inversely correlated with the initial plasma ghrelin levels.

EXPRESSION LEVELS OF GASTRIC GHRELIN INCREASES AFTER *H PYLORI* CURE

The effect of *H pylori* eradication on the ghrelin pro-

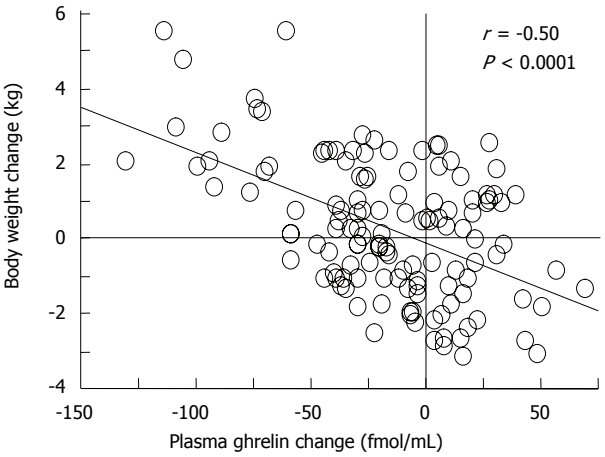

Figure 2 The relationship between the plasma ghrelin change and body weight change at 12 wk after *H pylori* cure. The alteration of plasma ghrelin levels correlated inversely with body weight change after *H pylori* cure. This figure is cited from *J Gastroenterol* 2006; 41: 954.

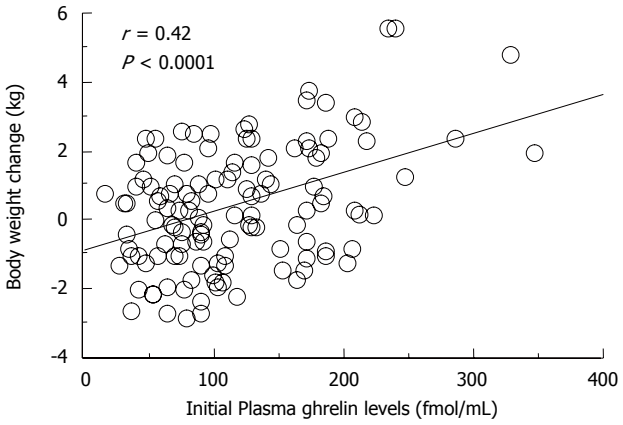

Figure 3 The relationship between the initial plasma ghrelin levels and body weight change at 12 wk after *H pylori* cure. Initial plasma ghrelin levels correlated positively with body weight changes. This figure is cited from *J Gastroenterol* 2006; 41: 954.

duction in the gastric mucosa was reported in several studies. Tatsuguchi *et al*[16] reported that ghrelin immunoreactive cells increase in the gastric mucosa after *H pylori* eradication irrespective of the recovery of glandular atrophy. Osawa *et al*[37] also reported that the number of ghrelin positive cells per oxyntic gland was increased in 77 patients and was unchanged in 57 patients after *H pylori* eradication. The number of ghrelin producing cells tend to increase despite the change of plasma ghrelin levels before and after *H pylori* cure. In recent reports, gastric glandular atrophy recovers gradually over the long term after *H pylori* eradication. Arkkila *et al*[38] reported that atrophy can diminish or even disappear, especially in the antrum, during a 1-year follow-up after eradication of infection. If glandular atrophy recovers by *H pylori* cure, the number of ghrelin producing cell may increase more and more. Osawa *et al*[37] compared gastric preproghrelin mRNA expression levels before and 12 wk after treatment using the corpus mucosa. Median preproghrelin mRNA expression was increased nearly 4-fold after *H pylori* cure. Preproghrelin mRNA expression was also increased in the antral mucosa. No correlation was observed between the changes in plasma ghrelin and those of gastric preproghrelin mRNA or ghrelin positive cells after *H pylori* cure. Similarly, Isomoto *et al*[21] reported that preproghrelin mRNA expression was increased in the corpus mucosa at 4 wk after *H pylori* cure. Therefore, gastric ghrelin production is enhanced after *H pylori* eradication even in patients with decreased plasma ghrelin concentrations.

BODY WEIGHT CHANGES CORRELATE INVERSELY WITH CHANGES IN PLASMA GHRELIN CONCENTRATION

Body weight gain is a well-known effect of *H pylori* eradication and plasma ghrelin concentration is influenced by body weight change[38,39]. The question as to whether ghrelin is involved in weight gain after *H pylori* cure has been discussed[19]. Figure 2 showed clearly that the change in plasma ghrelin is inversely correlated with body weight change after *H pylori* cure[37]. Plasma ghrelin decreased in 23 of 28 patients (82%) with more than 2 kg of weight gain, and in all 7 patients with more than 3 kg of weight gain. These data suggest that plasma ghrelin concentration after *H pylori* cure is more strongly influenced by body weight change than the increase of gastric preproghrelin mRNA and ghrelin producing cells.

In contrast, patients with less than 2 kg of body weight gain or with body weight loss had minor changes of plasma ghrelin levels. Increased plasma ghrelin levels after the cure in European studies can be associated with patients having minor change of body weight. The racial difference of enrolled subjects may account for the discrepancy. In this respect, Asians including Japanese are more prone to central adiposity than are white individuals[40]. As body fat storage is closely associated with plasma ghrelin levels, the racial difference of body fat distribution may account for the discrepancy.

INITIAL PLASMA GHRELIN LEVELS CAN BE A PREDICTIVE FACTOR OF BODY WEIGHT GAIN AFTER *H PYLORI* ERADICATION

Initial plasma ghrelin levels before eradication therapy were significantly higher in those whose plasma ghrelin decreased after treatment[37]. In addition, these subjects had a significantly greater increase in body weight than those with increased plasma ghrelin after treatment. Figure 3 shows the positive correlation between the initial plasma ghrelin levels and body weight changes. In particular, 12 of 14 patients (86%) with more than 200 fmol/mL of initial ghrelin levels had an increase in body weight, suggesting high levels of initial plasma ghrelin can be a predictive factor of body weight gain after *H pylori* eradication. The correlation between initial

plasma ghrelin levels and weight changes suggests the participation of ghrelin in the weight gain after *H pylori* eradication. The weight gain after *H pylori* eradication does not simply result from an increase in plasma ghrelin by the recovery of gastric ghrelin production.

However, additional research is needed to clarify the relationship between the body weight gain and the plasma ghrelin levels after *H pylori* cure in Western population.

CONCLUSION

Plasma ghrelin concentrations are influenced by the presence of chronic gastritis in association with *H pylori* infection. The decrease in gastric ghrelin production accounts for lower concentrations of plasma ghrelin in *H pylori*-positive individuals. Gastric ghrelin production increases after *H pylori* cure. Plasma ghrelin concentrations decrease in subjects with body weight gain after *H pylori* cure. Initial plasma ghrelin levels before eradication can be a predictive factor for body weight gain after *H pylori* cure.

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S- Editor Xiao LL **E- Editor** Ma WH