

Ghrelin in gastrointestinal diseases and disorders: A possible role in the pathophysiology and clinical implications (Review)

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Abstract. Ghrelin is a peptide hormone, which has been isolated from the stomach. It is localized mostly in endocrine cells in the oxyntic mucosa of the stomach. Ghrelin receptors are expressed equally in all parts of the gastrointestinal tract, with a similar level of expression in the mucosal and muscle layers. This peptide hormone has several functions, the most widely known is its growth hormone (GH)-releasing effect. Ghrelin plays an important role in regulating appetite, feeding and energy metabolism. It also plays a role in mediating immune response and inflammatory processes. Ghrelin stimulates gastric motility and emptying as well as motility in the small and large intestine. Ghrelin has been reported to be affected in several gastrointestinal diseases/disorders such as inflammatory bowel disease, coeliac disease, infectious diseases, functional disorders and diabetes gastroenteropathy. This indicates that ghrelin is involved in the pathophysiology of gastrointestinal diseases/disorders. Several studies have shown that ghrelin and its antagonist are a promising tool for treatment of several gastrointestinal diseases/disorders.

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1. Introduction

Ghrelin is a 28-amino acid peptide hormone, which has been isolated from the stomach (1). Ghrelin originates mostly from

endocrine cells in the oxyntic mucosa of the stomach, designated X/A, but small amounts of ghrelin were also found in both the small intestine and arcuated nucleus of the hypothalamus (1,2). Whereas ghrelin release seems to be increased by protein and fat ingestion, its release appears to be suppressed by carbohydrate ingestion (3). Ghrelin secretion in the stomach has been found to be modulated by both cholinergic and adrenergic arms of the autonomic nervous system (4). Ghrelin receptors are expressed equally in all parts of the gastrointestinal tract, with a similar level of expression in the mucosal and muscle layers (5).

Ghrelin has several functions, the best known is its growth hormone (GH)-releasing effect in the pituitary, where it acts synergistically with GH-releasing hormone (1,6). Ghrelin increases appetite and feeding, and plays a major role in energy metabolism and is one of the hormones that affects body composition (7,8). It also plays a role in mediating immune response and inflammatory processes (9,10). Furthermore, ghrelin seems to play an important role in regulating gastrointestinal motility. Thus, ghrelin stimulates gastric motility and emptying in mice, rats and humans (12-16). The stimulatory effects of ghrelin on gastric motility do not seem to be mediated via GH or motilin but by vagal nerve or directly on ghrelin receptors in the stomach (12). Moreover, this effect was described to be mediated by direct stimulation of the enteric neural pathway and capsaicin-sensitive afferent neurones (17). Ghrelin has also been reported to stimulate motility in the small and large intestine and shorten colonic transit time (18,19). In canines, however, ghrelin did not show any stimulatory effect on the fasted and fed motor activities in the stomach, duodenum, jejunum or colon (20).

Many gastrointestinal diseases and disorders exhibit gastrointestinal dysmotility and/or inflammation. As ghrelin seems to play an important role in gastrointestinal motility and immunology, the present review was undertaken in order to shed light on the possible role of ghrelin in the pathophysiology of gastrointestinal diseases and disorders and possible clinical implications.

2. Inflammatory and infectious gastrointestinal diseases

Serum ghrelin levels are significantly higher in patients with active ulcerative colitis (UC) and Crohn's disease (CD) than those in remission or controls (21-23). Circulating ghrelin levels in UC and CD patients were positively correlated with sedimentation, C-reactive protein and fibrinogen and negatively correlated with nutritional status parameters (23). It was

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concluded that ghrelin is important in determination of activity in inflammatory bowel diseases (IBD) patients and evaluation of nutritional status. Although this suggestion is attractive, there are simpler laboratory parameters that are currently used to evaluate the disease activity and the nutritional status of these patients.

Ghrelin has been reported to have potent anti-inflammatory properties through modulation of secretion of both pro- and anti-inflammatory cytokines from LPS stimulated macrophages through distinct cascades (10). It was suggested that ghrelin has therapeutic potential in controlling, modulating, or treating pathologic inflammatory conditions such as endotoxemic shock and UC. The therapeutic action of ghrelin was tested in a mouse model of colitis. In this animal model, ghrelin significantly ameliorated the clinical and histopathologic severity of the trinitrobenzene sulfonic acid-induced colitis. Thus, ghrelin treatment abrogates body weight loss, diarrhoea, inflammation and increases survival. The therapeutic effect is associated with down-regulation of both inflammatory and Th1-driven autoimmune response through the regulation of a wide spectrum of inflammatory mediators. In addition, a partial involvement of interleukin-10/transforming growth factor- β 1-secreting regulatory T cells in this therapeutic effect was demonstrated (9).

In children with coeliac disease, serum ghrelin was higher than those of controls and negatively correlated with body mass index (BMI). Ghrelin levels were lower after 6 months under a gluten-free diet compared with the levels detected on admission. Ghrelin levels were still higher compared with that of healthy children (24), though treatment with a life-long gluten-free diet caused a marked improvement or complete restoration of the intestinal mucosa. The incomplete restoring of ghrelin levels after a gluten-free diet are explained by the fact that nutritional deficiencies do not completely normalize and an increase in resting metabolic rate occur in patients with coeliac disease even after gluten-free diet treatment (25,26).

In adults with coeliac disease, ghrelin levels have been reported to be higher than control subjects and became normal, compared to controls after a gluten-free diet (27,28). It was reported, however, that circulating ghrelin levels were similar between 18 untreated adult women with coeliac disease and control subjects, but decreased after a gluten-free diet (29). Ghrelin cell density was found to be significantly reduced in adult patients with newly diagnosed coeliac disease (unpublished data).

It is unclear whether ghrelin levels correlate with intestinal mucosal lesion severity or not. Whereas Peracchi *et al* (27) reported that serum ghrelin levels correlated positively with intestinal mucosal lesion severity, Lanzini *et al* (28) could not confirm this observation. If the correlation between ghrelin levels and the severity of intestinal mucosal lesions in coeliac disease are proven true, that would be evidence of the involvement of ghrelin in the inflammatory process.

Whether circulating ghrelin levels in patients with autoimmune gastritis is affected is not clear. Whereas ghrelin serum levels were reported to be low, and to be the most sensitive and specific non-invasive marker for gastric body gastritis (30), ghrelin concentration decreased in patients with autoimmune atrophic gastritis and diabetes type 1 (31). In patients with chronic atrophic gastritis acetylated ghrelin

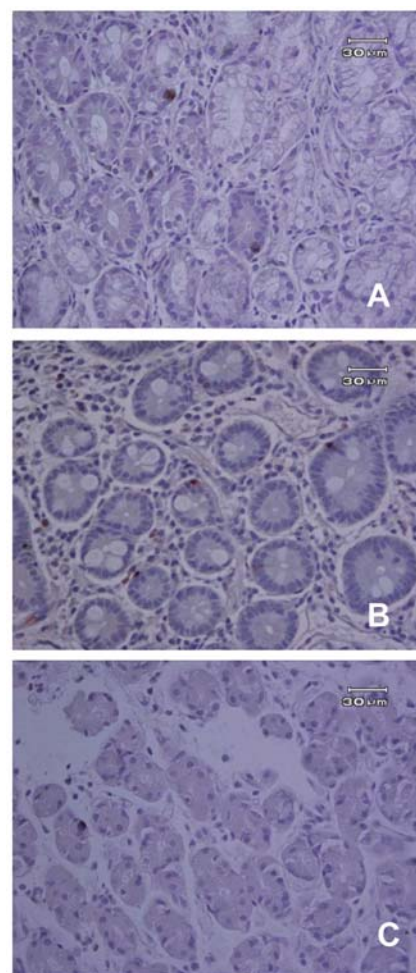


Figure 1. Ghrelin-immunoreactive cells in the oxyntic mucosa of a healthy subject (A), in a patient with IBS-diarrhoea (B) and in a patient with IBS-constipation (C).

levels increased in the gastric body and fundus. This finding was interpreted as an increase in acylating process as a compensatory process in response to gastric atrophy, a condition which causes a loss of ghrelin-producing cells and an increase in gastric pH (32).

Plasma ghrelin levels were reported to increase rapidly in response to *E. coli* endotoxin (33). On the other hand, ghrelin levels were found to fall in a state of acute inflammation brought about by injection of bacterial lipopolysaccharides (34). It was demonstrated further that the decrease in circulating ghrelin is not due to a decrease in ghrelin gene expression, but is instead likely to be due to an acute decrease in ghrelin secretion. The change in circulating ghrelin during acute inflammation required a prostaglandin second messenger, but did not require the synthesis of nitric oxide (34). It is interesting that IgG and IgA auto-antibodies against ghrelin were found in healthy women and that a sequence homology with ghrelin was identified among commercial and micro-organisms (35).

Helicobacter pylori infection is associated with a reduction in circulating ghrelin levels independent of sex and BMI. Ghrelin levels increased, however, 12 weeks after successful *H. pylori* eradication (36-38). The density of ghrelin-immunoreactive cells was lower in the oxyntic mucosa of patients infected with *H. pylori*. This decrease is associated

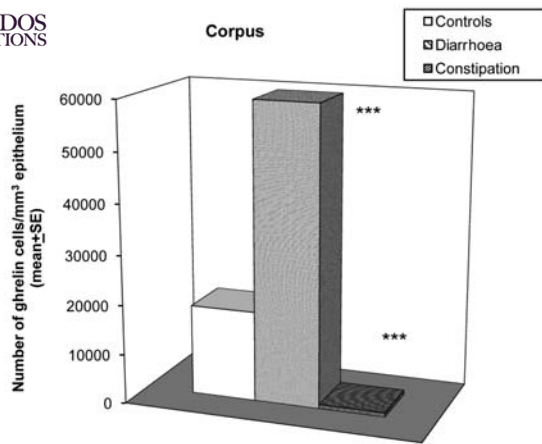


Figure 2. Ghrelin cell density in the oxytic mucosa of controls and patients with IBS.

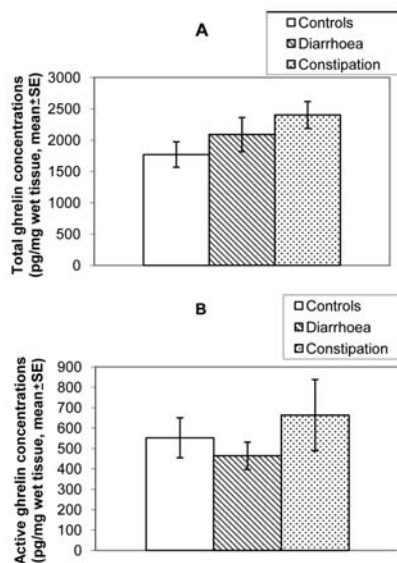


Figure 3. The concentration of total ghrelin (A) and active ghrelin (B) in tissue extracts of the oxytic mucosa of controls and patients with IBS.

with neutrophil activity, chronic inflammation and glandular atrophy induced by *H. pylori* infection (36,39). The low level of circulating ghrelin and low density of ghrelin cells in the oxytic mucosa is attributed to atrophic gastritis induced by *H. pylori* infection rather than to the infection process itself (36,40).

3. Functional gastrointestinal disorders

Serum ghrelin concentration has been reported to be significantly higher in dyspeptic patients than healthy controls (28,41). However, fasting desacyl and total ghrelin was found to be significantly lower in patients with functional dyspepsia of the dysmotility type than controls. On the other hand, total fasting ghrelin levels in these patients do not differ from postprandial levels in contrast to that found in controls. There is no association to the prolonged gastric emptying (42).

In irritable bowel syndrome (IBS) patients, ghrelin cell density in the oxytic mucosa has been reported to be significantly higher in IBS-diarrhoea and lower in IBS-

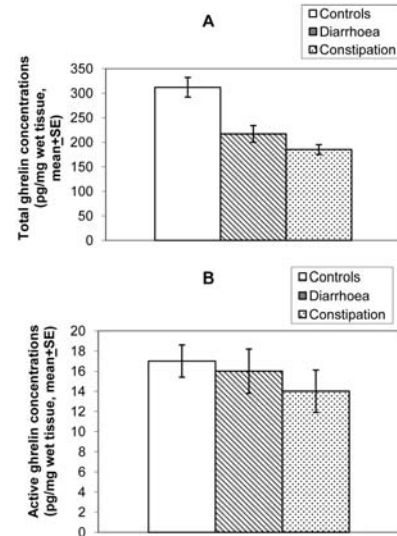


Figure 4. The total (A) and active (B) ghrelin concentration in tissue extracts of duodenal mucosa of controls and patients with IBS.

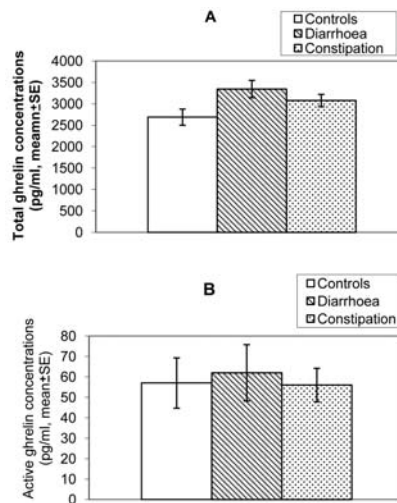


Figure 5. The levels of total ghrelin (A) and active ghrelin in the plasma of controls and in patients with IBS.

constipation patients than healthy controls (Fig. 1). The concentration of total or active ghrelin in oxytic mucosa and duodenum extracts as well as in plasma of these patients did not differ from that of controls (43) (Figs. 2-5). It was suggested that in order to compensate for the increase and decrease in the ghrelin cell density, the synthesis of ghrelin decreased and increased in IBS-diarrhoea and -constipation patients, respectively. They speculated further, that this compensatory mechanism is subjected to fatigue from time to time resulting in increased and decreased levels of ghrelin in IBS-diarrhoea and -constipation with a subsequent intermittent diarrhoea or constipation seen in these patients, respectively (43).

4. Diabetes gastroentropathy

Ghrelin cell density was decreased in the oxytic mucosa of pre-diabetic and diabetic subjects in an animal model for human diabetes type 1, NOD mice (44). In another experimental animal model of type 1 diabetes, streptozotocin-induced

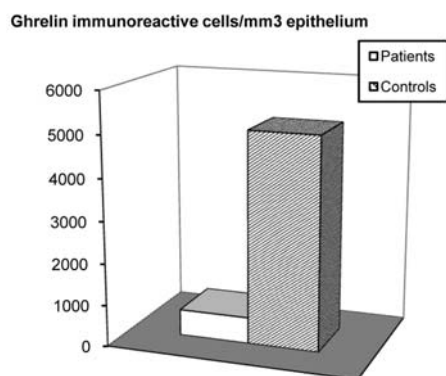


Figure 6. Ghrelin cell density in the oxyntic mucosa of controls and patients with diabetes type 1.

diabetes in rats, the concentration of ghrelin in the gastric mucosa was low and the ghrelin plasma level high (45). Similarly, the ghrelin cell density has been reported to be low in an animal model of human diabetes type 2, obese diabetic mice (44). In patients with diabetes type 1 ghrelin cell density was low in the oxyntic mucosa (Figs. 6 and 7). The ghrelin cell density in these patients correlates negatively with gastric emptying (46). Ghrelin promotes regeneration of β cells in streptozotocin-treated newborn rats (47).

Ghrelin injection given as a bolus dose at the end of a meal, accelerates gastric emptying in patients with diabetes and gastroparesis (48). In a randomised, double blinded, crossover study, intravenous infusion of ghrelin increased gastric emptying in patients with diabetic gastroparesis. This was independent of vagal tone (49).

5. Neoplasia

In patients with gastric cancer, ghrelin in the gastric mucosa is affected. Gastrectomy decreased the plasma level in these patients, regardless of the extent of gastric resection (50). Ghrelin serum levels were significantly lower in colon cancer patients than in healthy controls (51). On the other hand, Huang and co-workers (52) reported that plasma ghrelin levels did not increase significantly in cachectic gastric or colorectal cancer patients as compared with controls and were not correlated to the nutritional status.

Ghrelin immunoreactive cells have been found in gastric endocrine tumours and among the hyperplastic endocrine cells in the mucosa surrounding type I and II ECL-Ccs, where they showed diffuse, linear, nodular and adenomatoid patterns. Despite the frequent occurrence of ghrelin-immunoreactive cells in both the neoplastic parenchyma and oxyntic mucosa, plasma total ghrelin concentrations remained unchanged within the reference range and therefore cannot be used as a clinical marker to identify ghrelin expressing ECL-Ccs or ghrelin hyperplasia (53). Furthermore, ghrelin expression has been shown in 3 out of 12 neuroendocrine tumours of the gastrointestinal tract in patients with multiple endocrine neoplasia type 1 (54).

6. Bariatric surgery

In recent years, bariatric surgery tended to design procedures aiming at neuroendocrine changes instead of restriction and

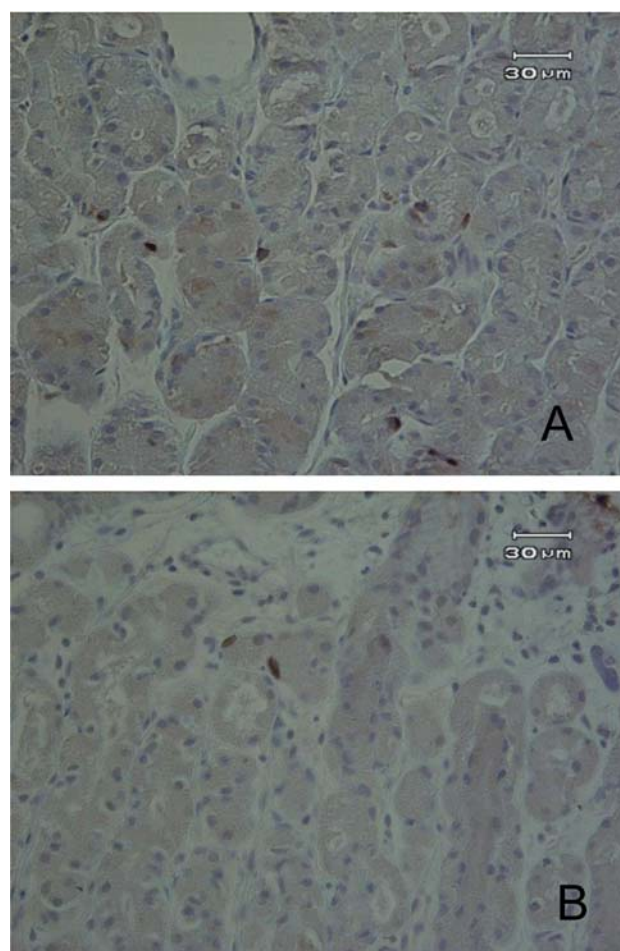


Figure 7. Ghrelin-immunoreactive cells in the oxyntic mucosa of a healthy subject (A) and in a patient with diabetes type 1 (B).

malabsorption. Since ghrelin plays an important role in regulating appetite, feeding and energy metabolism, different bariatric procedures have been evaluated with regard to this hormone.

Following Roux-Y gastric bypass, the plasma level of deacyl-ghrelin increases in non-diabetic obese patients, but not in diabetic patients (55-57). Patients operated by Roux-en-Y gastric bypass show an early and greater postprandial suppression of ghrelin level than patients operated by gastric banding (58).

The density of ghrelin-immunoreactive cells was reported to decrease 1 year following gastric banding in morbidly obese patients (59). Laparoscopic adjustable gastric banding leads to a decrease in fasting plasma ghrelin and is accompanied by a decrease of hunger (60). Unlike reducing diet or gastric bypass, following biliopancreatic diversion only an initial reduction of serum ghrelin concentration has been observed. Two months following biliopancreatic diversion, when food had nearly completely resumed, the value returned to the preoperative levels (61).

As a consequence of resection of gastric fundus, the prominent area of human ghrelin production, ghrelin is significantly reduced after laparoscopic sleeve gastrectomy but not after laparoscopic adjustable gastric banding. The reduction remains stable at follow-up for 6 months post-



ly, which may contribute to the superior weight loss compared with adjustable gastric banding (62). Following the digestive adaptation procedure, fasting ghrelin was found to be significantly reduced and diabetes to be improved. A five-year followup of patients operated with this procedure did not disclose either diarrhoea or malabsorption (63).

7. Conclusion

Ghrelin seems to be affected in several gastrointestinal diseases/disorders, indicating that this peptide hormone is involved in the pathophysiology of these diseases/disorders. Several studies have shown that treatment with ghrelin is effective in diabetes and idiopathic gastroparesis (64) as well as in colitis. Ghrelin and its antagonists appear therefore to be a promising tool in the treatment of gastrointestinal diseases/disorders.

Acknowledgements

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