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REVIEW

# Systemic Disease Associations with Disorders of Gut–Brain Interaction and Gastrointestinal Transit: A Review

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**Abstract:** Functional gastrointestinal disorders (FGID) are now classified within the Rome IV framework as disorders of gut–brain interaction (DGBI). Disorders of gastrointestinal transit (as defined by abnormalities on contemporary gastrointestinal motility testing) frequently are associated with symptoms that are also characteristic of DGBIs. In this narrative review, we outline a non-inclusive set of systemic diseases or risk factors that have been classically associated with DGBIs and disorders of gastrointestinal transit; these include diabetes mellitus, paraneoplastic syndromes, surgery, Parkinson's disease, systemic sclerosis, endocrinopathies, polypharmacy, and post-infectious syndromes.

**Keywords:** motility, neurogastroenterology, gastroenterology, mechanism

## Introduction

Functional gastrointestinal disorders (FGID) are now classified within the Rome IV framework as disorders of gut–brain interaction (DGBI).[1,2] In a worldwide survey of 73,076 respondents, over 40% of internet respondents indicated that they had a DGBI.[3] Physiologic tests of gastrointestinal transit are commonly ordered in patients with DGBIs to assist in targeting appropriate therapy.[4] Several multisystem disorders have been associated with the development of DGBIs and also with pathophysiologic tests suggestive of an abnormality in gastrointestinal transit. To aid the gastroenterologist in considering a broader differential when evaluating common gastrointestinal complaints in practice, we will review a non-inclusive set of disorders and conditions that overlap with both DGBIs and gastrointestinal motor dysfunction (Table 1).

## Methods

We searched PubMED for English-language full-text articles from 2011 to September 2020, using the search terms: "Gastrointestinal Motility" [Mesh] OR "gut-brain interaction" OR "brain-gut interaction" OR "DGBI" OR "functional gastrointestinal" AND ("pathophysiology"). A total of 592 abstracts and associated references were reviewed by two authors (RM and AS) toward inclusion in this review.

## Diabetes Mellitus

The estimated global prevalence of diabetes mellitus was 8.8% and is expected to increase over the next two decades.[5] A 20–28% of all diabetics and 26–32% of type

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**Table 1** Distinct Conditions Associated with Disorders of Gut–Brain Interaction and Gastrointestinal Motor Dysfunction

| Conditions and Disorders to Consider on the Differential Diagnosis |
|---|
| Diabetes mellitus |
| Endocrinopathy |
| Paraneoplastic syndrome |
| Parkinson's disease |
| Polypharmacy and medication-related causes |
| Post-infectious syndrome |
| Post-surgical |
| Systemic sclerosis |

2 diabetics may have neuropathy.[6–8] Diabetic neuropathy is a multisystem condition that has been implicated in gastrointestinal motor and sensory dysfunction mediated by the destruction of microvascular blood supply of the endoneurium of autonomic nerves, as well as intraneuronal depletion of NADPH due to increased sorbitol production.[9] Postmortem studies of histological changes in type 1 diabetic individuals found demyelination of the vagus nerve and inflammatory changes in autonomic ganglia.[10] In addition to extrinsic denervation, diabetes affects gastrointestinal motor function via loss of enteric pacemaker cells and damage to enteric interneurons. Gastric biopsies from patients with diabetic gastroparesis showed loss of interstitial cells of Cajal, decreased nerve fibers, and thickening of the basal lamina of smooth muscle cells.[11–13] In a murine model of type 1 diabetes, jejunal neuronal nitric oxide synthase expression was reduced and there was decreased ex vivo responsiveness to exogenous nitric oxide, suggesting that the effects of diabetic neuropathy on gastrointestinal motor function may not be limited to vagal nerve injury alone.[14]

Regarding sensory function, a population-based survey in Australia found that patients with diabetes more frequently complained of both upper and lower gastrointestinal symptoms characteristic of DGBIs.[15] One cross-sectional survey of type 1 diabetes found that 10% of patients were affected by symptoms of dyspepsia, nausea, postprandial fullness and early satiety.[16] Gastrointestinal motor function has been implicated in the pathophysiology of upper gastrointestinal symptom development, and the prototypical test of motor function is to measure emptying of a meal using gastric emptying scintigraphy.[17,18] One case–control study to evaluate gastric emptying in euglycemic type 1 diabetic patients (via 13C-octanoic acid breath testing) found that 38% of type 1 diabetic patients had delayed gastric emptying in comparison to healthy controls. However, the relationship between gastrointestinal symptoms and objective evaluations of gastric emptying remains controversial. On one hand, delayed gastric emptying may correlate with upper gastrointestinal symptoms based on a recent meta-analysis of prospective randomized controlled drug trials, recognizing challenges in universal adoption of standard testing protocols and potential differences related to individual drug mechanisms and advances in trial design over time.[17,19] On the other hand, gastric emptying may be labile and insufficient to distinguish between gastroparesis (as a disease that is conceptually attributed to the gastrointestinal motor function) and functional dyspepsia (as a DGBI).[4] Furthermore, postprandial hyperglycemia in diabetic patients may lead to delayed gastric emptying, while delayed gastric emptying can precipitate further hyperglycemia due to poorly coordinated timing in insulin release and nutrient availability.[20]

Wireless motility capsule testing is a whole-gut transit test using an indigestible pill that is cleared from the stomach by the Phase III migrating motor complex approximately one hour after gastric emptying of a standard meal.[21] Gastrointestinal transit correlates at least modestly between scintigraphy or wireless motility capsule, a finding that recognizes the inherent differences in the mechanistic constructs evaluated by each test.[22] Overall, efforts to clarify the role of gastrointestinal transit diagnostics embedded within management paradigms for upper gastrointestinal symptoms in broader practice are ongoing.[23]

Even in the absence of overt neuropathy, hyperglycemia can lead to symptoms associated with common DGBIs. Several studies have demonstrated that both medically induced hyperglycemia and hyperinsulinemia in healthy human subjects inhibits gastric migrating motor complexes and suppresses plasma motilin.[24,25] Hyperglycemia (glucose levels >200mg/dL) is known to acutely exacerbate nausea and vomiting symptoms in diabetics.[26] Among patients who have been formally diagnosed with gastroparesis, screening for diabetes mellitus is recommended, and clinicians should aim to achieve euglycemia in diabetic patients prior to or alongside testing and treatment related to a primary gastrointestinal motor disorder.[26]

## Paraneoplastic Syndrome

Paraneoplastic syndromes occur in the setting of an underlying malignancy and are responsible for a wide variety of

patient presentations. The estimated incidence of paraneoplastic syndrome is 8–15% among all cancer patients.[27] Mechanisms driving paraneoplastic syndromes include both immune and non-immune mediated processes. Paraneoplastic immune processes occur when the immune system develops a response against tumor antigens that cross-react with its own tissues. In contrast, non-immune-based mechanisms of paraneoplastic syndromes occur when malignant cells produce hormones or cytokines leading to metabolic derangements.[27–29]

Paraneoplastic syndromes can manifest as DGBIs as well as disorders related to gastrointestinal motor function, such as gastroparesis, chronic intestinal pseudo-obstruction, and pseudo-achalasia.[30–32] DGBIs associated with paraneoplastic syndromes often occur due to antibodies or immune cells infiltrating the enteric nervous system, interstitial cells of Cajal, and intestinal smooth muscle. The classic paraneoplastic syndrome associated with DGBIs involves anti-neuronal nuclear antibody (ANNA-1 or Anti-Hu), and can occur in combination with neurological symptoms such as cerebellar dysfunction. This paraneoplastic auto-antibody is particularly associated with small cell lung cancer.[33–35] Other recognized auto-antibodies associated with both paraneoplastic syndromes and gastrointestinal motor abnormalities include collapsing response-mediator protein 5 (CRMP-5), Nicotinic acetylcholine receptor antibodies, calcium channel antibodies, Purkinje Cell Cytoplasmic Autoantibody, Type 1 (PCA-1)/Anti-Yo and Voltage-gated potassium channel autoantibodies.[36,37]

In practice, clinicians should consider the possibility of a paraneoplastic syndrome on the differential diagnosis for a patient presenting with a sudden onset of unexplained gastrointestinal symptoms suggestive of a DGBI. Clinicians should also ensure that patients undergo age-appropriate cancer screening.[27]

## Surgery

Common elective surgeries are infrequently associated with the development of gastrointestinal motor and sensory dysfunction and DGBIs. Here, we exclude early post-operative conditions (resolving within the first 30 days after surgery) as well as structural disorders (such as ischemia and luminal narrowing). Instead, we review uncommon postoperative complications giving rise to conditions including achalasia, gastroparesis, and dumping syndrome.

Fundoplication is a common surgical procedure to treat medically refractory gastroesophageal reflux.[38,39] Rarely, fundoplication surgery can be associated with the post-operative development of secondary achalasia. Of 250 patients who underwent fundoplication for GERD, 7 patients had delayed onset of secondary achalasia one month after surgery.[40,41] Other authors have reported cases of hypercontractile or spastic disorders of peristalsis, recognizing that these manometry findings often have unclear clinical significance.[42] Hypercontractile disorders resolve in up to 70% of patients spontaneously in longitudinal cohorts and follow a benign course of treatment, recognizing gaps in knowledge specific to post-surgical populations.[43,44] Surgical guidelines advocate (but do not mandate) pre-operative esophageal manometry in patients referred for fundoplication. After surgery, consideration of these rare potential outcomes on the differential diagnosis is especially advocated in patients with post-operative dysphagia or non-cardiac chest pain.[45]

Like diabetic gastroparesis, the prototypical symptoms of post-surgical gastroparesis include nausea, vomiting, early satiety, or upper-abdominal discomfort (similar to symptoms consistent with functional dyspepsia).[26] In a longitudinal cohort of 38 patients who underwent truncal vagotomy with Jaboulay gastroduodenostomy (a 'surgical model of gastroparesis'), 52% of patients reported dyspeptic symptoms despite having undergone gastroduodenostomy.[46] Delayed gastric emptying can occur after surgeries in which the vagus nerve is transected or injured.[26] After lung transplant, delayed gastric emptying is a common complication in the months following surgery; the prevalence of delayed gastric emptying in the months following lung transplant is estimated to be between 24% and 74%.[47,48] Post-surgical gastrointestinal motor abnormalities have been attributed to intraoperative tissue damage, nerve injuries, and structural changes to enteric organs, some of which can be inherent to the nature of the surgical procedure.[49,50] In gastroparesis arising after lung transplant, the mechanism is posited to be inadvertent vagal nerve injury or toxic side effects of immunosuppressants, yet the precise mechanism is unknown.[47,51]

Dumping syndrome refers to symptoms associated with rapid gastric emptying; these may include reactive hypoglycemia, vasomotor symptoms due to osmotic fluid shifts from blood into the intestinal lumen, and diarrhea. In a survey of 360 bariatric surgery patients, 26% of laparoscopic sleeve gastrectomy patients and 41% of laparoscopic Roux-en-Y gastric bypass patients had presentations consistent with dumping syndrome.[52] In contrast to gastrointestinal motor abnormalities arising from

nerve injury, dumping syndrome after bariatric surgery may be due to structural changes to the stomach after resection, such as reduced gastric compliance causing higher intragastric pressure, or disruption of the enteric neuronal pathways along the greater curvature.[52,53]

Overall, a careful surgical history is frequently helpful in evaluating a patient for a suspected DGBI or gastrointestinal motor disorder to assist in clarifying the expected course and in clarifying treatment options and paradigms.

## Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disorder that occurs as a result of loss of dopaminergic neurons within the brain. The incidence of PD was recently estimated as 17 per 100,000 person-years.[54] The total economic burden of PD in the US in 2017 exceeds $51.9 billion per year, with estimated annual direct health costs comprising $25.4 billion and indirect and non-medical costs of $26.5 billion.[55]

The Braak Hypothesis suggests that the pathophysiology of PD begins with an unknown pathogen originating in the enteric nervous system and olfactory bulb before progressing to the midbrain.[56] This hypothesis may explain why certain non-movement symptoms such as anosmia and constipation may occur years before the onset of the classic motor symptoms of Parkinson's disease.[57,58] Interestingly, chronic constipation is a DGBI that is seen in approximately 70–80% of patients with PD and precedes diagnosis of PD in 87% of patients.[57]

This phenomenon of gastrointestinal motor function and development of gastrointestinal symptoms that are characteristic of DGBIs in patients with PD are reflected in animal models of the disease. Mice treated with 1-methyl-4-phenyl-1,2,3,6,tetrahydropyridine (MPTP; a parkinsonism-inducing neurotoxin) developed constipation similar to PD patients, and additionally had decreased intestinal tyrosine hydroxylase-positive neurons.[59] Studies with a different mouse model of PD, created by oxidopamine injections into the substantia nigra (to selectively destroy dopaminergic neurons), showed that the consequent delayed gastric emptying and constipation were associated with concomitant reductions in nitric oxidase synthetase-positive neurons within the myenteric plexus of the gastrointestinal tract.[60–62] Lastly, in support of the Braak Hypothesis, transgenic mice over-expressing alpha-synuclein that underwent a fecal microbiota transplant derived from PD patients had reduced gastrointestinal transit.[63] Ultimately, efforts to elucidate mechanisms of gastrointestinal symptom development characteristic of DGBIs and to elucidate mechanisms of gastrointestinal motor abnormalities in PD patients are ongoing.

## Systemic Sclerosis

Systemic sclerosis is an autoimmune disease characterized by fibrosis of organ systems, recognizing that variability exists as to the organ systems involved, the specific autoantibodies involved, and the presence of concomitant connective tissue diseases.[64] Four important subtypes of systemic sclerosis include limited cutaneous systemic sclerosis (formally known as CREST syndrome), diffuse cutaneous systemic sclerosis, systemic sclerosis sine scleroderma, and overlap syndrome.[64] While the prevalence of systemic sclerosis varies by region, a recent meta-analysis estimated the pooled prevalence of systemic sclerosis as 23 per 100,000.[65]

The pathogenesis of systemic sclerosis involves vascular injury, inflammatory response with cytokine and autoantibody production, activation of fibroblasts and deposition of extracellular matrix that is exacerbated with further immune cell recruitment.[64] Gastrointestinal motor abnormalities occur in approximately 90% of patients with systemic sclerosis and typically affects the esophagus (leading to gastroesophageal reflux disease). However, gastrointestinal motor abnormalities in systemic sclerosis can occur throughout the gastrointestinal tract.[64,66] Peristaltic activity is altered in patients with systemic sclerosis due to neural dysfunction, smooth muscle atrophy and muscle fibrosis. Interestingly, a subset of patients with systemic sclerosis have been found to have gastrointestinal symptoms consistent with DGBIs as well as gastrointestinal motor abnormalities without evidence of enteric fibrosis. In these patients, autoantibodies against components of the myenteric plexus have been associated with gastrointestinal symptoms, including antimuscarinic-3-acetylcholine antibody that binds to the MR3 receptor and blocks peristalsis, as well as anti-RNPC3 and anti-vinculin antibodies.[66] In contrast, autoantibodies associated with systemic sclerosis including anti-Topo I, RNAPIII and anti-CENP and anti-Ro were not found to be associated with gastrointestinal symptom severity.[67,68]

## Endocrinopathies

Disorders of the endocrine system are characterized by abnormal levels of hormones within the bloodstream, and include glandular dysfunction such as adrenal,

thyroid, and parathyroid disorders.[69] Adrenal insufficiency may present with nonspecific gastrointestinal symptoms such as vomiting, loss of appetite, or abdominal pain. Thyroid disorders affect the transit time of enteric contents; hypothyroidism is classically associated with constipation, whereas hyperthyroidism may be classically associated with diarrhea.[70] Hypoparathyroidism can present with steatorrhea due to malabsorption rather than alterations to gastrointestinal motor function, while hyperparathyroidism has been associated with constipation.[71]

The mechanism by which adrenal insufficiency leads to gastrointestinal symptoms is complex, although several mechanistic studies have elucidated several effects of the hypothalamic-pituitary-adrenal (HPA) axis on the gut. In a rat model, intracerebroventricular administration of CRF resulted in inhibition of gastric emptying in a manner that was both opioid-receptor and sympathetically dependent, but not vagally dependent. This same experiment found that intracerebroventricularly administered CRF in rats also inhibited small bowel transit and stimulated colon transit in a vagally dependent fashion.[72] Other in vivo studies found that administering intravenous glucocorticoids at near-physiological levels in rats resulted in intestinal changes in electrolyte transport via increased Na-K-ATPase activity, and also increased the intestinal transmural electrical potential difference.[73,74] In humans, HPA axis dysfunction – namely increased activity – has been implicated in IBS. Studies measuring salivary cortisol levels in response to psychological or visceral stressors have suggested increased HPA axis activity among IBS patients.[75,76] Furthermore, a meta-analysis of eight studies found an association between IBS and post-traumatic stress disorder, another disease in which HPA axis dysfunction is implicated.[77]

Studies into the mechanism by which thyroid disease affects gastrointestinal transit have produced conflicting results, with some authors reporting normal small intestinal transit times but other authors reporting the opposite.[70] Thyroid diseases in particular may relate to alterations in vagal tone, noting a possible association between hyperthyroidism and gastric pre-prandial brady-arrhythmias on electogastrography in mechanistic studies.[78] Lastly, the constipating effects of hyperparathyroidism may be attributed to hypercalcemia affecting intestinal smooth muscle excitability.[79]

## Polypharmacy and Medication Side Effects

While polypharmacy does not have a strict definition, this term commonly refers to taking more than 5 medications.[80] Older adults in particular are at risk of polypharmacy, and research suggests that this is in part due to unnecessary prescriptions.[81,82] A retrospective cohort study of elderly patients in the outpatient setting in Italy found that 39% had been exposed to polypharmacy at least once.[83] According to the National Center for Health Statistics, the percentage of Americans who used 5 or more prescription drugs in 2007 was 11%, while the percentage of older Americans aged 60 and over who used 5 or more drugs was 37%.[84] A cohort study of older adults found that the rate of polypharmacy among 2351 participants increased between 2006 and 2011.[85] Chronic constipation in particular is associated with polypharmacy, since opioids and anticholinergic medications are frequently used in polypharmacy regimens. Among healthy volunteers, opioid medications led to prolonged gastrointestinal transit as measured by a wireless motility capsule in comparison to placebo; patients with prolonged transit also had higher gastrointestinal symptom severity.[86] Other common gastrointestinal symptoms including dyspepsia are also frequently associated with polypharmacy.[87,88]

## Post-Infectious Syndromes

Post-infectious DGBIs and gastrointestinal motor dysfunction appear related to a disruption of the neural circuitry that links extrinsic vagal function, intrinsic neural and interstitial cells and the smooth muscle cells of the intestine.[89,90] Two recent meta-analyses found a higher incidence of SIBO among functional dyspepsia and IBS patients compared to health controls.[91,92] The most classically described post-infectious gastrointestinal disorders include post-infectious irritable bowel syndrome (as a DGBI) and post-infectious gastroparesis (as defined by gastrointestinal transit testing).

The prevalence of post-infectious IBS has been estimated as 10.1% of cases after resolution of infectious enteritis.[93] In bacterial gastroenteritis, host antibodies against bacterial cytolethal distending toxin B (CdtB) may cross react against the cytoskeletal protein vinculin.[94,95] Beyond the initial infection, the subsequent pathophysiology of post-infectious IBS is complex and includes mechanisms attributed to disruption of the normal host microbiome, chronically increased gut

permeability leading to low-grade inflammation, and possibly changes in enteroendocrine signaling pathways.[89] The clinical course of post-infectious IBS can last for years after the initial infection. The Walkerton Health Study found that 2 years after a large outbreak of bacterial gastroenteritis, 36.2% of study participants with clinically suspected gastroenteritis during the outbreak later met the (then contemporary) Rome I criteria for IBS, in comparison to 10.1% of controls who did not contract gastroenteritis.[96]

Viruses associated with gastroparesis include rotavirus, parvovirus, CMV, EBV, herpes family viruses and Norwalk virus.[97] There are limited published data on the clinical course of viral gastroparesis; two older case series describe that over half of patients spontaneously recover after 1–3 years, whereas the remainder may symptomatically improve but without complete resolution.[98,99] Among mice infected with Herpes simplex virus 1, there was an increased recruitment of macrophages to the ENS leading to increased production of reactive oxygen and nitrogen species and damage to neurons within the myenteric plexus.[100] In other experimental data with both animal models and patient tissue samples, a loss of CD206-containing macrophages (anti-inflammatory immune cells) in the antrum of the stomach was associated with gastric motor abnormalities, noting a correlation between lower numbers of CD206-containing macrophages and decreased number of interstitial cells of Cajal. These findings are also consistent with a recent multicenter cohort study reporting a dropout in interstitial cells of Cajal on full-thickness small bowel biopsy in gastroparesis/FD patients.[4,101]

## Conclusion

Several multisystem disorders have been associated with DGBIs and gastrointestinal motor abnormalities. Additionally, polypharmacy is a risk factor for developing gastrointestinal symptoms and gastrointestinal transit delays. Post-infectious etiologies represent an important subset of patients with DGBIs and gastrointestinal motor abnormalities. Considering these associations on the differential diagnosis poses an opportunity for gastroenterologists and non-gastroenterologists to align care for patients with these conditions.

## Disclosure

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