REVIEW ARTICLE

Gastrointestinal motility disorders in endocrine diseases

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ABSTRACT

Endocrine diseases may have systemic involvement. The aim of this paper is to review gastrointestinal and motility dysfunction in endocrine diseases. We review motility disturbances in thyroid disorders, acromegaly, Cushing syndrome, neurohypophysis disorders, diabetes, parathyroid diseases, and multiple endocrine neoplasia, with emphasis placed on the correlation with the blood levels of gastrointestinal hormones that may interfere with the brain-gut axis at various levels.

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Introduction   The motility of the digestive tract is regulated by the autonomic nervous system, enteric nervous system, and endocrine system.[1] Gut hormones, but also hormones delivered by nondigestive organs, are able to modulate gastrointestinal motility. A number of digestive symptoms related to gastrointestinal motility dysfunctions have been reported in endocrine disorders.[2] Other motility disorders are clinically latent but able to induce pathogenic changes.

The complex interactions between the central nervous system, hypothalamus, pituitary gland, autonomic nervous system, and enteroendocrine cells affect appetite and energy balance, regulate food intake, and influence gastrointestinal motility and digestive secretions.[3] Gastrointestinal hormones responsible for modulation of these functions include ghrelin, motilin, cholecystokinin, peptide YY, glucagon-like 1 peptide, pancreatic peptide, amylin, and apolipoprotein A-IV.[4-6] Some of these hormones influence the secretion of other hormones such as growth hormone, prolactin, adrenocorticotropic hormone (ACTH), or gonadotropins.[7,8]

Thyroid disorders   Altered intestinal motility and transit time are the main presentations of gastrointestinal motor dysfunction in thyroid disease.[9]

Hyperthyroidism   Patients with hyperthyroidism may experience diarrhea, steatorrhea, malabsorption, and dyspeptic symptoms. The frequency of these symptoms varies between 30% and 50%. Less often reported are vomiting[10] and dysphagia.[11]

Possible causes of dysphagia in thyrotoxicosis are neuromuscular dysfunctions,[12] thyrotoxic hypokalemic periodic paralysis,[13] and myasthenia gravis. Excess thyroid hormones may cause myopathy, which involves striated muscles of the pharynx and the upper part of the esophagus, responding well to early intensive treatment that includes antithyroid agents, β-adrenergic antagonist, and Lugol solution. Excess thyroid hormones increase the propagation velocity of contraction in the esophagus.[14]

Patients with hyperthyroidism frequently complain of epigastric pain, fullness, eructation, nausea, and vomiting,[2] dyspeptic symptoms being correlated to the activity of thyroid disease.[15] Up to 25% of patients with hyperthyroidism have mild-to-moderate diarrhea with frequent bowel movements. Intestinal hypermotility reduces small-bowel transit time.[9] Anorectal physiology is also impaired in hyperthyroidism when compared with controls; mean anal resting and squeeze pressures are lower, as is the rectal threshold of sensation to intrarectal distension.[16]

Thyrotoxicosis is characterized by severe sympathovagal imbalance, caused by sympathetic activity in the presence of diminished vagal tone.[17] An increase in β-adrenergic activity may be in part responsible for persistent vomiting observed

in some patients with thyrotoxicosis, because β-adrenergic antagonists improve the digestive symptoms.[10]

To explain the pathogenesis of dyspeptic symptoms, motility disorders have been studied using electrogastrographic, scintigraphic, and ultrasonographic methods.

Altered gastric myoelectrical activity of the type of postprandial tachygastria has been documented by electrogastrography in hyperthyroid patients with dyspeptic symptoms.[15] Barczyński and Thor[18] studied 50 patients with hyperthyroidism by simultaneous electrogastrography measurements and ultrasound assessment of gastric emptying and concluded that the decrease of vagal influence was expressed by impaired gastric myoelectrical activity, followed by a delay in gastric emptying.[18]

Other studies using scintigraphic techniques did not find impaired gastric emptying in hyperthyroid patients.[9,19] In the study by Pfaffenbach et al.,[15] the lack of correlation of impaired gastric myoelectrical activity with gastric emptying may suggest other mechanisms for these symptoms, such as smooth muscle disorders, electromechanical dissociation, incoordination of the antrum and duodenum caused by unbalanced local gastrointestinal hormones (e.g., ghrelin or gastrin). These local hormones may influence the afferent pathway of the brain-gut axis and thus modulate the motility in the gastrointestinal tract. There is growing evidence that ghrelin may affect gastrointestinal motility via specific receptors located on the myenteric, vagal, and central neurons.[20] Ghrelin accelerates gastric emptying and induces phase 3 of the migrating motor complex, acts on motor neurons in the myenteric plexus, activates a vago-vagal reflex, and stimulates central pathways.[20] The gastric motility disturbances observed in hyperthyroid patients are not modulated directly by plasma ghrelin levels,[21,22] but rather by gastric mucosal ghrelin levels. In an experimental study, increased gastric mucosal ghrelin immunoreactivity was observed in rats with hyperthyroidism, suggesting that mucosal gastric ghrelin may influence the myoelectrical alterations. Hypergastrinemia may also influence gastric and intestinal motility.[23] There is no evidence for motilin plasma disturbances in hyperthyroidism.[24] The complex interactions between mucosal gastrointestinal hormones and the brain-gut axis need further studies to explain digestive symptoms in hyperthyroidism.

Hypothyroidism　In hypothyroidism, decreased metabolic functions are also expressed in the gastrointestinal tract, most frequently by slugging intestinal motility, ranging from mild constipation to paralytic ileus and colonic pseudo-constipation.[25]

In severe cases, patients may experience oropharyngeal dysphagia caused by myxedema, but also distal dysphagia determined by reduced velocity and amplitude of esophageal peristalsis

and a decrease in lower esophageal sphincter pressure.[26] Using radioisotopic measurement, gastric emptying time of hypothyroid patients was significantly increased compared with controls,[27,28] explaining dyspeptic symptoms.[29] The pathogenesis of the gastric dysmotility is not fully understood. A number of theories have been proposed: deceleration of myoelectrical activity as shown in an electrogastrographic study,[29] autonomous neuropathy, interstitial edema, reduction in β-adrenergic receptors,[27] or the role of gastrointestinal hormones such as ghrelin. Even if ghrelin may affect gastrointestinal motility and its secretion may be modulated by thyroid hormones, the plasma level of this hormone in hypothyroidism was not different from that in controls.[22]

Constipation is the most frequent gastrointestinal symptom, followed by abdominal discomfort and bloating due to reduced peristalsis of the small intestine and colon. In severe cases, one may encounter ileus and colonic pseudo-obstruction. Studies on orocecal transit time in fasting patients with hypothyroidism using the pulmonary excretion of H_2 after the ingestion of a nonabsorbable carbohydrate, lactulose, provided inconsistent data. Some authors reported normal transit time of the small intestine,[30,31] and it was concluded that delayed colonic transit alone is likely to account for constipation in hypothyroidism. Animal studies also reported decreased frequency of rhythmic colonic activity in rats with thyroidectomy.[32] But other studies reported delayed small intestinal transit time.[33] More recently, small intestinal bacterial overgrowth was associated with hypothyroidism, concluding that excessive bacteria could modulate neuromuscular function of the small bowel,[34] explaining the diarrhea observed in some patients.

Investigating anorectal physiology by anal manometry and intrarectal balloon distension in hypothyroidism, Deen et al.[35] demonstrated that the threshold for rectal sensation was higher and the maximal tolerable volume is diminished compared with controls.

There is a significant association between the common bile duct stones and previously diagnosed hypothyroidism.[36] A stronger association between the common bile duct stones and hypothyroidism suggests a pathogenetic pathway other than merely the mechanism mediated by cholesterol metabolism. Using quantitative ^{99m}Tc HIDA cholescintigraphy, delayed emptying of the biliary tract was found in patients with hypothyroidism.[37] In experimental studies, thyroxine enhances the relaxation of the sphincter of Oddi,[38] so the lack of this hormone may result in an increased pressure of the valve, explaining high prevalence of bile stones in the common bile duct.

Gall bladder motility is not altered. On ultrasonography, no significant differences were noted for fasting, poststimulus gall bladder volumes, and gall bladder ejection fraction between euthyroid and hypothyroid subjects.[39] However,

the standardized ultrasonographic method for gallbladder emptying has some limitations: gall bladder is not static during fasting, and after a meal, intermittent emptying and refilling of gall bladder occurs. Ultrasonography measures the "net" gall bladder emptying, not the refilling.[39] Although cumbersome, additional evaluation with cholescintigraphy, which detects "absolute" gall bladder emptying and is not affected by gall bladder refilling, may provide complete assessment of motor function.[39]

To see if motility disturbances found in hypothyroidism may be explained by the effect of disturbed hormone gut profile, some investigations have been undertaken, especially experimental studies with prepro-vasoactive intestinal polypeptide (VIP)-derived peptides.[40] Unbalanced thyroid hormone status induced moderate changes in peptide expression in the gut, the most prominent being a 2-fold increase in all prepro-VIP-derived peptides in the gastric fundus of hypothyroid rats. VIP is a widespread neuropeptide involved in the autonomic nervous control of smooth muscle activity, blood flow, and secretion.[40] Contradictory data were reported about serum ghrelin levels in hypothyroidism. Some authors found reversibly increased ghrelin levels in hypothyroid patients,[41] while others did not observe any change.[22]

Acromegaly   This disease, due to excessive production of growth hormone, is associated with gastrointestinal complications, such as constipation, higher prevalence of colorectal polyps and cancer,[42] and higher prevalence of gallstones in patients treated with somatostatin.[43]

Motility disorders in these patients are expressed in a prolonged small intestinal transit time, which predisposes to small intestinal bacterial overgrowth,[44] and in a prolonged colonic transit time. This represents a risk factor for fecal anaerobic bacteria overgrowth with the impairment of bile acid metabolism, responsible in part for gallstone development.[45] In addition to these specific motility alterations, the treatment with somatostatin analogue decreases gut motility, worsening the consequences of slow gut transit.

Investigating the small-bowel transit time by standardized 10 g lactulose hydrogen breath test to estimate the orocecal transit time, Resmini et al.[44] observed significantly slower transit in patients than in controls, without significant differences between patients treated with somatostatin and untreated patients. These data suggest that acromegaly itself may cause motility alteration. The pathogenetic mechanisms that could explain this motility abnormality are still unknown. Autonomic intestinal impairment, similar to that demonstrated previously in the cardiovascular system, was incriminated.[46] Another pathogenic mechanism is related to hormone balance influenced by the complex interaction between growth hormone and ghrelin, as proved by Arosio et al.[47] Giving

ghrelin to acromegalic patients, the authors found that it affects both pituitary and gastro-entero-pancreatic hormones similarly to normal subjects. They concluded that ghrelin can play a role in linking the endocrine control of energy balance and growth with the regulation of gastrointestinal functions.[47]

Thomas et al.[45] performed radiological tests to investigate colonic transit and found an increased transit time of colon (66% longer) in acromegalic patients compared with controls, and it was even more increased during octreotide treatment.

In acromegaly, these motility disturbances also increase circulating level of insulin-like growth factor-1, which is a known mitogen that may stimulate the proliferation of intestinal epithelial cells by autocrine and paracrine actions.[42]

In acromegalic patients treated with somatostatin, ultrasound studies were carried out to evaluate gall bladder motility by calculating the volumes of fasting and postprandial gall bladder at 15 minutes for 2 hours.[43] The authors found increased gall bladder volume in both fasting and postprandial state, caused by profound suppression of released cholecystokinin.[43] This impaired gall bladder emptying explains the high incidence of gall bladder stones in acromegalic patients treated with somatostatin.

Hypothalamic-pituitary-adrenal axis disorders   Gastrointestinal symptoms, such as diarrhea and early satiety, are associated with hypothalamic-pituitary-adrenal axis suppression in healthy individuals.[48] Adrenal insufficiency may cause persisting vomiting, anorexia, hypoglycemia, unexplained weight loss, or abdominal pain.[49,50] In Cushing syndrome, caused by high cortisol blood levels, peptic ulcerations are found in the gastrointestinal tract.

Experimental studies showed that corticotropin-releasing factor (CRF), the first component of the hypothalamic-pituitary-adrenal axis, plays a central inhibitory role in the control of gastric emptying in rats.[51] It was also demonstrated that central nociceptin/orphanin FQ inhibits gastric emptying through an integrated orphaninergic system-CRF interaction, in which corticosterone plays a permissive role.[52] Ghrelin, a gastric hormone, stimulates ACTH and cortisol secretion in normal subjects, and this effect is generally sensitive to the negative glucocorticoid feedback. In patients with Cushing's disease, despite hypercortisolism, ghrelin still stimulates ACTH and cortisol secretion by binding on specific receptors present on the neoplastic tissue.[53]

The relationship between gastric emptying, adrenal steroids, and ghrelin has not been investigated yet in patients with Addison's disease.

Neurohypophysis disorders   Central diabetes insipidus caused by the deficiency of arginine vasopressin (AVP), also known as antidiuretic hormone, may manifest with vomiting and diarrhea, secondary to hypernatremia. There have been no

FIGURE Using the 2D ultrasonographic method as desribed by Bolondi et al.,[51] the gastric antrum is visualized on the sagital plane at the epigastrium at the level corresponding to the superior mesenteric artery – preprandial antral area (A) and postprandial antral area at 20 (B), 40 (C), and 60 minutes (D)
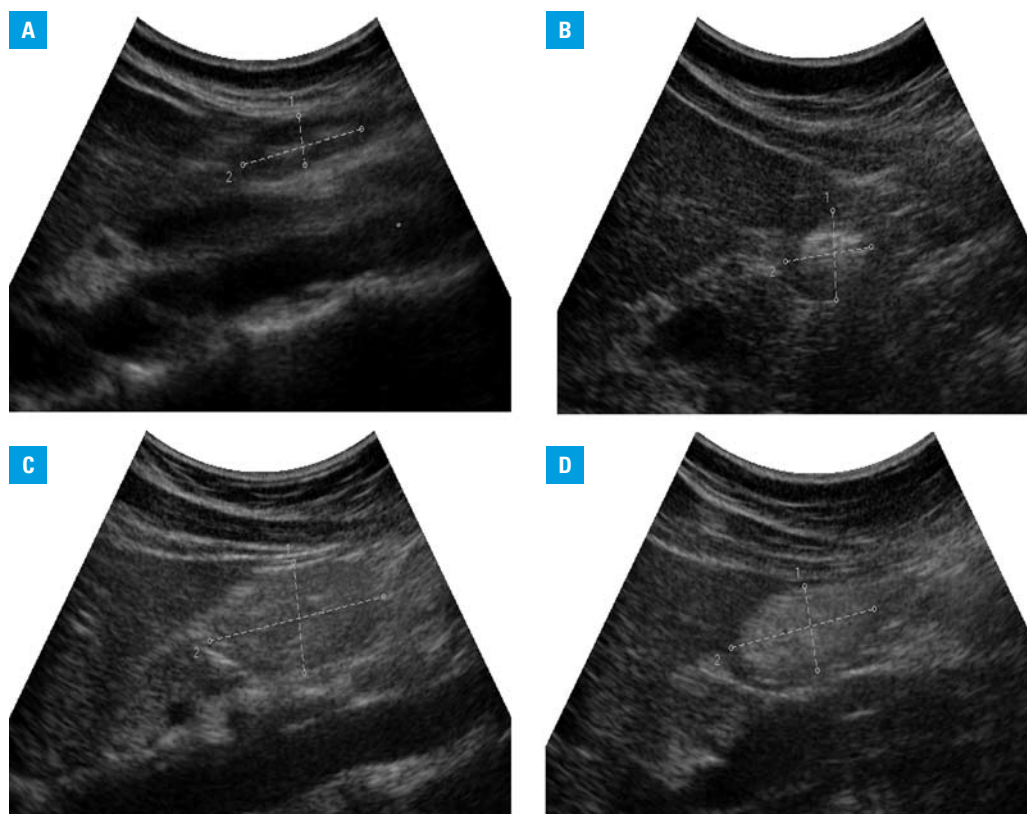
studies that investigate the role of gastrointestinal hormones or motility disturbances in diabetes insipidus.

Oxytocin and AVP receptors are expressed throughout the gastrointestinal tract,[54,55] suggesting a role of these hormones in gastrointestinal motility. Plasma AVP or oxytocin levels did not increase in response to meal-induced gastric distention, in healthy subjects in an early study conducted by Miaskiewicz et al.[56] Other studies concluded that oxytocin was released in response to a fatty meal in healthy subjects.[57] Oxytocin stimulates colonic activity in women,[58] and administration of oxytocin receptor antagonist delays gastric emptying.[59] The effect of oxytocin on gastrointestinal motility may be mediated by a direct effect on oxytocin or vasopressin receptors, or indirect through cholecystokinine release, or by affecting the vagus nerve.[60]

Diabetes The disorders of gastric and intestinal motility are considered as late manifestation of diabetes. Several dysfunctions have been described including dysrhythmias, antral hypomotility, gastroparesis, diarrhea, constipation, and fecal incontinence.

Electrogastrography studies suggest that gastric myoelectrical abnormalities occur in almost 40% of diabetic patients.[61] Gastric dysrhythmias (tachygastrias, bradygastrias, mixed or nonspecific dysrhythmias) are disturbances of the normal gastric pacesetter potentials and are associated with dyspeptic symptoms (nausea, epigastric fullness, bloating), hyperglycemia, and delayed gastric emptying.[62]

In an antroduodenal manometry study, recording multiple migrating motor complexes showed that interdigestive motor abnormalities of the stomach and duodenum are common in diabetic patients.[63] The authors also showed that antral hypomotility and abnormal duodenal motility patterns after a high-caloric meal are correlated with dyspeptic symptoms in diabetic patients.[63]

Gastroparesis is characterized by gastric hypotonia and retention without mechanical obstruction. This is mainly due to autonomic neuropathy. In our ultrasonographic gastric emptying study, using the Bolondi method (**FIGURE**),[64] we demonstrated significantly larger postprandial antral areas in diabetic patients than in controls.[65] Moreover, the gastric emptying was delayed compared with normal, with the cutt-off value of 170 minutes. There were no differences between the two types of diabetes. Factors associated with gastroparesis were poor short- and long- time control of glycemia and abnormal parasympathetic neuropathy, correlated with a long history of diabetes (**FIGURE**).[65]

Hyperglycemia decreases the postprandial antral contractions of pylorus by affecting the myoelectrical rhythm.[66] Glucose would also directly produce a dysfunction of the intracellular metabolism of the parasympathetic neurons and of the neuromuscular junctions.[67] The treatment of gastric motility disorders is based on the control of blood glucose and on prokinetic drugs such as dopamine antagonist (metoclopramide and domperidone) or motilin receptor agonist (erythromycin). The value of intrapyloric injection of botulinum toxin has not been proved yet.[68] Gastric

TABLE Effects of gastrointestinal hormones on glucose metabolism and gastrointestinal functions

Hormone	Effects on glucose metabolism	Gastrointestinal functions
ghrelin	acts on pancreatic β cells to inhibit insulin production and secretion inhibits glucose uptake in muscle and adipose tissue stimulates glucose production by the liver	leads to increased gastrointestinal motility possibly increases gastric acid secretion, preparing the gastrointestinal tract to process food
cholecystokinin	lowers glucose production through a neuronal network cholecystokinin resistance may contribute to hyperglycemia in response to high-fat feeding	inhibits gastric emptying stimulates pancreatic and bile secretion inhibits food intake
peptide YY	low serum peptide YY is linked to insulin resistance in first-degree relatives of subjects with type 2 diabetes	candidate for short-term satiety regulation
glucogon like-peptide 1	stimulates insulin release	inhibits gastric emptying inhibits secretion of gastric juices
oxyntomodulin	stimulates intestinal glucose uptake in experimental models	inhibition of food intake

electric stimulation was proposed considering gastric myoelectrical abnormalities found on electrogastrography studies and shown significant reductions in the symptoms of drug-refractory gastroparesis.[69]

Intestinal enteropathy in diabetic patients is expressed by diarrhea, constipation, or fecal incontinence. Diarrhea is caused by impaired motility in the small bowel that leads to bacteria overgrowth, decreased sympathetic inhibition and pancreatic insufficiency. Constipation may result from neuronal dysfunction in the large bowel, along with impairment of the gastrocolic reflex. Abnormal internal and external anal sphincter function caused by neuropathy can lead to fecal incontinence.[70] Treatment of intestinal enteropathy is directed towards symptomatic relief, such as glycemia reduction, antidiarrheals or broad-spectrum antibiotics for diarrhea, or osmotic laxatives for constipation.[70]

In a recent experimental study on diabetic mice, Yamamoto et al.[71] defined the role of the interstitial Cajal cells, which express c-kit receptor tyrosine kinase and are considered the pacemaker cells for gastrointestinal movement in type 2 diabetes. They observed delayed gastric emptying, prolonged whole-gut transit time, irregular frequency of isometric tension in the small intestine, smaller areas of c-kit-positive cells in the antrum, small intestine, and colon, demonstrating the involvement of Cajal cells in the gastroenteropathy of type 2 diabetes.

Gastrointestinal hormones (ghrelin, cholecystokinin, peptide YY, glucagon-like peptide, oxyntomodulin) influence glucose and energy metabolism at different levels: by altering food intake and body weight, and thereby insulin sensitivity; by affecting gastric delay and gut motility, and thereby meal-related fluctuations in glucose levels; by affecting insulin secretion, and thereby plasma glucose levels; and by affecting tissue specific insulin sensitivity of glucose metabolism (**TABLE**).[72-76]

In diabetic patients with gastroparesis, plasma ghrelin levels are lower than in those without impairment of gastric emptying,[77] and parenteral administration of exogenous ghrelin enhances gastric empting.[78] In hemodialysis patients with diabetic nephropathy, even if plasma ghrelin levels are significantly elevated compared with healthy subjects, the suppression of ghrelin plasma levels after ingestion of a test meal persists longer than 120 minutes, explaining impaired gastric emptying.[79]

In patients with diabetes, this brain-gut-hormone network is profoundly imbalanced. There are ongoing studies aimed at identifying a causal treatment with some of these hormones: adiponectin, ghrelin, or leptin, and with resveratrol.[80] (**TABLE**).

Parathyroid diseases   Parathyroid hormone is the primary regulator of calcium physiology. Hypoparathyroidism is associated with steatorrhea that may improve with medium-chain triglycerides, correction of hypoparathyroidism, or administration of vitamin D. Hyperparathyroidism results in constipation because of the reduction in neuromuscular excitability by high calcium levels.[81] Impaired growth hormone secretion to ghrelin is common in patients with primary hyperparathyroidism, and it is due to a deleterious effect of hypercalcemia at the hypothalamic level.[82]

Parathyroid hormone-related protein is a protein member of the parathyroid hormone family that has normal functions. It is occasionally secreted by cancer cells (breast cancer, certain types of lung cancer including squamous cell carcinoma). In experimental studies, this protein appears to be a potent smooth muscle relaxant,[83] decreasing gastric emptying.[84] The mechanism involves the activation of hypothalamic urocortins 2 and 3 through vagal afferent pathways and the suppression of gastroduodenal motor activity.[84]

Islet cell tumors of the pancreas   The clinical presentation of patients with pancreatic endocrine tumors varies from complaints of abdominal pain and nausea to debilitating diarrhea. The study of these tumors offers a better understanding on the motility effects of some gastrointestinal tumors. The most illustrative tumor is somatostatinoma, characterized by a marked decrease in

secretory and motility gastrointestinal function. The clinical presentation includes cholelithiasis (70%), mild diabetes (60%), steatorrhea (30%–68%), hypochlorhydria (33%–53%) and weight loss.[85] As discussed above, gall bladder stones are caused by hypomotility of the gall bladder and of the colon, which determines changes in bile acid metabolism, with a higher concentration of deoxycholic acid. Steatorrhea is determined not only by decreased bile secretion and excretion, but also by small intestine bacterial overgrowth caused by hypomotility of the small bowel.

In patients with gastrinoma, diarrhea is a steatorrhea caused by precipitated bile salts in an acid environment of the duodenum.[85] In VIP-oma, diarrhea has a secretory mechanism. Some of these tumors are associated with pituitary lesions and hyperparathyroidism in multiple endocrine neoplasia type 1.[85]

Multiple endocrine neoplasia type 2 Multiple endocrine neoplasia type 2 (MEN 2) is characterized by medullary thyroid carcinoma and other endocrinopathies. In addition, some patients with MEN 2A develop Hirschsprung's disease. All patients with MEN 2B have intestinal neuromas and megacolon. MEN 2 patients manifest a host of gastrointestinal symptoms, including diarrhea associated with hypercalcitonemia of medullary thyroid carcinoma, constipation associated with hypercalcemia, and most notably Hirschsprung's disease with significant symptoms of constipation, pain, distension, and difficulty swallowing. Hirschsprung's disease is characterized by the absence of autonomic ganglionic cells within the distal colonic parasympathetic plexus, resulting in obstruction of the rectum and megacolon. Gastrointestinal ganglioneuromatosis is characterized by thickening of the myenteric plexus and hypertrophy of ganglion cells anywhere. These cause ganglionic dysfunction and abnormal sphincter function at various levels, with loss of normal bowel tone, distension, segmental dilatation, and megacolon. Some patients develop diarrhea due to small intestinal bacterial overgrowth.[86]

Conclusions Many endocrine conditions are associated with symptomatic or asymptomatic alterations of gastrointestinal motility. Clinical manifestations of endocrine disorders may originate in the gastrointestinal tract, but they should be actively looked for to be detected.

Modulation of the brain-gut axis by gastrointestinal hormones in endocrine disorders is still not very well understood. Further experimental studies are needed, focusing on identification of neuropeptides in the tissue of the gastrointestinal tract.

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Zaburzenia motoryki przewodu pokarmowego w chorobach układu wewnątrzwydzielniczego

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STRESZCZENIE

Choroby układu wewnątrzwydzielniczego mogą prowadzić do zajęcia innych układów i narządów. Celem pracy był przegląd zaburzeń motoryki przewodu pokarmowego w chorobach endokrynologicznych. Autorzy omawiają zaburzenia motoryki w chorobach tarczycy, akromegalii, zespole Cushinga, zaburzeniach przysadki, cukrzycy, chorobach przytarczyc oraz mnogiej gruczolakowatości wewnątrzwydzielniczej, ze szczególnym uwzględnieniem związku tych zaburzeń ze stężeniem hormonów jelitowych, które mogą oddziaływać na oś mózgowo-jelitową na różnych poziomach.

Erratum

Krzymień J, Kobli T, Nazar M. Multicenter, open-label, nonrandomized, observational safety study in subjects using insulin aspart in basal-bolus regimen for the treatment of diabetes. Pol Arch Med Wewn. 2010; 120 (11): 444-450.

Page 448, Table 3: Body mass for type 1 diabetes should be 64.5 ±18.3 rather than 64.7 ±18.3 at the baseline visit and 64.7 ±17.8 rather than 7.48 ±1.00 at the final visit. Body mass for type 2 diabetes should be 86.1 ±16.9 rather than 86.6 ±16.9 at the baseline visit and 85.6 ±14.5 rather than 7.60 ±0.90 at the final visit. The table with correct values is shown below.

Page 449, Table 5: Number of patients with type 1 diabetes who reached the levels of HbA_{1c} <7% should be 190/482 rather than 19/480. The table with correct values is shown below.

TABLE 3 Body mass and body mass index change at the end of a 13-week study

	n	Baseline visit	Final visit	Mean change	*P*
body mass					
type 1 diabetes	840	64.5 ±18.3	64.7 ±17.8	0.25 ±2.63	NS
type 2 diabetes	1224	86.1 ±16.9	85.6 ±14.5	−0.51 ±1.95	NS
BMI					
type 1 diabetes	821	23.1 ±4.4	23.2 ±3.2	0.12 ±1.0	NS
type 2 diabetes	1188	30.8 ±5.1	30.6 ±4.4	−0.17 ±1.1	NS

Data are shown as means ± SD

Abbreviations: see **TABLES 1** and **2**

TABLE 5 Proportion of patients reaching therapeutic goals at the final visit. Data shown as absolute numbers and percentage

Therapeutic target	Type 1 diabetes	Type 2 diabetes	Total population
HbA_{1c} ≤6.5%, n (%)	71/482 (14.7)	38/655 (5.8)	117/1195 (9.8)
HbA_{1c} <7%, n (%)	190/480 (39.4)	158/655 (24.1)	375/1195 (31.4)
HbA_{1c} (set by physicians), n (%)	79/479 (16.8)	82/631 (17)	171/1157 (14.8)

Abbreviations: see **TABLE 4**

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