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Ravages of Diabetes on Gastrointestinal Sensory-Motor Function: Implications for Pathophysiology and Treatment

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Abstract Symptoms related to functional and sensory abnormalities are frequently encountered in patients with diabetes mellitus. Most symptoms are associated with impaired gastric and intestinal function. In this review, we discuss basic concepts of sensory-motor dysfunction and how they relate to clinical findings and gastrointestinal abnormalities that are commonly seen in diabetes. In addition, we review techniques that are available for investigating the autonomic nervous system, neuroimaging and neurophysiology of sensory-motor function. Such technological advances, while not readily available in the clinical setting, may facilitate stratification and individualization of therapy in diabetic patients in the future. Unraveling the structural, mechanical, and sensory remodeling in diabetes disease is based on a multidisciplinary approach that can bridge the knowledge from a variety of scientific disciplines. The final goal is to increase the understanding of the damage to GI structures and to sensory processing of symptoms, in order to assist clinicians with developing an optimal mechanics based treatment.

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Introduction

Diabetes mellitus (DM) is a chronic disease requiring lifelong medical attention in order to limit the development of potentially devastating late complications and to manage them if they occur. The most recent data from the International Diabetes Federation (IDF) indicated that diabetes affected 382 million people worldwide in 2013, a number that is expected to grow to 592 million by 2035 [1]. Therefore, diabetes is one of the major public health problems. A great proportion of the healthcare expenditures is spent on the treatment of its associated morbidity [1].

Gastrointestinal (GI) disorders are common in diabetic patients [2–4]. As many as 75 % of patients attending DM clinics report significant GI symptoms [3]. Common complaints include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting, and diarrhea. The symptoms may be severe and substantially decrease quality of life. The entire GI tract from the esophagus to the anorectal region can be affected. The involved parts of the GI tract may manifest different sensory-motor disorders [5, 6]. The pathogenesis of these disorders in diabetes is complex, multi-factorial (autonomic neuropathy (AN), glycemic control, psychological factors, etc.) and is not well-understood [7]. Over recent years, the role of the enteric nervous system (ENS, considered part of the autonomic nervous system) is becoming more evident [8, 9•] in addition to AN [10]. Furthermore, diabetes-induced histomorphological and biomechanical remodeling [11•] may also play an important role in the development of GI sensory-motor abnormalities. Understanding the mechanisms of GI sensory-motor disorders is key for optimizing treatment and for finding new therapeutic approaches.

In this review, diabetes-induced GI histomorphological changes will be briefly described. Secondly, we discuss the GI sensory-motor dysfunction related to diabetes and how to test this in the clinic. Finally, the clinical implication for pathophysiology and treatment is discussed.

Diabetes-Induced Histomorphological Changes

It is well known that diabetes causes AN, which leads to different complications [12]. The GI tract is connected to the autonomic nervous system through the sympathetic and parasympathetic components. Consequently, the effects of diabetes on the gut are due to AN. Segmental demyelination and axonal degeneration in the nerves have been found in diabetic patients [13, 14]. Vagal fibers show structural changes in diabetic rats [15]. The number of motor vagal ganglia and sensory sympathetic ganglia was reduced in both diabetic patients and animal models [16]; but the overall density and morphology of vagal efferent fibers was unchanged in animal models of diabetes [17].

In addition to AN causing GI disturbances the role of ENS is becoming more evident. This is a partly independent network of neurons and glial cells which is mainly structured in the myenteric plexus and submucosal plexus formed by ganglia and neurons connected through bundles of nerves that run in the course of the entire GI tract [18]. Some animal studies have shown that the number of enteric neurons in most parts of the GI tract were reduced [9•]. Degeneration changes such as axonal swelling have also been observed in a diabetic animal model [19]. Furthermore, diabetes affects the nitrergic neurons early and the cholinergic enteric neurons later as demonstrated in a diabetic animal model [20]. Another study of colonic tissue obtained from diabetic subjects showed that the number of nitrergic neurons decreased whereas the number of cholinergic neurons was unchanged [8]. In addition to the autonomic nervous system including ENS, the interstitial cells of Cajal (ICC) are also associated with diabetic GI disorders [7, 9•]. ICCs are non-neuronal, non-glial cells present throughout the GI tract and within multiple layers of the wall. These cells function as the pacemaker, generating electrical activity resulting in slow waves [21]. Furthermore, ICCs are involved in the neurotransmission between the autonomic nervous system and enteric neurons and between enteric neurons and smooth muscle cells in the GI wall [22]. Studies in diabetic animal models showed that the number of ICCs were reduced in the stomach [23], small intestine [24, 25], and colon [26]. Human studies in diabetic patients also showed reduced number of ICC in the stomach of patients with gastroparesis [27] and in the colon [28]. Therefore, the changes in the autonomic nervous system, ENS and ICC play an important role in the disorders of GI sensory-motor function.

In addition to the above-mentioned diabetes-induced changes, pronounced histomorphological remodeling of structures in the GI wall occur in diabetes patients as well as in diabetic animals [6, 11•]. Remodeling is observed in different parts of the GI tract as outlined below (Table 1):

- *Esophagus*: One human study reported that among six cases of diffuse muscular hypertrophy of the esophagus, four cases were associated with DM [29]. Another human study found that the esophageal wall and especially the mucosa-submucosa layer had increased thickness in diabetic patients [30]. Studies in streptozotozin (STZ)-induced diabetic rats confirmed that the total and mucosa-submucosa thicknesses of the esophagus are increased [31, 32]. Furthermore, increased collagen fraction in the mucosa-submucosa layer of the esophagus was found in the non-insulin dependent diabetes (NIDDM) rat model [33].
- *Stomach*: A morphological study demonstrated that the gastric mucosa thickness increased in DM rats compared to controls [34]. A histopathological study of the human stomach in DM patients with severe gastroparesis showed prominent collagenization and smooth muscle atrophy of the muscle layer [35]. This kind of structural changes in the stomach together with the sensory-motor dysfunction may contribute to the delayed gastric emptying and associated symptoms in diabetic patients.
- *Small intestine*: Many studies have shown that DM causes morphological and histological alterations in the small intestine [6]. Examples are increased intestinal weight, length and weight per unit length [36], increased mucosal surface area [37–39], increased number of goblet cells per villus [40], increased layer thickness [36] and muscle mass [41], and increased proliferating cell nuclear antigen (PCNA) [7].
- *Colon*: Several studies have demonstrated morphological and histological remodeling in the colon, for example: (1) changes in the innervation of colon in the STZ diabetic model shortly after the induction of diabetes [42]; (2) abnormalities of endocrine cells in the colon in a NIDDM animal model [43]; (3) reduced density of ghrelin-immunoreactive cells in animal models of diabetes type 1 and 2 [44]; and (4) increased thickness of the subepithelial collagen layer in diabetic patients [45].

The histomorphological GI remodeling in diabetes affects the biomechanical properties of the GI wall, which subsequently may affect the sensory-motor function. This remodeling has mainly been demonstrated in the last decade [11•]. Biomechanical remodeling such as alterations of stress distribution and increased wall stiffness related to diabetes will alter the tension and stress distribution in the vicinity of the mechanosensitive afferents. In Addition, the structural and

deformational remodeling may alter the zero setting (baseline activity) and responsivity of the mechanosensitive afferents. Hence, the morphological changes and biomechanical remodeling of the diabetic GI tract will likely affect the sensory-motor function.

Sensory-Motor Dysfunction

In various studies, around 50 % of DM patients complain of GI symptoms that may be related to sensory dysfunction [46–48]. These include symptoms such as vomiting, diarrhea, abdominal discomfort, constipation, and fecal incontinence (Table 1) [49•]. The symptoms are often severe and substantially compromise quality of life. Diabetes-related GI dysfunction may also impair glucose control. Hence, the resultant malnutrition, weight loss and glucagon release may lead to fluctuations in blood sugar levels. This cycle likely increases the risk of other systemic complications. Therefore, there has been an increased focus on improving treatment of GI complications in diabetes patients. The pathogenesis of diabetic GI symptoms is complex, but probably related to changes in the nervous system at different levels [7]. In the sections below, the contributions of the autonomic, peripheral, and central nervous system to GI

Table 1 Gastrointestinal changes in diabetes

Organs	Histomorphologic changes	Mechanical property changes	Motility changes	Main symptoms
Esophagus [2, 3, 6, 7, 9•, 11•, 13, 29–33, 46]	Increased wall thickness and wall area Increased collagen fraction in the mucosa-submucosa layer Axonal changes in the extrinsic and intrinsic parasympathetic fibers Degeneration of large myelinated vagal nerve fibers Decreased number of ICC	Increased stiffness in all directions Decreased residual strains Decreased longitudinal shortening and radial stretch during distension	Increased amplitude and number of peristaltic contractions Increased number of spontaneous and non-propagating contractions Multi-peaked contractions Decreased LES pressure amplitude	Heartburn Dysphagia Chest pain
Stomach [2, 3, 6, 7, 9•, 11•, 14, 23, 25, 27, 34, 35, 44, 46]	Increased gastric mucosa thickness Decreased number of ICC Decreased smooth muscle and prominent collagenization in severe gastroparesis Decreased number of enteric neurons Decreased smooth muscle expression of MLCK	Decreased gastric compliance Increased circumferential stiffness	Decreased number of antral MMC Decreased postprandial antral activity including antral contractions Pyloric dysmotility	Postprandial nausea Vomiting Early satiety Bloating Weight loss Abdominal pain
Small intestine [2, 3, 6, 7, 9•, 11•, 19, 24, 36–41, 46, 52]	Increased intestinal weight, length, and weight per unit length Increased mucosal surface area Increased number of goblet cells per villus Increased smooth muscle mass Increased layer thicknesses Increased proliferating cell nuclear antigen (PCNA) Decreased ICC volume Decreased number of enteric neurons Decreased expression of MLCK in the smooth muscles	Decreased residual strain in duodenum Increased residual strain in jejunum and ileum Increased circumferential and longitudinal stiffness Decreased stress relaxation	Increased or decreased frequency and amplitude of antropyloroduodenal contractions Increased MMC cycle duration Early recurrence of the MMC and clusters of contractile activity	Diarrhea Discomfort Pain Pseudo-obstruction
Large Intestine [2, 3, 6–8, 9•, 11•, 26, 28, 42–46]	Changes in the innervation Abnormalities of endocrine cells Impairment of nitrergic enteric neurons Decreased ICC number Early activation of the apoptosis cascade Decreased density of ghrelin-immunoreactive cells Increased thickness of subepithelial collagen Increased colon weight per unit length, wall thickness and area, and increased layer thicknesses Decreased number of enteric neurons	Increased residual strains Increased circumferential and longitudinal stiffness	Increased spontaneous activity Increased stretch-induced rhythmic motor activity	Fecal incontinence Constipation Diarrhea

symptoms in DM are outlined. For a more extensive review, the readers are referred to Drewes et al. [50].

Peripheral diabetic AN affects the sensory nerve supply to the gut as well as the ENS [51]. AN is one of the most prevalent diabetic complications affecting up to 30–40 % of patients with long-standing disease [50]. Hence, GI symptoms are correspondingly prevalent [46]. Gastric emptying largely depends on vagal nerve function, which can be severely disrupted in DM [7]. Studies using cardiac autonomic nerve function tests to assess the involvement of the autonomic nerve system in diabetic patients have indicated that the prevalence and severity of dysmotility of the small intestine is substantially higher in DM patients with AN compared to those without [52]. Diarrhea is found in 20 % of diabetic patients, particularly those with known AN [53]. However, other factors other than AN also contribute to the symptoms, because up to 75 % of patients seen in diabetes clinics report significant GI symptoms [7].

Changes in sensory function with disordered peripheral and central processing of visceral afferent signals from the GI tract may also be responsible for the symptoms. This is obvious as the metabolic changes in DM also affect other nerve fibers including those innervating the gut. Unmyelinated and small size myelinated fibers running in parallel with the sympathetic nerves mainly mediate the sensory GI innervation. Although normal esophageal sensation was found in one study [54], in two others, DM patients had hyposensitivity to esophageal stimulation [55, 56•]. Likewise, hyposensitivity was also found in the rectum [49•]. The hyposensitivity observed in DM strongly supports the presence of peripheral neuropathy and it seems to affect most GI segments. These observations were supported by a recent study that showed decreased cutaneous and rectal sensations in diabetes patients with prominent GI symptoms [57]. Because the rectal and cutaneous sensitivities were also associated with abnormal heart rate variability, it is evident that all fiber types were affected. The hyposensitivity may explain why some patients with severe motility disorders do not report GI symptoms. In contrast, many patients experience increased pain and allodynia (pain to stimuli such as feces and air in the gut that is normally not painful) due to changes in the central nervous system outlined below. Thus, the impaired function of the peripheral afferent nerves is partly counterbalanced (or even overruled) by increased central (spinal and/or brain) neuronal excitability. Another study in the human esophagus supports the presence of neuronal abnormalities as an impaired contractile activity with an imbalance in distension-induced contractions [30]. Furthermore, it has been shown that the changes are widespread in the GI tract and generalized to nerves in all layers of the gut [55]. Finally, generalized neuronal damage affecting the sensory-motor, autonomic and central neuropathies was also found in a study where the degree of peripheral hypoesthesia was associated with both heart rate variability and impaired "gating" of incoming afferent activity to the brain [58]. Pain and other conscious sensations are processed in the brain and traditionally a "bottom-up" model has been suggested, i.e., damage to peripheral nerves causes central reorganization [49•]. On the other hand, it cannot be excluded that spinal, brainstem, or brain changes due to central neuropathy contribute to the generalized sensory changes. Such sensory defects may result in various types of symptoms. For example, less sensation during filling of the rectum may lead to constipation and overflow diarrhea. Some patients suffer from abdominal pain without obvious reasons. It is well-known that the peripheral somatic neuropathy in DM is often painful and can occur spontaneously or provoked by noxious or non-noxious stimuli [59]. In the same way, peripheral visceral neuropathy in DM may result in neuropathic-like abdominal pain. As central nerve lesions in humans such as in spinal cord injuries and stroke also may give rise to pain, "diabetic encephalopathy" (see below) may also result in sensory symptoms per se [60, 61].

As indicated previously, the central nervous system (CNS) is also affected by the neuropathy and recent research has shown that there are major changes in the CNS in patients with GI disorders. For example even though GI motility is intact in patients with severe CNS damage, it is partly centrally regulated, and therefore brain changes will invariably affect gut function [62]. In animals with diabetes, changes in the paraventricular nuclei of the hypothalamus as well as the dorsal motor nuclei have been described [7]. Changes in these areas affect GI function and motility. For example in preclinical studies, a pathway including the area postrema, nucleus tractus solitaries and the dorsal motor nucleus of the vagal nerve was shown to greatly impact the control of GI function including motility [7]. Such changes in motility may indirectly lead to symptoms [61]. Simple measures such as assessment of the referred pain to experimental stimulation of the gut can be used to explore the CNS. Referred pain is partly due to convergence between visceral and somatic afferents in the dorsal horn of the spinal cord, and any central hyperexcitability will increase the size of the referred pain area [63]. As increases in the referred pain areas were seen following stimulation of the upper gut in DM, this indicates a wide distribution of central sensitization [55].

Assessment of CNS alterations is mainly done via either electrophysiological or imaging methods. The resting electroencephalography (EEG) has been used to investigate the brain in patients with diabetes. This has revealed differences in brain connectivity and information flow but EEG has not yet been used to explore neuropathy or sensory changes [64, 65]. However, studies with evoked potentials (EPs, for details see next section) have shown evidence of altered central processing to visceral stimulation in diabetes patients with GI symptoms [66, 67]. In most studies, pathological EPs were found (prolonged latencies, decreased and variable amplitudes)

[67]. Based on multiple recordings it is also possible to model the corresponding brain sources. It has been demonstrated that diabetes patients had different shifts of the sources in the pain matrix, which were related to the GI symptoms [67, 68]. Especially the shift of dominant electrical activity in the insula is interesting as the insula is considered to be one of the main centers from where the upstream activation of visceral information is controlled. The findings were partly validated as greater the GI symptoms, the more anterior the insular activity was located [69•]. Finally, we investigated how the EPs and underlying brain networks were modified in diabetes patients [54, 66]. Changes were found in three brain networks as follows: (1) brainstem/operculum/frontal cortex, (2) operculum/cingulated, and (3) mid-cingulate/anterior-cingulate/operculum/deep limbic structures. The shift in operculum activity was related to the severity of GI symptoms and decreased autonomic reactivity. In the second network, the operculum activity was increased whereas the cingulated activity was decreased. These changes were associated with decreased physical quality of life. Finally, in the third network deep limbic structures were localized deeper in patients. This was also associated with decreased physical quality of life. Hence there is evidence that brain electrical activity and communication between centers thought to be active in sensory processing is abnormal in diabetes patients and this may explain some of the clinical symptoms.

In brain imaging, magnetic resonance (MR) is the dominating method. In general, brain MR studies in diabetics have shown atrophy of the brain in areas responsible for verbal, visual memory, executive functioning and information processing [70]. It was recently shown that diabetes patients with peripheral neuropathy showed reduction of cortical thickness in right postcentral gyrus compared to patients without neuropathy [71]. In patients with long-standing DM and GI symptoms, we found evidence for microstructural changes in brain areas involved in visceral sensory processing [72]. The microstructural changes were for some areas associated with GI symptoms and abnormalities such as bloating and presence of gastroparesis, and with other autonomic dysfunctions. Hence, the microstructural central changes may be involved in the pathogenesis of GI symptoms. A schematically overview of the findings can be seen in Fig. 1 and for further detail the reader is referred to [50].

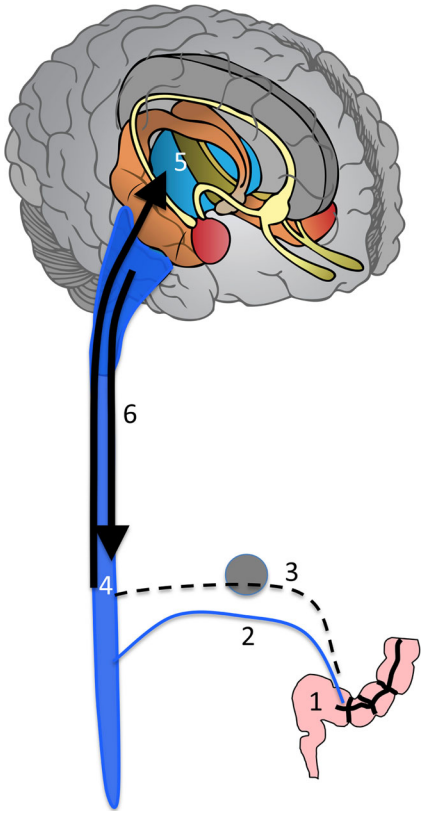

Fig. 1 Schematic drawing of the different nerves and pathways that potentially may be affected in patients with DM. *1* structural changes in the gut wall with subsequent secondary nerve changes, as well as primary neuroplastic changes in the ENS, *2* affection of primary visceral afferents, *3* changes in the sympathetic and parasympathetic ganglia and nerves, *4* spinal hyperexcitability and remodeling, *5* upstream changes in the limbic system (*colored*) and other supraspinal areas belonging to the so-called "pain matrix", and *6* deficient descending control

Testing of Sensory-Motor Dysfunction and GI Biomechanics

Proper testing of a complex system like the GI tract requires advanced technology that can provoke the system and measure relevant output parameters. It is important to control the stimulus and to measure the sensory response despite its subjective behavior. The sensory response may be recorded in various ways ranging from the use of visual analogue scales (VAS) to imaging technology and neurophysiological methods. EEG records the electrical activity on the scalp produced by activation of neurons in the brain. The activity can be recorded as either EPs following an external stimulus or in the resting state [73]. Compared with imaging methods, EPs have a better time resolution in milliseconds and reflect the neuronal changes directly. However, the spatial resolution is not as good but as different aspects (direct measure of the neuronal activity vs. the metabolic response) are assessed, electrophysiological and imaging methods can be regarded as complementary. Advances in imaging methods, such as MR, single photon emission computed tomography (SPECT) and positron emission tomography (PET), are increasingly being applied to explore symptom mechanisms. These advances are frequently coupled with experimental stimulation and have significantly furthered our understanding of the central processing. Results using these technologies in diabetes patients are provided previously in this review.

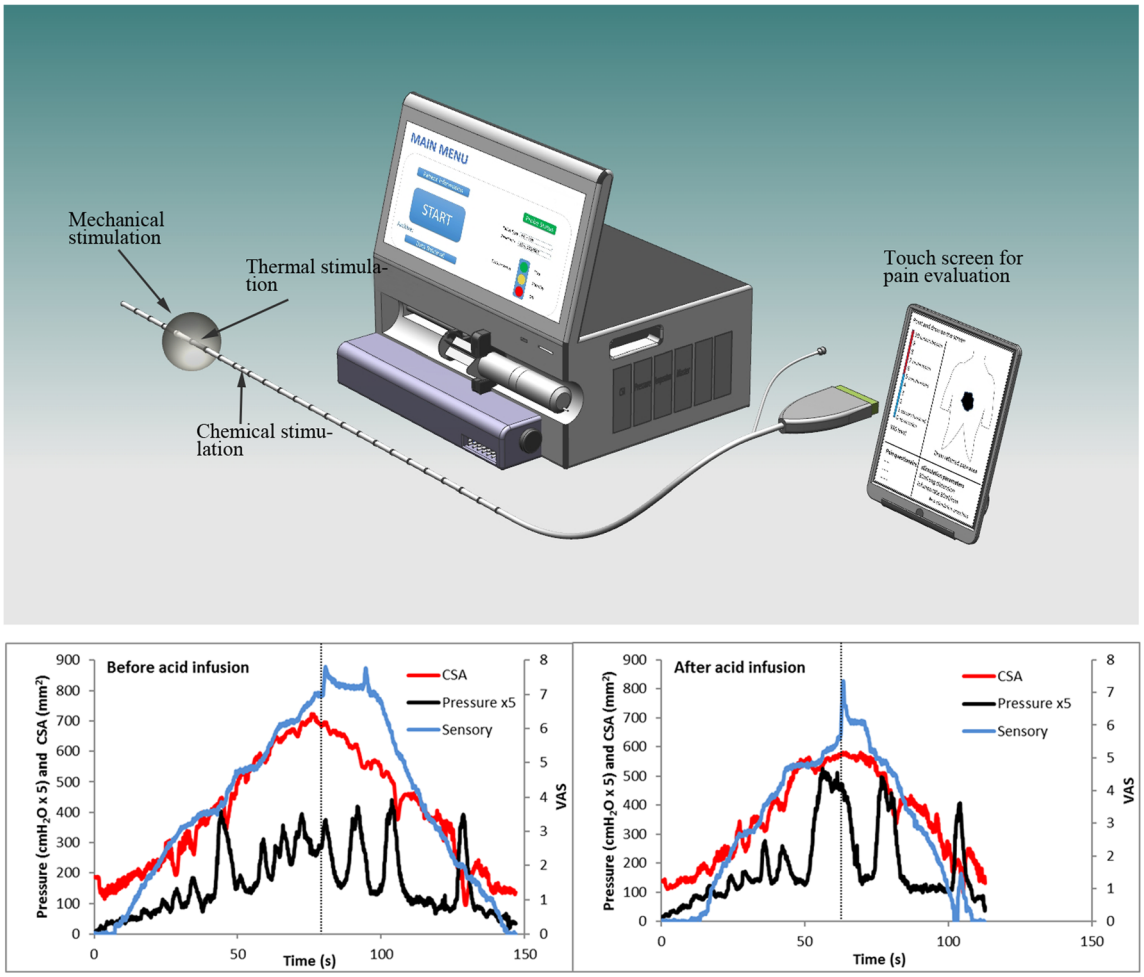

Fig. 2 Schematic drawing of the multimodal system (*top*) and examples of data recordings (*bottom*). The probe in the schematic is capable of mechanical (bag distension), thermal (recirculation of fluid inside the bag) and chemical stimulation (injection through side hole). The touch screen allows the patient or examiner to enter sensory data using a VAS scale or outlining the referred pain area. The bottom figures show bag distensions before (*left*) and after (*right*) acid stimulation in the esophagus of a healthy volunteer. The volume infusion into the bag makes the cross-sectional area (CSA) and pressure increase (note that the pressure is multiplied by 5 for scaling purposes in the figure). The pump is reversed when the volunteer indicates on the VAS that the moderate pain level is reached (VAS = 7). The pattern before and after acid stimulation is different with the major differences being that the moderate pain level is reached faster and at a lower CSA after acid stimulation compared to before stimulation. Furthermore, the contractile pattern is different with high amplitudes and long-lasting contractions after acid stimulation. These data are indicative of acid evoked hypersensitivity. The sketch was kindly provided by Sun Daming

The function of the GI tract is essentially mechanical. Ingested food and liquid bolus are transported from the pharynx to the stomach by a propagating wave of contraction that is initiated with a swallow. The ingested food is broken down in the stomach and intestines and most food components are absorbed. Remaining components and secretions are expelled from the body through the large intestine and anal canal. Symptoms relating to the mechanosensory system are frequent in diabetes. The symptoms may relate to irregularities in the mechanical function, alterations in the homeostatic state, in the environment of the mechanoreceptor or from the signaling of the central nervous system as indicated elsewhere in this review [74]. Both research based and clinical tools for studying the mechanosensory function are limited and associated with sources of error and confounding, and should be interpreted carefully [74–76].

Afferent nerves contain receptors that are mechanosensitive and are primarily located in the myenteric plexus and in the muscle layers. The mechanoreceptors are embedded in the complex geometric, morphologic and mechanical structure of the GI wall. A popular way of provoking the GI tract is to conduct a bag distension test in the lumen with concomitant measurement of the bag volume and pressure. However, there is a pressure drop throughout the wall. Therefore, intraluminal pressure is not the stimulus per se but merely a proxy for the mechanical force imposed in the vicinity of the mechanoreceptor sites. Rather than being directly sensitive to luminal pressure, the receptors react to changes in the local mechanical stresses and strains. For example, circumferential stretch is a potent stimulus. For the determination of mechanical properties, it is critical to appreciate that the GI wall is multilayered.

Thus, each layer has its own unique mechanical properties in different directions (anisotropy) particularly when exposed to very large stresses and strains. Hence, large 3D deformational theory must be applied when the biomechanics of the GI tract is investigated [75, 76].

As mentioned above the most popular way of studying the mechanosensory function in humans is by distension. The gold standards for assessment of gastric function are gastric emptying tests and the barostat [77, 78]. In mechanosensory studies, it is essential to be able to control and reliably measure the mechanical stimulus, which cannot be done merely by assessment of pressure or volume. While several technologies exist we would emphasize the most advanced namely the multimodal probe [79, 80] and endoscopic ultrasonography (EUS) [81]. In brief, the multimodal probe provides mechanical stimulation (bag distension) along with other stimulation modalities (thermal, chemical and electrical) with simultaneous assessment of the symptom level and quality of the symptoms. Figure 2 depicts a schematic of the multimodal system and examples of data recordings. The multimodal technology is based on the impedance planimetric principle where it is possible to quantitate tension (the stress resultant and moment) and strain [75, 82]. EUS provides a circumferential image of the lumen geometry and the esophageal wall in real-time. EUS has been used primarily to access longitudinal muscle layer contraction but can also be used for computation of stress-strain relations [74].

When studying the mechanosensory aspects of GI function, factors such as the stimulation protocol (magnitude, duration, mode, etc.) warrant consideration as the mechanical response (usually observed as secondary peristalsis) as well as the sensory response will depend on the preconditioning behavior and nerve adaptation [74, 76]. Controlling the mechanical stimulus and assessing the various components in the mechanosensory system remains complex and requires a multidisciplinary approach in order to avoid erroneous conclusions.

Clinical Implications

It seems reasonable to believe that better diabetic control will prevent structural changes and improve the mechanical function. Diabetic patients with GI symptoms have changes in the autonomic nervous system but also in the primary sensory nervous system of the GI tract and in the CNS. One study showed impaired gastric accommodation and gastric hyposensitivity in 60 % of patients with diabetes [83]. Due to these relatively recent findings, future targets in treatment of GI symptoms may be based on modulation of the neuroplastic changes, either pharmacologically or with afferent nerve stimulation. Classical treatment may be based on visceral analgesics including anti-depressants and anti-convulsive agents. However, several new drugs such as prucalopride and linaclotide have the potential to improve motility as well as visceral pain and other sensory symptoms [84, 85]. There are no controlled studies in diabetic patients, but these drugs may improve symptoms especially in patients where motility dysfunction is documented. Gastric pacing is another recent approach that has been documented to improve gastroparesis and associated symptoms such as nausea and vomiting [86]. The direct effect is likely not on motility but rather through to modulation of the different brain signaling pathways. It has been shown that vagal nerve stimulation activates inhibitory nerve pathways from the brainstem. These dampen the incoming afferent traffic thereby decreasing symptoms [87]. Although still in its early stages, less invasive methods such as cutaneous stimulation of vagal afferents may also change pain and motility [88].

Finally, many antidiabetic drugs can potentially protect against harmful changes in the CNS. New antidiabetic drugs such as the incretin hormones may be beneficial, for example GLP-1 receptors are found in the heart, lungs, kidneys, the GI tract and in the brain [89, 90]. GLP-1 also acts as a neuropeptide with direct effect on regulation of vagal activity. Thus, these drugs may be beneficial help to improve GI symptoms. There may also be a neuroprotective function [91]. Future research with such drugs in humans is highly warranted.

Conclusions

The sensory-motor properties of the GI tract in diabetic patients are complex and remain incompletely understood. However, in recent years a vast amount of scientific and clinical studies has advanced our understanding of the system. It is evident that damage to neural as well as non-neural structures in the GI tract as well as central changes are important for the altered sensory-motor properties in diabetes patients. Advances in technologies such as multimodal stimulation, imaging and electrophysiology have been applied to the field and have improved this understanding. This may herald a bright future in terms of clinically applicable investigations but also in stratifying and individualizing patient management. Nevertheless, further research is needed in both health and disease, to realize this goal.

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Compliance with Ethical standards

Conflict of Interest Hans Gregersen has received a patent for a multimodal motility device that is broadly relevant to some of the work described in this article.

Donghua Liao, Anne Mohr Drewes, Asbjørn Mohr Drewes, and Jingbo Zhao declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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