Autonomic Visceral Neuropathy and Gastrointestinal Disorders

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Chapter Objectives

- The autonomic nervous system consists of the enteric, parasympathetic and sympathetic nerve systems. In the early stages of autonomic neuropathy, the vagal nerve seems to be the most vulnerable consequently compromising its function.
- Autonomic neuropathy is one of the most burdensome symptoms in patients with diabetes mellitus. It is, however, frequently under-diagnosed.
- In patients with long-standing diabetes, up to 40% suffer from gastrointestinal symptoms.
- Symptoms induced by visceral neuropathy cover the entire gastrointestinal tract and include nausea and vomiting, bloating, early satiety, diarrhoea and constipation.
- Both hyperglycaemic and hypoglycaemic episodes coalesce to form a cumulative indirect cascade which initiates and maintains neuroinflammation in diabetic autonomic neuropathy.

Introduction

The brain-gut axis is a bidirectional nexus of the sensory input from the gastrointestinal (GI) tract and efferent pathways, which is involved in secretion of digestive hormones, homeostatic regulation and gut motility. This axis comprises among others the autonomic nervous system (ANS), comprising the enteric nervous system (ENS) and parasympathetic and sympathetic branches, which have a delicate regulatory interaction. Therefore, the ANS has an essential role, and any dysfunction leads to impaired mediation of visceral regulation. Consequently, damage to the ANS such as development of diabetic autonomic neuropathy (DAN) is one of the most burdensome complications to diabetes, yet frequently under-diagnosed. These complications cause symptoms in the GI tract such as nausea, vomiting, diarrhoea and constipation; see Fig. 54.1. It is difficult to diagnose DAN, but it may be defined as impaired functions of the involved nerves controlling the involuntary body functions such as the cardiovascular, urinary, pulmonary and digestive systems [1]. Cardiac autonomic neuropathy is a measureable impaired regulation of the heart function, leading to dysrhythmias such as atrial fibrillation, tachycardia and even cardiac arrest [2]. Patients with cardiac autonomic neuropathy develop an impaired adaptability of the heart rate, assessed as reduced heart rate variability [3]; see Chap. 59 for further elaboration. In this chapter we focus upon autonomic gastrointestinal neuropathy in patients with diabetes, explaining the underlying pathophysiology and the symptomatology in the GI tract.

Diabetic autonomic neuropathy could be defined as impaired functions of nerves controlling involuntary body functions.

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J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-030-11815-0_54

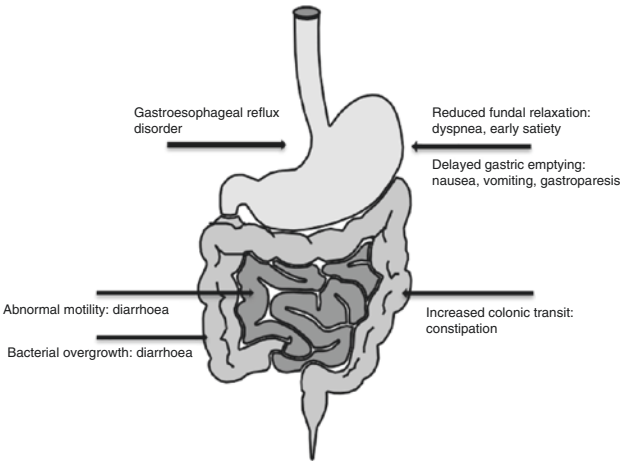

Fig. 54.1 Gastrointestinal disorders related to autonomic neuropathy

Neuropathy in Diabetes Mellitus

Neuropathy can objectively be demonstrated in 40–50% of who are diagnosed with diabetes for >20 years [4]. Recent research has shown that structural changes in endoneuronal capillary morphology and vascular reactivity exist prior to neuropathy in patients with type 2 diabetes [5]. Furthermore, such endoneuronal hypoxia was associated with reductions in nerve conduction velocities. The pathophysiology underlying these findings is however complex and multifactorial and includes neuronal changes within Schwann cells, axons and the microvascular compartment [6]. In addition, several biochemical mechanisms triggered by, e.g. hyperglycaemia or hypoglycaemia also lead to neuropathy, which will be elaborated in this chapter; see Fig. 54.2.

The ENS innervates the gastrointestinal tract, gallbladder and pancreas with motor neurons, sensory neurons and interneurons. ENS controls the fluid transport between the gut and its lumen, local blood flow as well as the gut motility. These functions are maintained as the ENS receive and integrate the incoming information leading to efferent transmission, which regulate the digestive system from the brainstem. Thus, there is a close connection to the central nervous system (CNS) in order to balance physiological demands. Due to the enormous amount of neurones that corresponds closely to the number in CNS, the ENS is by some recognized as the second brain [7, 8]. All these neurones and their interconnections are vulnerable to DAN [9].

The neuronal tissue in the brain might undergo changes as well [10, 11]. Animals where diabetes has been induced showed changes in the CNS. Furthermore, functional brain imaging and electroencephalographic recordings in patients with diabetes confirm functional and structural brain changes [3]. The imaging studies demonstrated mainly microstructural changes in brain areas involved in visceral sensory processing in patient with diabetes and GI symptoms. The encephalographic studies indicated that altered insular processing of sensory stimuli could be the key player in symptom generation. In particular one study found that the deeper the insular electrical source was located, the more GI symptoms the patients experienced [12]. These studies with electroencephalography were often conducted in combination with quantitative sensory testing, and mostly it was found that stimulation of the GI organs induced hyposensitivity. This is in line with patients suffering from somatic diabetic neuropathy where pain and other sensations typically are associated with hypoalgesia to stimulation of the skin. The imaging findings and electrophysiological changes within the brain were associated with GI symptoms in patients with diabetes; therefore they might represent a biomarker for disease severity and hence be a new therapeutic target for neuromodulation or pharmacological therapy [3]. In Fig. 54.3 a conceptual model illustrating the different nerve pathways that may contribute to the GI symptoms in DM is shown.

In the early stages of DAN, alterations in the ENS are masked and difficult to detect. However, the vagal nerve due to its length and widespread appearance is most vulnerable to impaired function, and thus most work regarding DAN characterizes the vagal function [13]. The vagal nerve is the longest of the cranial nerves, and among other functions, it transmits signals from the gut wall receptors, sensitive to chemical and mechanical stimuli, controlling gut motility, secretion and feeding behaviour [14]. Patients with diabetes and GI symptoms experience gastric retention and a delay in transit with segmentation of barium column within the small intestine, which was similar to changes found in patients with vagotomy [15, 16]. It has been shown in animal studies that the presence of glucose-responsive neurons has been identified in the CNS which may alter the vagal efferent activity [17]. Therefore, the systemic changes in blood glucose experienced in both hyper- and hypoglycaemic episodes might have a direct effect on the parasympathetic tone. Increased blood glucose level increases the level of oxidative stress and pro-inflammatory cytokines involved in neuroinflammation. Recent studies have shown that both electrical and pharmacological stimulation of the vagal nerve reduces the level of pro-inflammatory cytokines in both healthy subjects as well as experimental inflammatory and autoimmune diseases [18, 19]. Hence, enhanced vagal tone might activate the cholinergic anti-inflammatory reflex and may have the potential to modulate the immune system [20, 21]. Therefore, it is plausible that enhanced vagal activity might have a protective function on diabetes-induced neuroinflammation. Taken together, the multifaceted mechanisms linked to ENS and ANS explain the variety of symptoms underlying DAN [22].

Fig. 54.2 Structural changes and biochemical mechanism triggered by, e.g. hyperglycaemia or hypoglycaemia may induce visceral neuropathy

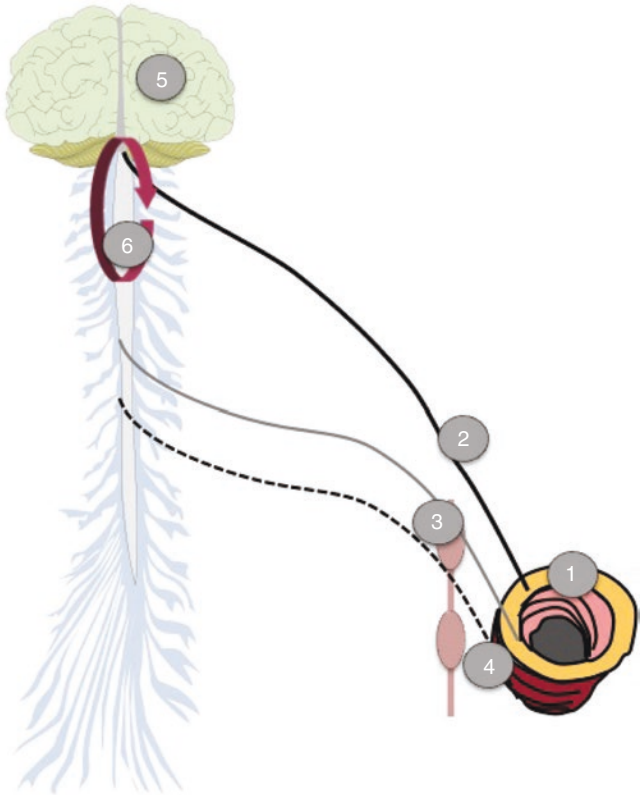

Fig. 54.3 Nerve pathways and mechanisms that may contribute to gastrointestinal symptoms in patients with diabetes mellitus: (1) biochemical, vascular and degenerative changes in the enteric nervous system; autonomic neuropathy that may affect (2) the vagal nerve (black line) and (3) sympathetic pathways (grey line) and indirectly modulate sensations from the gut; (4) affection of visceral (and somatic in case the peritoneum is involved) afferents (dotted line) mediating sensations such as pain; and (5) structural and functional changes in the brain (and spinal cord), together with (6) affection of spino-bulbo-spinal loops

In experimental models of diabetes, reduced levels of neurotrophic support, including insulin-like growth factor and nerve growth factor, have been found. These findings have implicated reduced endoneuronal blood flow and thereby causing neuronal damage. The consequence of such impairment in blood flow also leads to alteration of the nitric oxide metabolism and the Na^+/K^+ ATPase activity [23]. Furthermore, animal studies indicated that a changed Na+/K+ pump function may occur as a result of C-peptide deficiency. This may cause shunting glucose through the polyol pathway leading to increased levels of sorbitol and alteration of nerve excitability recovery cycle, which ultimately leads to neuronal damage [24, 25]. A last mechanism to mention is nerve damage through complement activation, as it has been reported in several peripheral neuropathies [26, 27]. A study on chronic peripheral neuropathy in children found a cell surface deficiency of the protein CD59, which is a complement regulatory protein. Furthermore, sural nerve biopsies from patients with diabetes have shown presence of activated complement proteins and membrane attack complex neoantigen [26]. Complement activation might be a potential new area to investigate when explaining autonomic neuropathy.

The Hyperglycaemia Hypothesis

Consequences of hyperglycaemia are increased intracellular glucose level and cellular toxicity. This glucotoxicity alters cell function in different ways causing increased level of diacylglycerol (which in turn activates protein kinase C) and synthesis of polyols and hexosamines that accumulate intracellularly [28–30]. These metabolic pathways are summarized in Fig. 54.4 and are shortly explained in the following:

A minor branch of glycolysis is the hexosamine biosynthesis pathway, where fructose-6-phosphate converts to glucosamine-6-phosphate, which is a rate-limited enzyme. Hexosamine accumulates intracellularly causing oxidative stress. Secondly, another intracellular metabolic pathway is the polyol. When the polyol pathway is activated, it may cause reduction of Na^+/K^+ ATPase activity and osmotic damage and intracellular oxidative stress [31]. Thirdly, increase in diacylglycerol and protein kinase C pathways is believed to increase the activity of cytosolic phospholipase A2 and produce prostaglandin E_2 as well as other pro-inflammatory mediators, which inhibits cellular (Na^+/K^+) ATPase [32, 33].

The exact mechanism by which these pathways lead to altered cell function is not fully understood, but taken together they coalesce to induce oxidative stress [34]. In the mitochondria, levels of free radicals, such as nitrogen species and superoxide, rise. However, the ability to gather free radicals is reduced because of a reduction of the proton donor nicotinamide adenine dinucleotide [29]. Additionally this mechanism may activate an enzyme, poly(ADP-ribose) polymerase, of great importance to deoxyribonucleic acid

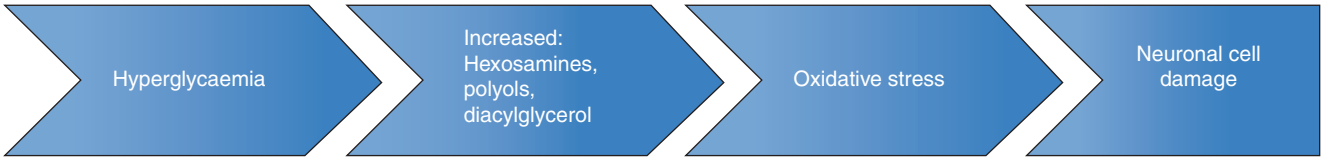

Fig. 54.4 Hyperglycaemia induces an increased level of hexosamines, polyols and diacylglycerol within the cell, which may cause oxidative stress inducing cell damage

repair, and this activation may cause breakup of the deoxyribonucleic acid strands. The consequence of this mechanism is critically low level of adenosine triphosphate in, e.g. Schwann cells, possibly leading to neuronal death [35].

When superoxide level rises, an inhibition of the key enzyme in glycolysis (glyceraldehyde-3-phosphate dehydrogenase) is manifest, resulting in enhanced activity in the involved biochemical pathways including further production of polyols, hexosamines, poly(ADP-ribose) polymerase and advanced glycation end products and thereby closing the loop of a vicious cycle [36]. For further reading the following references are recommended: [35–37].

It has been found that the hyperglycaemia theory may be more valid for patients with type 1 than type 2 diabetes. Additionally, a Cochrane review found that improved glucose control prolongs the onset of peripheral sensorimotor neuropathy in type 1 DM, whereas it only had a modest, non-significant relative risk reduction in patients with type 2 DM after a follow-up period of 4 years. On the contrary, when the follow-up period was 15 years for the same cohort, the effect of increased glucose control showed significant risk reduction [38–40]. Even though these studies were conducted on peripheral axons, similar mechanisms are likely present in other nerve tissues, such as the ANS.

Finally the formation of advanced glycation end products contributes to the intracellular non-enzymatic glycation of proteins, in which the extracellular matrix interacts with various receptors and possibly leads to pro-inflammatory gene expression that further amplifies the process [37].

The Influence of Severe Hypoglycaemia

Prolonged and severe hypoglycaemia may result in increased release of excitatory amino acids, which may cause uncontrolled triggering calcium influx. This again activates proteolytic enzymes that are known to cause neuronal damage [41]. Furthermore hypoglycaemic levels of glucose may be counter-regulated through hormones inducing an acute rise in blood viscosity and haematocrit levels, which influences capillary blood flow especially when structural changes of the metabolic pathways and vessel of the neurons are already present [42].

Taken together, the biochemical pathways induced by hyperglycaemia and consequences of hypoglycaemia coalesce to form a cumulative indirect cascade that can initiate and summate neuroinflammation, as is observed in DAN.

Table 54.1 Possible diabetic neuropathy-induced gastrointestinal symptoms

Diabetic neuropathy-induced symptoms
Nausea
Vomiting
Reflux
Gastroparesis
Bloating
Constipation
Diarrhoea

Gastrointestinal Disorders in Diabetes Patients

Diabetic neuropathy may induce gastrointestinal symptoms, which will be elaborated in the following section (see Table 54.1). In several studies patients with diabetes have reported more symptoms originating from the GI tract in comparison to people without diabetes [43–45]. Up to 20% of patients with diabetes have diarrhoea, and up to 60% suffered from constipation [15, 46]. One study reported that long-term type 1 DM was accompanied by increased frequency of upper GI symptoms [47, 48]. On the other hand another study found the prevalence of upper gastrointestinal symptoms, abdominal pain and constipation was not significantly increased [49]. The prevalence of these symptoms varied which could have different explanations. However, due to lack of consensus, the assessment of GI symptoms varies, and thus to ensure consistency between study sites, it has been suggested to use the Diabetes Bowel Symptom Questionnaire in future epidemiological and clinical studies [50].

Gastrointestinal Reflux Disease

Patients with diabetes often suffer from nausea and vomiting [51]. One reason may be autonomic neuropathy-induced gastro-oesophageal reflux disease (GORD), where gastric content into the oesophagus causes complications or symptoms. Symptoms include heartburn and regurgitation.

Clinical findings in GORD may also include laryngitis, chronic cough and bronchospasm [52]. GORD could be seen in patients with DAN due to a hyperglycaemia induced lower oesophageal sphincter pressure and increased amount of transient lower oesophageal sphincter relaxations. Furthermore, studies report that impaired relaxation of the gastric fundus might cause early satiety and dyspeptic symptoms that also influence the symptom pattern in GORD [53].

Patients experiencing reflux should in many cases undergo endoscopy possibly accompanied by biopsy. Acidic and non-acidic content in the oesophagus can be assessed with pH-impedance monitoring, and the swallowing and sphincter functions can be investigated with oesophageal high-resolution manometry, which is especially relevant in diabetic patients where neuropathy is suspected.

Reflux treatment is individual and determined by severity and progress. First of all it is important to avoid provoking factors such as large meals, coffee and alcohol. Symptoms caused by reflux can be treated with proton-pump inhibitors, but occasionally antacids, H_2 blockers or foaming agents are used. However symptoms such as nausea and vomiting are mainly controlled from the brain; therefore it is mandatory to consider dysfunction of the CNS when other causes are ruled out [3]. It is expected that the alterations in the CNS system persist even long after the primary cause (if any) is ruled out.

Gastroparesis

The most common cause of gastroparesis is diabetes, and of all cases of gastroparesis, about one-third originates from diabetes-induced gastroparesis [54, 55]. The cumulative incidence for gastroparesis is approximately 5% for patients with type 1 DM and 1% for type 2 DM [56]. Even though gastroparesis proceeds with the presence of delayed gastric emptying, most research have focused on this topic, as it is present in 30–50% with long-lasting diabetes [57]. The typical patient experiencing symptomatic gastroparesis has a long history of insulin-dependent diabetes and poor glycaemic control lasting for several years. In some cases recent onset of gastroparesis is the only diabetic complication experienced by the patient. Other symptoms may include nausea, vomiting, bloating, early satiety and epigastric pain [58]. Furthermore, gastroparesis predisposes for small intestinal dysfunction in up to 80% of those presented with clinical symptoms, which may lead to small intestinal bacterial overgrowth or interaction between host and gut microbiota [59]. One study investigating the microbiome in patients with type 1 diabetes even indicated that the patients had a decreased diversity, reduced stability and more classified members in their microbiome compared with healthy controls [60].

The detailed anamnesis is crucial when diagnosing a patient with gastroparesis, and validated questionnaires such as the PAGI-SYM are used to assess the patient-reported symptoms [61], from which the Gastroparesis Cardinal Symptom Index (GSCI) can be calculated. To investigate a gastroparetic patient, gastroscopy is often needed to rule out differential diagnosis such as celiac disease, ulcers and cancer. If symptoms resemble those seen after truncal vagotomy (mild gastric dilation, poor to no peristalsis, residual gastric secretions despite a prolonged fast, atonic duodenal bulb and open pylorus), then the diagnosis is straightforward. However a proportion of these patients have no such gastroscopic symptomatology [15, 62]. In such cases motility investigations such as scintigraphy or radiopaque markers are needed [63]. Scintigraphy is in most laboratories the "gold standard" to assess gastric emptying time, where retention of a meal labelled with ^{99m}Tc sulphur colloid is compared to normal reference values [57]. Recently, the wireless motility capsule (such as the SmartPill), which consists of a portable receiver, a wireless transmitting capsule and displaying software, has been taken into use. Following consumption of a standard meal, the participant swallows the capsule, which samples and transmits pressure, pH and temperature data, from which segmental transit times (including gastric emptying time) can be derived [64, 65].

Alternative tests to assess gastric emptying include breath tests which measure the non-radioactive isotope ^{13}C-labelled digestible substance and measure the metabolized isotope in the breath, emptying of radiopaque markers from the stomach by use of fluoroscopy, ultrasonography, ultrasound and the paracetamol absorption test which is valid for gastric emptying of liquid meals [57, 63, 66–69].

The treatment of gastroparesis is challenging, but patients should be encouraged to focus on glycaemic control. Constipation – if present – should also be adequately treated. Furthermore symptoms can be diminished by use of pharmacological agent that increases motility such as erythromycin or (off-label) prucalopride. In theory patients with concomitant functional disorders or bloating may benefit from low fermentable oligo-, di- and monosaccharides and polyol diet (low FODMAP) diet [70]. It is a dietary intervention under investigation in dysmotility disorders, which is why it might benefit diabetic patients with neuropathy-induced dysmotility [71]. Avoidance of these carbohydrates should be global and not individual in order to reduce symptoms, and it is important to recognize that ingestions of FODMAPs are not the cause of the disease but limited intake may represent an opportunity to reduce the patients' symptoms [70]. Another dietary intervention has been studied by Olausson et al. [72]. In this study patients with diabetes mellitus and gastroparesis were to eat a small particle diet. They found that patients on this diet improved in key symptoms such as nausea and vomiting. Furthermore, gastric electrical stimulation has been approved by the US Food and Drug Administration to alleviate symptoms in gastroparesis. The underlying mechanisms are debated, and a growing body of evidence points towards alteration of the

sympatico-vagal balance rather than enhancing gastric motility [73]. Nonetheless, the procedure has shown to decrease both symptom frequency and severity [74]. A potentially new method is stimulation of the vagal nerve during the skin together with deep breathing. This has been shown to increase gastric contractions in healthy volunteers [75], but to date no studies in diabetes exist.

Diarrhoea

Diarrhoea is observed in up to 20% of patients. Diarrhoea can be present as episodic, loose stool consistency and periods with normal bowel function alternating with constipation [15, 59]. The cause of idiopathic diabetic diarrhoea is not known; however the most recognized explanation is shifted sympatico-vagal balance as both sympathectomy and truncal vagotomy can cause diarrhoea. It may be caused by rapid transit or slow transit together with bacterial overgrowth [59, 76]. Even though autonomic neuropathy often induces prolonged transit times, it may also indirectly cause diabetic diarrhoea [15]. Furthermore, a study found that long-standing diabetes was associated with a decrease in number of interstitial cells of Cajal as well as decreased inhibitory innervation and an increase in excitatory innervation causing diarrhoea [77].

Abnormal and dis-coordinated motility of the small bowel may also lead to small intestinal bacterial overgrowth, which potentially also causes diarrhoea [78]. Thirdly faecal incontinence due to *anorectal dysfunction* can be present due to a weakened internal anal sphincter and lowered rectal sensory threshold [79]. Finally, as insulin is a trophic hormone for the acinar and ductal cells in the pancreas, *pancreatic exocrine insufficiency* must be considered, especially when steatorrhoea is found, and as a parallel, patients with pancreatitis may have demolished the visceral nerves [80]. Appropriate test with pancreatic enzyme therapy or pancreatic function tests are recommended.

Diagnosis of neuropathy-induced diarrhoea serves to exclude differential diagnosis that can lead to chronic watery diarrhoea, for example, microscopic colitis or irritable bowel syndrome. If differential diagnosis can be excluded, the diagnosis of idiopathic diabetic diarrhoea can be made (non-specific radiological findings and clinical symptoms) [15].

In order to treat patients with severe and long-lasting diabetic neuropathy-induced diarrhoea, there are four important targets: (1) hydration, nutrient deficiency and correction of electrolyte deficiencies; (2) symptomatic treatment with, e.g. codeine or loperamide, as antidiarrhoeal medication by prolonging transit time and reduction of peristalsis; (3) treatment of underlying causes such as bacterial overgrowth with probiotics/antibiotics; or (4) enzyme supplementation in case of exocrine pancreas insufficiency [81].

Constipation

Motility disorders, more specifically reduced colonic transit time due to dysfunction of the ENS and ANS, lead to constipation [53, 82]. A study investigating the prevalence of constipation in diabetics showed that 60% reported constipation, and thus it is the most commonly reported symptom. Furthermore the same study reported that 76% of the patients suffered from at least one GI symptom [15]. Furthermore reduced bowel motility may result in specific constipation that occasionally leads to overflow incontinence that influences the clinical picture [81]. Of note, 80% of patients with diabetic diarrhoea also suffered from periods with constipation.

Constipation can be evaluated with radiopaque markers, scintigraphy or different capsules as mentioned above and recently reviewed in [64]. In patients with functional gastrointestinal disorders, a reduction in caecal and colonic contractility as well as bloating and distension was associated with excessive fermentation in the caecum assessed as a higher pH drop across the ileocaecal junction [83]. A recent study found that patients with type 1 diabetes had prolonged small bowel transit, colonic transit, gastric emptying and whole-gut transit time compared with healthy controls. Furthermore prolonged colonic transit time in association with an increased fall in pH across the ileocaecal junction was found [65].

Similar findings were shown in a recent paper where the wireless motility capsule was used to show pan-enteric prolongation of gastrointestinal transit times and a more acidic caecal pH, which may represent heightened caecal fermentation in diabetics [65].

Constipation could be due to alterations in the microbiota - or vice versa - however the exact mechanism on how alterations in microbiota influences the colonic motility is unknown. One study indicates that the breakdown of short-chain fatty acids induces acidic milieu and thus modifies motility rhythm in the hindgut [84]. In support of this, animals who received antibiotics were shown to modulate their gut microbiota, which consequently improved their glucose tolerance and sensitivity to insulin [85]. Similar mechanisms are plausible in humans but need yet to be investigated in further detail.

Constipation may be treated conservatively with regular exercise, increased intake of dietary fibres and focus on hydration. Medical interventions may include bulk fibres or osmotic laxatives. Frequently osmotic active drugs are also

used in combination with enemas. The reader is referred to an article by Rao S.C. for further detail [86].

In chronic constipation due to autonomic neuropathy and slow transit, newer drugs such as prucalopride, a selective 5-HT receptor agonist, may prove to be useful as it enhances colonic transit. Furthermore, lubiprostone stimulates secretion of electrolyte secretion and colonic water through activating of type 2 chloride channels in enterocytes. Another plausible target in the future is altering the composition of the microbiota through dietary alterations or faecal transplantation.

Diagnosis of Diabetic Autonomous Neuropathy

The clinician should ideally investigate the GI symptoms as described in section "Constipation" of this chapter. Additionally when gut symptoms arise in patients with diabetes, autonomic neuropathy should always be suspected, especially if the patient also suffers from distal symmetric polyneuropathy. Conventional measures of the autonomic function are indirect methods that rely on cardiovascular reflexes. However the detection of early and subtle abnormalities in the parasympathetic system remains controversial, as the methods are relatively insensitive to sympathetic deficits [1, 87]. Classically, the ANS function has been correlated to recordings of the peroneal nerve [1, 88]. However, these methods are unspecific, invasive and time consuming, which could explain why the most popular and the most utilized are time-domain-derived parameters of heart rate variability or sudomotor reflex testing. One way to measure real-time brainstem vagal efferent activity known as cardiac vagal tone is with the NeuroScope, a non-invasive measurement using ECG electrodes to detect phase shift in the beat-to-beat RR interval, which is described in detail elsewhere [89]. However, diagnosing DAN may be complicated as there is poor association between autonomic function testing and experienced GI symptoms [1].

There is no consensus regarding the optimal test parameters [90–92], and the shortcomings of each method and their interpretation are responsible for the lack of formal diagnosing of DAN. Thus, such diagnosis is frequently delayed, the causes of which are most certainly multifactorial but arguably include the non-specificity of presenting symptoms, the lack of clinician appreciation and the limited availability of specialized diagnostic services. Nevertheless, diagnosis of DAN is important as it has a pivotal role in the pathophysiology of a number of diabetes-induced complications.

Concluding Remarks

Manifest DAN is one of the most burdensome symptoms, yet frequently under-diagnosed. The autonomic neuropathy induces symptoms such as nausea, vomiting, bloating, early satiety, diarrhoea and constipation, which undoubtedly compromise quality of life in these patients. The frequent presence of GI symptoms in patients with diabetes should make the clinician focus on DAN. Conservative and symptomatic treatment should accompany the suspicion of DAN, and if possible the underlying cause should be treated. Ideally treatment should be individualized as the symptom complex differs between patients. New emerging therapies are in pipeline, and future research will undoubtedly result in improvement of the armamentarium clinicians have available for treatment of the severe complications associated with DAN.

Multiple Choice Questions

1. In patients diagnosed with diabetes for >20 years neuropathy can be demonstrated in:
   (a) 0–10%
   (b) 10–20%
   (c) none
   (d) 40–50%
   (e) 70–80%
2. The autonomic nervous system comprises
   (a) The sympathetic, parasympathetic branch
   (b) The enteric nervous system and parasympathetic and sympathetic branches
   (c) The sympathetic branch
   (d) The parasympathetic and enteric nervous system
   (e) The brain, the so-called second brain "the enteric nervous system" and the sympathetic branch
3. In patients with long-standing diabetes, up to how many percentage of the patients suffer from GI symptoms such as nausea and vomiting?
   (a) 10%
   (b) 12%
   (c) 20%
   (d) 25%
   (e) 40%
4. Which part of the gastrointestinal tract can be affected by visceral neuropathy?
   (a) The upper GI tract
   (b) The lower GI tract
   (c) The bowel
   (d) Only the anorectal part of the GI tract

(e) It is possible that the neuropathy cover the entire gastrointestinal tract causing symptoms such as nausea and vomiting, bloating, early satiety, diarrhoea and constipation

5. In order to treat patients with reflux, which statement is most correct?
   (a) The only treatment is avoiding provoking factors such as large meals.
   (b) The only treatment is medical including combinations of antacids and proton-pump inhibitors.
   (c) First of all it is important to avoid provoking factors such as large meals, coffee and alcohol. Symptoms caused by reflux can be treated with antacids, H_2 blockers, proton-pump inhibitors or foaming agents
   (d) Constipation treatment should be the first option.
   (e) Currently no treatment exists.
6. The typical patient experiencing symptomatic gastroparesis is
   (a) A newly diagnosed type 1 diabetic
   (b) A patient with a long history of insulin-dependent diabetes and poor glycaemic control lasting for several years
   (c) A diabetic with extreme alcohol abuse
   (d) A newly diagnosed type 2 diabetic
   (e) A patient with a long history of well-controlled diabetes
7. Hypoglycaemia has been shown to cause cell damage but how?
   (a) It increases levels of NO in the entire body.
   (b) Unhealthy levels of calcium leave the cell.
   (c) Reduction in release of excitatory amino acids protecting the cell
   (d) Increased release of excitatory amino acids, which may cause uncontrolled triggering calcium influx. This again activates proteolytic enzymes that are known to cause neuronal damage
   (e) The production of reactive oxygen species is limited.
8. In order to treat patients with diabetes and diarrhoea, which statement is most correct?
   (a) Hydration, nutrient deficiency and correction of electrolyte, antidiarrhoeal medication to prolonging transit time and reducing peristalsis as well as reducing faecal volume in order to control symptoms. Treatment of underlying cause
   (b) Antidiarrhoeal medication for 1 week
   (c) Hydration, nutrient deficiency and correction of electrolyte and treatment of underlying cause such as bacterial overgrowth which should be treated with antibiotics
   (d) Hydration, nutrient deficiency and correction of electrolyte and treatment of underlying cause such as anorectal dysfunction
   (e) Surgery of the intestines
9. Which of the following statements about the pathophysiological explanation behind visceral neuropathy is most correct?
   (a) Hyperglycaemia is the only main player in inducing oxidative stress.
   (b) Hypoglycaemia is the only main player in pro-inflammatory mechanism.
   (c) Hyperglycaemia and hypoglycaemia are the only main players in inducing neuronal damage.
   (d) Peripheral and autonomic neurons, as well as their interconnections, are particularly vulnerable to hyperglycaemia. It is obvious that any increase in glucose is associated with increased risk of injury to the organ including neuropathy
   (e) Hyperlipidaemia is the main player alone to induce oxidative stress and pro-inflammatory mechanisms.
10. The measurements of GI symptoms have varied in many studies. What should the researcher be aware of in future studies?
   (a) Every patient with gut symptoms should be offered an upper endoscopy locating symptoms.
   (b) Every patient with gut symptoms should be offered an upper endoscopy as well as an colonoscopy to investigate the entire gastrointestinal tract.
   (c) In future epidemiological and clinical studies, the Diabetes Bowel Symptom Questionnaire is suggested as a consistent method to measure GI symptoms
   (d) A computed tomography scan of the body should be conducted in order to cover every symptom in patients with diabetes.
   (e) The variation is unavoidable and must be accepted.

Correct Answers

1. (d) 40–50%
2. (b) The enteric nervous system and parasympathetic and sympathetic branches
3. (e) 40%
4. (e) It is possible that the neuropathy cover the entire gastrointestinal tract causing symptoms such as nausea and vomiting, bloating, early satiety, diarrhoea and constipation
5. (c) First of all it is important to avoid provoking factors such as large meals, coffee and alcohol. Symptoms caused by reflux can be treated with antacids, H_2 blockers, proton-pump inhibitors or foaming agents
6. (b) A patient with a long history of insulin-dependent diabetes and poor glycaemic control lasting for several years

7. (d) Increased release of excitatory amino acids, which may cause uncontrolled triggering calcium influx. This again activates proteolytic enzymes that are known to cause neuronal damage
8. (a) Hydration, nutrient deficiency and correction of electrolyte, antidiarrhoeal medication to prolonging transit time and reducing peristalsis as well as reducing faecal volume in order to control symptoms. Treatment of underlying cause
9. (d) Peripheral and autonomic neurons, as well as their interconnections, are particularly vulnerable to hyperglycaemia. It is obvious that any increase in glucose is associated with increased risk of injury to the organ including neuropathy
10. (c) In future epidemiological and clinical studies, the Diabetes Bowel Symptom Questionnaire is suggested as a consistent method to measure GI symptoms

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Further/Suggested Reading

Brock C, Brock B, Pedersen AG, Drewes AM, Jessen N, Farmer AD. Assessment of the cardiovascular and gastrointestinal autonomic complications of diabetes. World J Diabetes 2016;7(16):321–32. This article is recommend as further reading if one is interested in knowing more about the cardiovascular system and the gastrointestinal tract in relation to DAN.

Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. Ann Intern Med 1983;98(3):378–84. Provides an overview of gastrointestinal symptoms in patients with diabetes.

Rayner CK, Samsom S, Jones KL, Horowitz M. Relationships of upper gastrointestinal motor and sensory function with glycemic control. Diabetes Care 2001;24(2):371–81. A great article to read if you wish to know more about the effect of acute change in blood glucose toward the upper gastrointestinal tract.

Sangnes DA, Søfteland E, Biermann M, Gilja OH, Thordarson H, Dimcevski G. Gastroparesis- causes, diagnosis and treatment. Tidsskr Nor Laegeforen 2016; 136(9):822–6. https://doi.org/10.4045/tidsskr.15.0503. This article provides a thorough knowledge about gastroparesis including in relation to diabetes.