CLINICAL ASPECTS OF THE DIGESTIVE AUTONOMIC NEUROPATHY IN DIABETES MELLITUS: A REVIEW

LAURA POANTĂ, RALUCA PAIS, FLAVIU RUSU, DAN L. DUMITRAȘCU

2nd Department of Internal Medicine, University of Medicine and Pharmacy Iuliu Haţieganu, Cluj Napoca

Abstract

Autonomic neuropathy (AN), also called visceral neuropathy, is a disease of the autonomic nervous system affecting mostly the internal organs. In diabetes mellitus this is a frequent but undiagnosed complication. Digestive autonomic neuropathy can affect all the segments of the digestive tract. Over 50% of the patients with diabetes mellitus suffer from gastrointestinal tract symptoms. The most frequent signs and symptoms associated with digestive autonomic neuropathy are: esophageal motility disorders and GERD, delayed gastric emptying, small bowel dysfunction and colonic dysfunction (diarrhea, constipation, and abdominal pain).

A large number of studies showed that diabetic autonomic neuropathy have consequences for long-term prognosis and quality of life of the affected patients, so it is of a great importance to diagnose this complication in early stages.

Keywords: diabetes mellitus, autonomic neuropathy, digestive symptoms.

ASPECTE CLINICE ALE NEUROPATIEI AUTONOME DIGESTIVE ÎN DIABETUL ZAHARAT

Rezumat

Neuropatia autonomă sau vegetativă este o boală a sistemului nervos vegetativ ce afectează în special organele interne. În diabetul zaharat, neuropatia vegetativă este o complicaţie frecventă, dar adesea nediagnosticată. Neuropatia autonomă digestivă (NAD) poate afecta toate segmentele tractului digestiv. Peste 50% dintre pacienţii cu diabet zaharat acuză simptome de natură digestivă. Cele mai frecvente simptome şi semne asociate NAD sunt: tulburările de motilitate esofagiană şi boala de reflux gastroesofagian, golirea gastrică întârziată, disfuncţia intestinului subţire şi a colonului (diaree, constipaţie şi dureri abdominale).

Un număr mare de studii au arătat că NAD are consecinţe însemnate asupra prognosticului pe termen lung şi a calităţii vieţii pacienţilor afectaţi, de aceea este extrem de importantă diagnosticarea precoce a acestei complicaţii.

Cuvinte cheie: diabet zaharat, neuropatie autonomă, simptome digestive.

Introduction

Recent estimates indicate that in the year 2000 there were over 150 million people in the world with diabetes, and this number will double by 2030. Diabetes is a chronic disease defined by elevated plasma glucose, which correlates with increased risk of micro-vascular damage, reduced life expectancy, significant morbidity, increased risk of macro-vascular complications (ischemic heart disease, stroke and peripheral vascular disease) and diminished quality of life [1,2,3].

Diabetes mellitus can be considered a disease of the modern world with a great impact on morbidity, mortality and the quality of life of the affected individual. Being a chronic disease it requires lifelong treatment and the costs are important. WHO showed that for one diabetic patient the costs were over 10.000 USD in one year, while for a non-diabetic patient the health costs were around 2.000 USD. The total number of individuals with DM is in continuous growing, and so are the overall costs for their health [2,3].

Autonomic neuropathy (AN), also called visceral neuropathy, is a disease of the autonomic nervous system

Articol intrat la redacţie în data de: 30.03.2010
Acceptat în data de: 07.04.2010
Adresa pentru corespondenţă: laurapoanta@yahoo.com

affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs. Most commonly, autonomic neuropathy is observed in persons with long-standing diabetes mellitus type 1 and 2. AN develops slowly and without significant symptoms at the beginning, and the prevalence varies widely with the study methods and end-points, reaching 100% in hospitalized patients in some studies [2,3,4].

The diagnosis of AN should be made in early stages, called sub-clinical neuropathy, which are: after the first year from the onset of DM type 2 and after the first 3 years from the onset for DM type 1 [5,6]. The most important etiopathogenic factors involved are: the gender (females are more affected than the males), a higher body mass index, the age, and a poor glycemic control. From the diabetic patients with symptomatic AN, 25 to 50% are prone to die in the next 5 to 10 years, which represents another reason for the early diagnosis and treatment of those complications [4,5,6].

The main clinical signs and symptoms of autonomic neuropathy in DM are: abnormal changes in pupillary diameter; hypoglycemic episodes without symptoms; cardiovascular signs and symptoms, like orthostatic hypotension or abnormal control of heart rate with nocturnal tachycardia, cardiac denervation syndrome; gastrointestinal signs and symptoms like dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, diarrhea and/or constipation [2,3,4]; neurological signs: symmetrical anhydrotic areas, hyperhidrosis; genito-urinary signs: erectile dysfunction, retrograde ejaculation, neurogenic bladder.

Digestive autonomic neuropathy (DAN)

DAN can affect all the segments of the digestive tract. Up to 60% of the patients with diabetes mellitus suffer from gastrointestinal tract symptoms [6,7,8]. This complication remains often undiagnosed or overlooked by the clinician. The most frequent signs and symptoms associated with DAN are: delayed gastric emptying, colonic dysfunction (diarrhea or constipation), abdominal pain, small bowel dysfunction (malabsorption) which can interfere with oral therapy in DM patients [7,8,9].

Pathogenesis of DAN

The peristaltic abnormalities are connected with a disturbance of the autonomous nervous system, but there are also other factors involved, e.g.: hydroelectrolitic disturbances, diabetic microangiopathy, enteral nervous system dysfunction, acute hyperglicemia, abnormal secretion of neuropeptides, and the presence of *H. Pylori* infection.

Other incriminated factors, which are positively associated with the presence of gastrointestinal symptoms, are: the patient's age, the disease duration and poor control of diabetes mellitus [8].

Abnormal peptide secretion may also be part of the physio-pathology of digestive complications in diabetics. Borg J et al [10] found reduced postprandial secretion of oxytocin in patients with delayed gastric emptying; increased CCK secretion in patients with oesophageal dysmotility, and increased gastrin secretion in patients with autonomic neuropathy.

Diabetic neuropathy is clearly influenced by glucose control: normal blood sugar can prevent the onset or slow down the disease progression [10,11]. Factors involved in diabetic neuropathy pathogenesis are: metabolism, macro and microangiopathy, autoimmune destruction of C nervous fibers, and abnormal action of growth factor [11,12].

Chronic hyperglycemia leads to a lot of biological changes, such as an impaired resistance to oxidative stress, which accelerates the nerve destruction [13,14]. Several studies have demonstrated that levels of nerve growth factor (NGF) are reduced significantly in diabetic neuropathy [15,16,17].

Clinical aspects in connection with the involved segment

DAN may be involved in the dysfunction of any segment of the gstrointestinal tract

Esophageal involvement

The involvement of superior digestive tract occurs in over 30% of the DM patients, the percent being higher when modern techniques, like esophageal scintigraphy, are used [9,18,19].

Esophageal disorders correlated with autonomic neuropathy are: smaller esophageal contractions, less peristaltic waves, reduced pressure in lower esophageal sphincter. As consequence gastro-esophageal reflux is more frequent in DM patients than in general population and diabetic patients with autonomic neuropathy seem to have an increased incidence of reflux esophagitis [4,19]. Kinekawa et al. [20] showed a significant relationship between diabetes mellitus and the gastro-esophageal reflux and esophageal motility dysfunction.

Forgacs S et al. [21] found in 45% of their group of diabetic patients functional abnormalities like wavy esophageal contours, irregular spontaneous contractions and functional diverticula. Also, esophageal transit time was markedly prolonged, but the clinical symptoms of dysphagia were usually mild or absent.

There are also other diseases more frequent in DM, beside motility disorders, like "black esophagus" (necrotizing esophagitis); over 20% of patients with this disease are also diagnosed with diabetes mellitus [8,9]. Kuriki et al. [22] have demonstrated that males with diabetes are almost 1.7 times more likely to develop esophageal carcinoma in comparison to non-diabetics. Esophageal candidiasis it is also more frequent in diabetes mellitus, especially in type 1 [8].

Borgstrom PS et al [23] showed that dysphagia does

not seem to be a frequent symptom in diabetic patients but, when present, warrants a detailed analysis of pharyngeal and oesophageal function in order to reveal the underlying cause.

Diagnosis is made using techniques like 24 hours ambulatory pH monitoring, esophageal manometry, and scintigraphy. Abnormal manometry was associated with peripheral neuropathy (PN) in some studies [24], but the gastro-esophageal acid reflux has no correlation with the presence of PN.

In this study [24] there were no significant correlations between radionuclide esophageal emptying, manometric changes and symptoms. Gastrointestinal symptoms were more common in the presence of autonomic neuropathy and delayed esophageal emptying was more severe in the presence of PN, but abnormal esophageal emptying was present in patients with neuropathy as frequently as in patients without [24].

It seems that the presence of diabetic complications (eg retinopathy), duration and control of diabetes, and fasting blood sugar did not influence the frequency of abnormal esophageal emptying. One study [25] suggests that diabetic gastropathy can occur in the absence of significant diabetic complications. Abnormal esophageal manometry in diabetics is commonly observed, but is not necessarily accompanied by significant functional disturbances or symptoms.

Treatment consists of: prokinetics, mucoprotective substances, antacids, H2 blockers, and proton pump inhibitors. Although these drugs are effective, they do not necessarily influence the underlying causes of the disease by improving the esophageal clearance, increasing the lower esophageal sphincter pressure or reducing the frequency of TLESRs [26].

Some studies showed an improvement of esophageal and gastric motility after 2-week treatment of oral erythromycin in patients with non-insulin-dependent diabetes mellitus [27].

There is a paucity of data that demonstrate a difference in efficacy of treatments for GERD among diabetics.

Outcome data for these disorders is lacking, likely because it is so difficult to define when this common disorder is specifically involved in the presence of motility disorders of the esophagus [28].

Figure 1 and figure 2 show two recordings of esophageal manometry, reflecting DAN.

Gastric involvement

Gastroparesis is defined the reduction in motor activity of antrum and fundus of the stomach, with gastric dysrrhithmia and pyloric spasm; it has an important impact on quality of life of the affected individual, but it is to often ignored by the clinician. The majority of cases are idiopathic, and long standing diabetes mellitus is responsible for about 25-30% of cases [29].

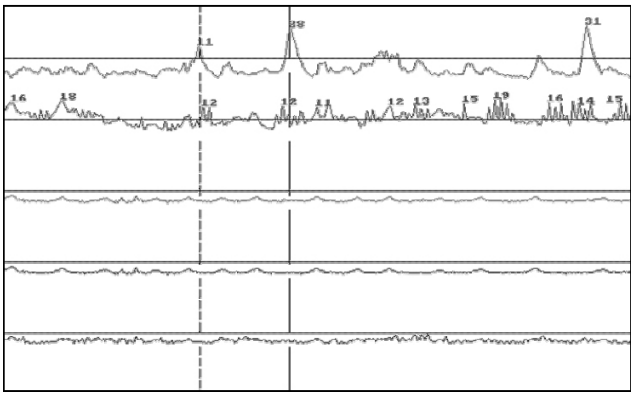

Figure 1. LES (Low esophageal sphincter) hypotonia in diabetic autonomic neuropathy.

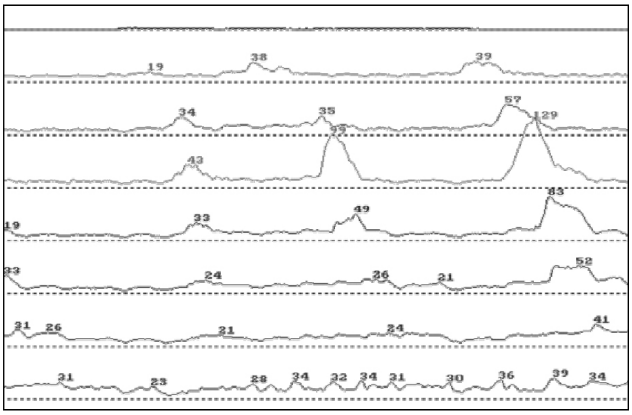

Figure 2. Hypomotility in the lower esophageal body in diabetic autonomic neuropathy.

The exact onset of gastroparesis is hard to be established because the disease is asymptomatic in the first stages and for a long period of time, and the symptoms, when present, are highly uncharacteristic. The onset may be acute with symptoms mimicking pyloric stenosis. Its cardinal features include nausea, vomiting, bloating, early satiety and discomfort. Weight loss, dehydration, electrolyte disturbances and malnutrition may develop in severe cases [7,29,30].

Asymptomatic patients may present the association an insufficiently controlled disease with a higher incidence of hypoglycemic episodes secondary to unequal absorption of ingested food. Food retention results in acceleration of fermentation which can determine diarrhea and progressive weight loss [30].

There are periods free of symptoms, but gastroparesis is progressive, chronic and may be disabilitating. There is no clear association between length of disease and the onset of delayed gastric emptying [30,31].

According to Revicki DA et al. [32] the assessment of severity is important for appropriate management. One method is the Gastroparesis Cardinal Symptom Index,

which is a sum of 3 subscales (ranging from 1–3) for the three main symptom complexes: postprandial fullness/early satiety, nausea/vomiting and bloating.

The diagnosis of gastroparesis may be confirmed by demonstrating gastric emptying delay during a 4-hour scintigraphy (gastric emptying scintigraphy-GES) [30].

GES has emerged as the most widely used test for the assessment of gastric emptying. According to Szarka LA & Camilleri M, the typical indications for GES are: unexplained nausea, vomiting, and dyspeptic symptoms; assessment of gastric motility prior to fundoplication for GERD; assessment of gastric motility prior to surgical treatment in colonic inertia and to screen for gastroparesis in diabetic patients who are being considered for treatment with medication that may further delay gastric emptying [31,32,33].

Magnetic resonance imaging (MRI) has been studied in last years, but further validation is needed before MRI is ready for applications in clinical practice. Additional attributes, as compared to GES, are: the ability to resolve wall motion, and to assess extragastric organs, along with absence of radiation [33].

Functional ultrasonography is a relatively inexpensive, safe, noninvasive method to assess gastric emptying. Duplex Doppler techniques have been used to study transpyloric flow of liquid meals. In the future, 3D ultrasonography could become the most convenient test, but it still needs further validation. So, nowadays GES remain the golden standard to assess gastric function, including in diabetes patients [33].

There is a proposed classification of gastroparesis severity which may be useful in the approach of a diabetes mellitus patient with gastrointestinal symptoms and in treatment decisions.

According to Abel et al [34] **grade 1** means *mild gastroparesis*, with symptoms relatively easily controlled, the patient is able to maintain weight and nutrition on a regular diet or minor dietary modifications alterations.

Grade 2 means *compensated gastroparesis*, with moderate symptoms and partial control with pharmacological agents. The patient is able to maintain nutrition with dietary and lifestyle adjustments, and requires rare hospital admissions

Grade 3 is *gastroparesis with gastric failure*. The patient has *r*efractory symptoms despite medical therapy, has also the inability to maintain nutrition via oral route, and needs frequent hospitalizations.

Treatment consists in frequent, small meals and psychological support; also, several drugs are available, but with limited efficacy, like prokinetics and antiemetics which are the most wide-spread medicaments used [20,35,36].

Metoclopramide is a dopamine receptor antagonist which is widely used, as well as domperidone. Cisapride (5-HT4 receptor agonist) proved itself very useful but it has been withdraw. With metoclopramide, patients may develop tolerance over time and the side effects may limit its use in up to 30% of patients. Irreversible late dyskinesia is a serious side effect that occurs in 1–10% of patients treated for more than 3 months [37]. The efficacy of domperidone matches that of metaclopramide and cisapride [37], but its effect on solid-phase gastric emptying is lost by 6 weeks [35,37].

The efficacy of erythromycin in gastroparesis has not been fully demonstrated yet [37]. Erythromycin improves gastric emptying, but only a minority of patients will benefit with regard to symptoms amelioration [38].

Botulinium injections are thought to decrease pylorospasm and accelerate gastric emptying. Gastric electrical stimulation proves itself useful in refractory cases [37], but this method is, at present, limited to a few centers.

In a large, heterogeneous series of patients with gastroparesis who were managed in a tertiary center, the majority (74%) required long-term prokinetic therapy [39]. The postsurgical group, and those with idiopathic gastroparesis associated with prominent abdominal pain or a history of physical or sexual abuse, were the most refractory to pharmacologic therapy.

The prognosis in diabetic gastroparesis has been assumed to be poor, but follow-up over at least a decade indicates that this is not necessarily the case, with no increase in mortality over patients with diabetes and a normal rate of gastric emptying [40]. Neither the rate of emptying nor symptoms changed markedly over a similar period [41].

Small bowel involvement

Disturbed gastric and small intestinal motility is a clinical problem that is very often overlooked. Many patients with diabetes mellitus suffer from upper and lower GI symptoms. The reported prevalence of these symptoms varies among different ethnic groups/populations [42]. The interdigestive gastric and small intestinal motility is often affected. There is only a weak correlation between symptoms and objectively measurable motor disturbances. Patients with severe upper gastrointestinal symptoms usually have disturbed motility, but most patients with impaired motility are asymptomatic [42].

Recent studies have clearly shown that, in addition to autonomic neuropathy, acute metabolic derangements are likely to contribute to disturbed motility. Elevated glucose levels impair gastric and small intestinal motility during fasting and after food intake. Hyperinsulinemia *per se* has effects similar to hyperglycemia on the stomach and small bowel, and may be a mediator of the effects of hyperglycemia in healthy subjects. The impact of insulin on motility in diabetic patients is still unclear. Treatment of the gastric motility disorder should include a stabilization of gastric emptying. Different therapeutic modes may be useful, e.g. application of prokinetic drugs and optimizing

the metabolic situation [43].

Impaired bowel function in diabetics can significantly influence diabetes compensation and vice versa. On the other side, as we've already stated, unsatisfactory diabetes compensation can result in manifestation of digestive problems [44].

There are distinct clinical entities, like: diarrhea with steatorrhea, with concomitant pancreatic disease; diarrhea with malabsortion; chronic diarrhea without steatorrhea, which is considered to be a genuine diabetic diarrhea and primary malabsorbtive syndrome [8,36,45]. Chronic diarrhea obvious has a great impact on the quality of life of DM patient. The pathogenesis of diarrhea remains obscure, although it appears to be related to the development of autonomic neuropathy, which may cause several abnormalities including altered gut motility [46].

The study of oro-cecal transit time provides additional information in diabetes mellitus patients with GI symptoms. Valdovinos et al. [47] suggested a practical algorithm based on three sequential assessments: first, tests of blood and stool specimens and flexible sigmoidoscopy to detect evidence of malabsorption or disease in the distal colon; second, small bowel aspirate and biopsy if the results of initial blood or stool tests are abnormal or anorectal function tests if those test results are normal; and, finally, measurement of gastrointestinal transit or therapeutic trials with opioids, clonidine hydrochloride, and, rarely, cholestyramine resin or octreotide acetate (or both methods).

The management can be difficult but many therapies, including antibiotics to eradicate bacterial overgrowth, as well as antidiarrheal agents, oral and topical clonidine, and somatostatin analogues may be effective in controlling diabetic diarrhea [48].

Large bowel involvement

The hyposensitivity in the gut was accompanied by an increase in the somatic referred pain areas indicating central neuronal changes. The multi-modal and multi-segmental sensory testing approach indicates that the sensory nerves are widely affected in the GI tract and generalized to nerves in all layers of the gut. Changes in the neuronal pain matrix including interactions between peripheral and central pain mechanisms may be involved in the pathogenesis of gastrointestinal symptoms in long-standing diabetes. Future targets in the treatment of gastrointestinal symptoms in diabetic patients with autonomic neuropathy could be based on modulation of the central nervous system excitability [49,50].

Large bowel changes due to autonomic neuropathy involve mainly the impairment of the motility and leads to chronic constipation [9,12]. Constipation can be an extension of diabetic diarrhea or it can precede diarrhea, but it can also exist independent, particularly in older diabetics [8].

Large bowel symptoms in diabetics were more frequent then in controls and were significantly associated with poor glycemic control, neuropathy and retinopathy, but not with duration of diabetes [51].

Chronic constipation, in addition to diarrhea, gall bladder dysfunction and incontinence, is increasingly regarded as a serious problem and is now considered in the current guidelines [8,52]. Certain medications including metformin, amylin analogues (i.e. pramlintide), glucagon-like peptide 1 analogs (i.e. exenatide, liraglutide), anticholinergic agents, antidepressants, calcium-channel blockers, and others may contribute to GI symptoms observed in patients with diabetes [51,52].

Diagnosis: oro-cecal transit time and ano-rectal manometry measures the resting pressures generated by the sphincter complex of the anus may be helpful in diagnosis [52].

Treatment consists of symptomatic treatment of both diarrhea and constipation with specific drugs like loperamide or laxatives.

Given the global diabetes pandemic, it is of outmost importance to not only diagnose and treat present patients with diabetes mellitus and its comorbidities, but also to help prevent the development of further disease burden by educating children and adolescents about healthy lifestyle modifications (avoidance of overeating, meals control, healthy food choices, increased physical and reduced sedentary activity), as changing behavior in adulthood has proven to be notoriously difficult [53].

Ano-rectal incontinence

Fecal or ano-rectal incontinence represents a complex disorder. It is nowadays accepted that not only elderly, but younger adults are also frequently affected. Its incidence varies from 2% in the general population, to 60% in elderly. Diabetes mellitus is also a cause of ano-rectal incontinence in approximately 20% of all patients. The incontinent patients experience impaired internal anal sphincter tone and diminished resting pressure of the anal canal [54].

Ming Sun W et al. [55] demonstrated, more than a decade ago, that basal and squeeze pressures were reduced in the diabetic patients compared with the control subjects. In diabetic patients there was a greater tendency for repetitive rectal contractions in response to rectal distension and reduced rectal compliance. Their results indicate that aetiology of faecal incontinence in diabetic patients is multifactorial and suggest, for the first time, that instability of the internal sphincter probably plays a major role.

In clinical practice the most useful tests are the ano-rectal manometry and the anal endosonography.

Figure 3 shows the ano-rectal manometry of a case with anal sphincter hypotonia due to DAN.

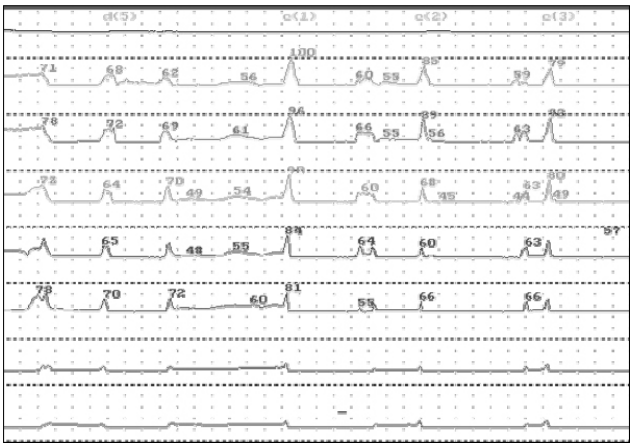

Figure 3. Anal sphincter hypotonia in diabetic autonomic neuropathy.

Treatment depends on the cause and severity of fecal incontinence; it may include dietary changes, medication (like loperamide), bowel training, or surgery. "Social continence" may be achievable for some people using a bowel management program that cleans out the colon daily. Ano-rectal biofeedback combined with electrical stimulation may be effective in selected cases [56].

As a synthesis of the prevoius problems discussed, we can state that in diabetics different compartments of the gut are affected by gastrointestinal motor abnormalities and that these segments are probably regulated by independent or different control mechanisms [57]. The analysis of complaints of the upper and lower gastrointestinal tract in diabetes mellitus is very important as the delayed diagnosis puts patients at risk [58,59].

To make a correct diagnosis is crucial; this includes the study of symptom characteristics, detection of abnormal patterns of gastrointestinal function (like gastric emptying, oro-cecal and colonic transit, ano-rectal function), potential involvement of the autonomic nervous system (sympathetic, parasympathetic), and the overall impact on the patient's quality of life [58,59,60].

Differential diagnosis involves a lot of diseases and syndromes like: idiopathic orthostatic hypotension, Shy-Drager syndrome, hypopituitarism, pheochromocytoma, Chagas disease, amyloidosis, hypovolemia of different causes, insulin adverse effects, other drugs adverse effects, alcoholic neuropathy, heart failure, diarrhea and constipation of various causes, erectile dysfunction of other causes (organic or psychological) [5,6,7].

It is essential to study both the upper and the lower GI tract. Interpretation of dyspeptic symptoms as functional should rule out the presence of alarm symptoms like weight loss, anemia, and positive occult fecal blood [58].

Table 1. Gastrointestinal studies useful in analyzing GI tract.

Gastrointestinal segment	Technique
Esophagus	Barium meal; manometry; endoscopy; scintigraphy;
Stomach	Barium meal; Functional ultrasonography; scintigraphy (golden standard);
Small bowel	Oro-cecal transit time;
Large bowel	Oro-cecal transit time; ano-rectal manometry;
Ano-rectal sphincter	Ano-rectal manometry;

Those investigations will analyze the motility of the GI tract. To assess the presence of autonomic neuropathy, some other tests may be useful: supine and standing blood pressure, for general sympathetic adrenergic function, heart rate and blood pressure response to Valsalva maneuver, or the sudo-motor axon reflex test [11]. Also, symptoms and signs of autonomic dysfunction can be evaluated by taking the clinical history, looking after other signs and symptoms of autonomic dysfunction such as: orthostatic hypotension, heartburn and/or regurgitation, gastric symptoms (epigastric pain, postprandial fullness, belching), bowel disorders, sweating disorders, bladder dysfunction and, in males, impotence [61,62].

One of the largest studies [63] to evaluate this association focused on 1101 subjects who were recruited from outpatient clinics and the community. Gastrointestinal symptoms were significantly associated with the presence of other diabetic complications, particularly autonomic and peripheral neuropathy. Patients with at least one diabetic complication were significantly more likely to report constipation, gastroesophageal reflux, dyspepsia, frequent abdominal pain, and fecal incontinence. It seems that GI symptoms in diabetes mellitus are linked to diabetic complications, particularly peripheral neuropathy, and to poor glycemic control [63].

On the other hand, Phillips LK et al. [64] showed that gastrointestinal symptoms and abnormal intestinal motility, which are generally regarded as manifestations of gastrointestinal "autonomic dysfunction," cannot be strongly connected with abnormal cardiovascular autonomic function.

Finally, the blood glucose concentration is both a determinant of and determined by gastrointestinal function [7,61]. The careful control of blood glucose of the diabetic patient is seems to be the only therapy which counteracts specifically the pathogenesis of autonomic neuropathy [7,8,45].

Conclusion

There is nowadays no doubt that diabetic autonomic neuropathy will have consequences for long-term prognosis and quality of life of the affected patients, so it is of a great importance the early diagnosis of this insidious complication. Gastrointestinal autonomic neuropathy

involves the entire gastrointestinal tract but remains often not diagnosed. The most frequent complications are the motility disturbances, which interferes even with the absorption of the oral hypoglycemic medication.

Even though these motor abnormalities are due to the involvement of the autonomic nervous system, there are other responsible factors discused.

The investigation of the digestive complications implies the exclusion of other diseases which could produce such symptoms, gastric emptying studies, manometry, ultrasound evaluation of the gastric emptying, radiolabel studies of the colonic transit.

There is also available therapy for gastrointestinal complications and because of this the early diagnosis is very important.

Acknowledgement: Research supported from CNCSIS project number 1277 of Ministry of Education.

References

1. Diabetes Atlas, 3rd edition. International Diabetes Federation; 2006. 1-19.
2. Tierney L M, McPhee S J, Papadakis M A. Current medical Diagnosis & Treatment. International edition. New York: Lange Medical Books/McGraw-Hill 2002. pp. 1203–15.
3. Wiener C, Fauci AS, Braunwald E, et al. Harrison's Principles of Internal Medicine 17th edition. McGraw-Hill 2008.
4. Boulton AJ, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956-58.
5. Spollett GR. Diabetic neuropathies: diagnosis and treatment. Nurs Clin North Am .2006; 41; 697-717.
6. Vinik A, Erbas T, Recognizing and treating diabetic vegetative neuropathy. Clev Clinic J Med. 2001. 68 (11): 928 – 44.
7. Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. Diabetes Care. 2003; 26: 1553–1579.
8. Rossol S. MMW Fortschr Med. 2007; 149 (44): 39-42.
9. American Diabetes Association. Standards of medical care in diabetes—2006. Diabetes Care. 2006; 9 (S1): S4–S42.
10. Borg J, Melander O, Johansson L, et al. Gastroparesis is associated with oxytocin deficiency, oesophageal dysmotility with hyperCCKemia, and autonomic neuropathy with hypergastrinemia. BMC Gastroenterol. 2009; 25 (9): 17.
11. Vinik AI. Diabetic neuropathy: pathogenesis and therapy. Am J Med. 1999 Aug 30; 107 (2B):17S-26S.
12. Vinik AI, Park TS, Stansberry KB, et al Diabetic neuropathies. Diabetologia. 2000; 43(8):957-73.
13. Cameron NE, Cotter MA. Metabolic and vascular factors in the pathogenesis of diabetic neuropathy. Diabetes. 1997; 46 (S2): S31-S37
14. Low PA, Nickander KK, Tritschler HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. Diabetes. 1997; 46 (S2):S38-S42.
15. Apfel SC, Arezzo JC, Brownlee M, et al. Nerve growth factor administration protects against experimental diabetic sensory neuropathy. Brain Res. 1994; 634: 7-12
16. Vincenti AM, Brownlee M, Russell JW. Oxidative stress and programmed cell death in diabetic neuropathy. Ann N Y Acad Sci. 2002; 959: 368-383
17. Du X, Matsumura T, Edelstein D, et al. Inhibition of GAPDH activity by poly (ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest. 2003; 112: 1049-1057.
18. http://www.mayoclinic.com/health/autonomicneuropathy/DS00544/DSECTION=risk-factors.
19. Bjelakovic G. Diabetes mellitus and digestive disorders. Acta Fac Med Naiss. 2005; 22 (1): 43-50.
20. Kinekawa F, Kubo F, Matsuda K, et al. Esophageal function worsens with long duration of diabetes. J Gastroenterol. 2008; 43: 338–44.
21. Forgács S, Osváth J, Kéri Z et al. Esophageal dysfunction in diabetes mellitus. Acta Diabetologica. 1979; 16 (3): 227-34.
22. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev. 2007; 16: 83–9.
23. Borgström PS, Olsson R, Sundkvist G et al. Pharyngeal and esophageal function in patients with diabetes mellitus and swallowing complaints. British J Radiol. 1988; 61: 817-21.
24. Murray FE, Lombard MG, Ashe J, et al. Esophageal function in diabetes mellitus with special reference to acid studies and relationship to peripheral neuropathy. Am J Gastroenterol. 1987; 82(7): 625-31.
25. Keshavarzian A, Iber FL, Nasrallah S. Radionuclide esophageal emptying and manometric studies in diabetes mellitus. Am J Gastroenterol. 1987; 82(9): 840-3.
26. Storr M, Meining A, Allescher HD. Pathophysiology and Pharmacological Treatment of Gastroesophageal Reflux Disease, Dig Dis. 2000. 18 (2): 93-102.
27. Chang CT, Shiau YC, Lin CC, et al. Improvement of esophageal and gastric motility after 2-week treatment of oral erythromycin in patients with non-insulin-dependent diabetes mellitus. J Diabetes Complications. 17 (3): 141-44.
28. Wise JL, Murray JA. Oral, pharyngeal and esophageal motility disorders in systemic diseases. GI Motility online (2006) doi:10.1038/gimo40.
29. Igaz P, Tulassay Z. Gastroparesis and its treatment options. Orv Hetil. 2008; 2; 149 (9):393-8.
30. Smith DS, Ferris CD. Current concepts in diabetic gastroparesis. Drugs. 2003; 63 (13):1339-58.
31. Moldovan C, Dumitrascu DL, Demian L et al. Gastroparesis in diabetes mellitus – an ultrasonographic study. Rom J Gastroenterol. 2005; 14 (1): 19-22.
32. Revicki DA, Rentz AM, Dubois D, et al: Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. Aliment Pharmacol Ther. 2003; 18: 141–150.
33. Szarka LA, Camilleri M. Clinical Imaging. Clin Gastroenterol Hepatol. 2009 7 (8): 823-27.
34. Abel TL, Bernstein RK, Cutts T et al. Treatment of gastroparesis: a multidisciplinary clinical review. Neurogastroenterol Motil. 2006; 18: 263–83.
35. Dumitrascu DL, Weinbeck M: Domperidone versus metoclopramide in the treatment of diabetic gastroparesis. Am J Gastroenterol. 2000; 95: 316–17.
36. De Block CE, De Leeuw IH, Pelckmans PA, et al. Current concepts in gastric motility in diabetes mellitus. Curr Diabetes Rev. 2006 Feb;2(1):113-30.
37. Gumaste V, Baum J. Treatment of gastroparesis: an update.

Digestion 2008; 78:173-79.
38. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. Am J Gastroenterol. 2003; 98: 259–63.
39. Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. Dig Dis Sci. 1998; 43: 2398-404.
40. Kong MF, Horowitz M, Jones KL, et al. Natural history of diabetic gastroparesis. Diabetes Care. 1999; 22: 503-7.
41. Jones KL, Russo A, Berry MK, et al. A longitudinal study of gastric emptying and upper gastrointestinal symptoms in patients with diabetes mellitus. Am J Med. 2002; 113: 449-55.
42. 42. Koch CA, Uwaifo GI. Are gastrointestinal symptoms related to diabetes mellitus and glycemic control? Eur J Gastroenterol Hepatol 2008; 20 (9):822-5.
43. Abrahamsson H. Gastrointestinal motility disorders in patients with diabetes mellitus. J Intern Med. 1995; 237 (4):403-9.
44. Perusicová J. Gastrointestinal complications in diabetes mellitus. Vnitr Lek. 2004; 50 (5): 338-43.
45. Clouse RE, Mayer EA, Aziz Q, et al. Functional abdominal pain syndrome. Gastroenterol. 2006 Apr; 130 (5):1492-7.
46. Dooley CP, Newihi HM, Zeidler A, et al. Abnormalities of the migrating motor complex in diabetics with autonomic neuropathy and diarrhea. Scand J Gastroenterol. 1988;23(2):217-23.
47. Valdovinos MA, Camilleri M, Zimmerman BR. Chronic diarrhea in diabetes mellitus: mechanisms and an approach to diagnosis and treatment. Mayo Clin Proc. 1993 68 (7): 691-702.
48. Ogbonnaya KI, Arem R. Diabetic diarrhea. Pathophysiology, diagnosis and management. Arch Int Med. 1990; 150(2): 262-7.
49. Phillips LK, Rayner CK, Jones KL, et al. An update on autonomic neuropathy affecting the gastrointestinal tract. Curr Diab Rep. 2006; 6 (6):417-23.)
50. Frøkjaer JB, Andersen SD, Ejskaer N, et al. Gut sensations in diabetic autonomic neuropathy. Pain. 2007; 131(3): 320-9.
51. Abid S, Rizvi A, Jahan F, et al. Poor glycaemic control is the major factor associated with increased frequency of gastrointestinal symptoms in patients with diabetes mellitus. J Pak Med Assoc. 2007; 57 (7): 345-9.
52. Hasbeck M. Autonomic neuropathies in diabetes mellitus: diagnosis therapy risks. Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete 1993; 48: 1 62-76.
53. Koch CA, Uwaifo GI. Are gastrointestinal symptoms related to diabetes mellitus and glycemic control? Eur J Gastroenterol Hepatol. 2008; 20 (9): 822-5.
54. Andromanakos N, Filippou D, Skandalakis P, et al. Ano-rectal incontinence. Pathogenesis and Choice of Treatment. J Gastrointest Liver Dis. 2006; 15 (1), 41-49
55. Ming Sun W, Katsinelos P, Horowitz M, et al. Disturbances in anorectal function in patients with diabetes mellitus and faecal incontinence. Europ J gastroenterol hepatolog. 1996; 8 (10): 1007-1012.
56. Privitera AC, Oliveri CE, Randazzo G, et al. Biofeedback therapy for faecal incontinence: our experience. Chir Ital. 2009; 61(2): 149-54.
57. Wegener M, Börsch G, Schaffstein J, et al. Gastrointestinal transit disorders in patients with insulin-treated diabetes mellitus. Dig Dis. 1990; 8 (1): 23-36.
58. Portincasa P, Maggipinto A, Berardino M, et alAssessing gastrointestinal symptoms and perception, quality of life, motility, and autonomic neuropathy in clinical studies. J Gastrointestin Liver Dis. 2009; 18 (2): 205-11.
59. Frøkjaer JB, Søfteland E, Graversen C, et al. Central processing of gut pain in diabetic patients with gastrointestinal symptoms. Diabetes Care. 2009 Jul; 32(7):1274-7.
60. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006; 130: 1480-1491.
61. Quan C, Talley NJ, Jones MP, et al. Gain and loss of gastrointestinal symptoms in diabetes mellitus: associations with psychiatric disease, glycemic control, and autonomic neuropathy over 2 years of follow-up. Am J Gastroenterol. 2008 Aug; 103 (8):2023-30.
62. Sabu MC, Priya TT. Amelioration of experimental diabetic neuropathy and gastropathy in rats following the oral administration of an herbal formulation of Diabo-SS extract. J Basic Clin Physiol Pharmacol. 2008; 19 (1):29-36.
63. Bytzer P, Talley NJ, Hammer J, et al. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. Am J Gastroenterol. 2002; 97(3): 604-11.
64. Phillips LK, Rayner CK, Jones KL, et al. An update on autonomic neuropathy affecting the gastrointestinal tract. Curr Diab Rep. 2006; 6 (6): 417-23.