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Review article

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DIABETES MELLITUS AND DIGESTIVE DISORDERS

SUMMARY

Since diabetes mellitus affects every organic system, it affects gastrointestinal tract as well. The precise extent of digestive disorders associated with diabetes mellitus is unknown. Few mechanisms may lead to these manifestations including autonomic neuropathy, diabetic microangiopathy, poor glycemic regulation, altered production of glucagon and insulin, and increased susceptibility to gastrointestinal infections. Esophageal disorders like reduced amplitude of esophageal contractions, reduced lower esophageal sphincter pressure, and abnormal acid reflux occur commonly in patients with diabetes mellitus. Diabetes is included in a certain number of stomach disorders and is considered responsible for undefined dyspeptic symptoms. In oposite to manifestations in the stomach which are usually asymptomatic, manifestations on small intestine related to diabetes are much more symptomatic. Diarrhoea and steatorrhea are frequent among diabetics. Obstipation is probably the most common gastrointestinal symptom in patients with diabetes. Obstipation can be an extension of diabetic diarrhoea, which happens more often, or it can, less frequently, precede diarrhoea, but it can exist independently of any kind of digestive disorders, particularly in older diabetics. In patients who suffer from diabetes there is a complex relation between exocrine and endocrine pancreas component: pancreatitis can produce diabetes, and diabetes is often associated with deteriorated exocrine pancreas secretion. Common complication of diabetes mellitus is fatty liver. Diabetes mellitus and liver cirrhosis are often associated. Diabetes may precede or be the cause of cirrhosis of the liver and vice versa, cirrhosis of the liver may precede or cause diabetes. There is an unexplained higher incidence of gall stones in patients with diabetes mellitus. Adequate and urgent recognition of gastrointestinal manifestations of diabetes mellitus is important for treatment of these patients.

Key words: **diabetes mellitus, digestive disorders**

INTRODUCTION

Since diabetes mellitus affects every organic system, it affects gastrointestinal tract as well. Complications involving the gastrointestinal tract are an important cause of morbidity in patients with diabetes mellitus (1). The precise extent of digestive disorders associated with diabetes mellitus is unknown (2). Few mechanisms may lead to these manifestations including autonomic neuropathy, diabetic

microangiopathy, poor glycemic regulation, altered production of glucagon and insulin, and increased susceptibility to gastrointestinal infections (3,4).

Gastrointestinal manifestations in these patients have been attributed to disordered motor function as a result of the irreversible autonomic neuropathy (5). Recently, the hypothesis has been raised that poor glycemic control may be a major cause (6,7). Diabetic autonomic neuropathy, one of the main causes of diabetes mellitus digestive disorders, can produce alterations in each segment of the gastrointestinal tract (8–12).

Abnormal gastric emptying is a frequent and important complication of diabetes mellitus. Gastric emptying of solid or nutrient-liquid meals is slow in about half of outpatients with longstanding type 1 (13) or type 2 (14) diabetes. Disordered gastric emptying may be associated with upper gastrointestinal symptoms, (15) impaired glycemic control, (16) and changes in drug absorption (17).

DIABETIC ACIDOSIS

Anorexia, nausea and vomiting are the usual early symptoms of diabetic acidosis and they appear in about 75% of the cases. Gastric dilatation is frequent during acidosis and is primarily responsible for vomiting. Gastric dilatation may be, in a way, in relation to high values of ketonic bodies and systemic acidosis, but the increasing blood glucose level may contribute to provoking a reduced gastric motility. Because of the gastric dilatation, gastric emptying is often recommended in patients with diabetic acidosis. When this is done, small amounts of blood may be found. This is rarely a reason for concern, because, almost always, the amount of blood in is very small (18).

However, severe bleeding may occasionaly appear as a part of diabetic acidosis (19). Usually, those are superficial erosions in esophageal or gastric mucosa, as well as in the congestion of gastric mucosa associated with cappilar haemorrages. The cause of severe bleeding may be Mallory-Weiss syndrome (the split of mucosa of esophageogastric conjuction) that develops during an urgent vomiting. Bleeding from duodenal ulcer is unusual in patients with acidosis especially because it rarely affects them, unlike non-diabetics.

Abdominal pain during diabetic acidosis may occasioanally be very severe and when it is associated with an increased number of leucocytes in peripheral blood (8% of the cases) it suggests an acute abdominal process. Acute apendicitis or some other acute abdominal diseases may precede the occurrence of diabetic acidosis in a way similar to that of any other infection (20).

Acute pancreatitis causes main diagnostic difficulties. The pain and ileus remain unidentified during diabetic acidosis. As a result of this, clinically unidentified pancreatitis is found during the follow-up autopsy in 10-15 % of patients who died during diabetic acidosis (21). In each patient with diabetic acidosis and abdominal pain, an intrabdominal process should be excluded.

TABETIC PAIN

Diabetics can rarely feel a sharp, sudden abdominal pain of clear distribution identical to the pain pattern in gastric crises of tabes dorsalis. The episodes of pain combined with nausea and vomiting may persist for many hours during the day (tabetic pain). These pains seem to be an unusual manifestation of diabetic neuropathy (22).

INTESTINAL ABSORPTION OF GLUCOSE

Metabolic abnormalities in diabetes include a disrupted normal absorption of glucose from small intestine. Vinnik and associates (23) published convincing facts on this subject obtained from experiments on humans who supported earlier animal experiments, showing that intestinal absorption of glucose is twice as high in diabetics as in normal people. Insulin apparently does not have an effect on the absorption of glucose.

ESOPHAGUS

Neuropathy, as a common complication of diabetes mellitus, may affect the motor nerves and the autonomic nervous system (24–27). Esophageal disorders such as reduced amplitude of esophageal contractions, less numerous peristaltic waves, decrease in velocity of peristalsis, increased number of spontaneous, spastic, and repetitive contractions, appearance of multipeaked contractions, reduced lower esophageal sphincter pressure, impaired esophageal transit, and abnormal acid reflux occur commonly in patients with diabetic autonomic neuropathy (28,29,30). The pathophysiology of these abnormalities is mainly caused by vagal nerve dysfunction (28). Kinekawa and Lluch (31,32) found oesophageal motility disorder and gastro-oesophageal reflux in diabetic patients at a higher prevalence than among the general population.

STOMACH

Diabetes is included in a certain number of stomach disorders and is considered responsible for undefined dyspeptic symptoms. Generally, gastric

function is inhibited in diabetes. The disorders found cannot explain with certainty the difficulities and often, they are not associated with clinical manifestations.

Retention of stomach contents in diabetic patients was not described in the preinsulin era which coincided with the pre-X-ray era. There are reports in literature about retention with widely open pylorus because of "the neural reasons" (33). The term "gastroparesis diabeticorum" was first used by Kassander (34). The term gastric atonia or the insufficiency of pylorus is also mentioned, but only in relation to an ulcer disease in the absence of anatomical changes responsible for retention. Pathogenically, gastropathy of diabetics is usually associated with the neuropathy of autonomous vegetative system. The lesions of motor functions are connected with the lesions of vagal nerve because of the similarity with the condition after vagotomy. Actually, it was considered that diabetes in progression can lead to partial and total vagotomy, which has not been proved. Degenerative changes in oesophageal neural plexus were described in two diabetics who suffered from diabetic gastropathy during autopsy. Some researchers ascribed a certain importance to zinc which was added to insulin and to the disorder of metabolism of extracellular potassium, which has not been proved. Duration, as well as an inappropriate treatement of diabetics, are emphasized as factors in the works of many authors.

Clinical presentation of diabetic gastropathy

The beginning of gastropathy is undetermined because of the insidious nature of disorder and the lack of characteristic symptoms. Rarely, the disease can have an acute beginning. It is usually episodic. It can be manifested in a very broad spectrum of clinical variations, from asymptomatic forms to an acute disorder, which may resemble pyloric stenosis. Patients usually have epigastric pain, nausea, occasional vomiting of food which they ate the day before. Flatulence, anorexia, abdominal bloating and postprandial regurgitation are less frequent and are found in about 20% of the patients (34). What is typical is that patients with asymptomatic gastric retention may have unstable diabetes, which is characterized by sensitivity to insulin and the incidence of hypoglycaemic episodes.

This does not occur because those patients would be particularly sensitive to insulin or because of the hypofunction of the adrenal cortex, but because of the food retention in the stomach and irregular absorption.

Food retention in the stomach is responsible for excessive increase of bacteria whose toxic products, including the fermentation products in the stomach, can affect the intestine causing hypermotility and diarrhoea. Patients may lose weight progressively. The loss of weight can be followed by inexplicable deterioration of diabetes control, vague abdominal pains, nausea and vomiting. The periods of occasional spontaneous improvements during which stomach symptoms disappear are described, diabetes control improves and body shows a tendency towards gaining weight.

The improvement occurs regardless of a stable radiological image of abnormality. Although this period is clinically characterized by the phases of exacerbation and remission, the condition usually progresses to a chronic process with characteristic symptoms that are undoubtedly associated with gastropathy. It cannot be stated with certainty whether the improvement of gastric atonia is associated with diabetes control, because the control partially depends on the stomach function (35).

Usually, there is a slight epigastric sensitivity during the clinical examination, and possibly, the signs of stomach dilatation. Radiologically, this complication shows the same image as in patients who were vagotomized. Peristalsis is disrupted, it is slow, ineffective and irregular so that we find the food and barium retention in the stomach. The combination of gastropathy and diarrhoea is also described. On the basis of radiological research, it is possible to distinguish two kinds of gastropathy: gastroparesis and gastroplegia.

Treatment

Mainly, the pessimistic reports about the success of the treatment of diabetic gastropathy prevail (36). A strict realization of diabetic treatment is a basic measure in every patient. Wooten and Meriwether (37) accomplished satisfactory results in 4 out of 9 patients when the oral nutrition was substituted with parenteral. After returning to oral nutrition with 6 small dietary meals a day, diabetes became unstable again. It is also known that insulin with short-term activity causes more frequently unpleasant hypoglycaemic reactions in these patients than depo-insulin. The combination of insulin and tolbutamid was also used in the treatment of a small number of patients, but without satisfactory effect.

Generally speaking, the use of peroral hypoglycaemics in the case of impaired function of the upper gastrointestinal tract does not seem logical. The application of anticholinergics is not justified, although it is sometimes done, because the application of these drugs may deteriorate the condition. The improvement after the subcutaneous injection of bethanechol in individual cases is described (38). Beneficial effect of prostigmin is observed. In some cases, the blockers of cholinesterase has also

proved to be useful. Today, gastrointestinal prokinetics are being tried out: methoclopramyde and domperidon.

SMALL INTESTINE

Opposite to manifestations in the stomach, which are usually asymptomatic, manifestations on small intestine related to diabetes are of a far greater symptomatic significance for a patient (36). The small bowel may be greately involved in diabetes mellitus, resulting in diarrhoea and malabsorption (3).

In diabetic patients, a group of chronic disorders of intestines consist of:

1. Chronic diabetic diarrhoea without steatorrhea, which is considered to be a genuine diabetic diarrhoea.
2. Diabetic diarrhoea with steatorrhea.
3. Diarrhoea and steatorrhea in diabetics because of the chronic insuffiency of exocrine function of pancreas.
4. Primary malabsorptive syndrome and diabetes.

Chronic diabetic diarrhea without steatorrhea

The first case of diabetic diarrhoea as a rare complication of diabetes was described by Joslin in 1912 (39). The exact pathogenesis of diarrhoea-steatorrhea is still undetermined. Many factors are mentioned:

– autonomous neuropathy
– the lack of vitamins
– insufficiency of exocrine function of pancreas
– bacterial contamination of the superior parts of digestive tract
– damage of intestinal mucosa

There is a high incidence of neuropathy in these patients, including all of its forms- peripheral, autonomous and visceral, so that many researchers think that neuropathy causes the appearance of diabetic diarrhea-steatorrhea (40).

Some ascribed a certain meaning to other factors such as the lack of vitamins, disorder of exocrine pancreas function, bacterial contamination of the superior parts of digestive tract, and the damage of intestinal mucosa (41).

This type of diarrhoea is typical of younger people with anamnesis of long-standing and inappropriately controlled diabetes which is characterized by frequent hyperglycaemia, hypoglycemia and ketoacidosis. The symptoms usually occur 5–10 years after the established diagnosis of diabetes. It is more frequent in men than in women. Regularly, in anamnesis of the patient, there is diarrhoea which lasts a few days, weeks or months and rarely years. The most typical symptom is intermittence of diarrhoea attacks with exacerbations and remissions of different duration which cannot be foreseen.

Diarrhoea is usually abundant, watery, urgent and frequent (20–20 times/24 hours). It can be induced by the meals, emotional factors, although in most cases it is not easy to evaluate the provoking factors.

Diarrhoea occurs mostly late at night, during the night and early in the morning. Sometimes, it occurs only at night – "diabetic night diarrhoea". Night incontinency of the stool is frequent. The pain does not occur in the abdomen, although the difficulty and slight pain similar to cramps may precede defecation.

Stools are abundant, watery, rare, brown in colour, homogeneous without the presence of blood or purulent. Different functional tests for diagnosis of malabsorption syndrome (Schilling test, the amount of fats in the stool, the level of serum calcium, sodium, and phosphate) in most patients are pathological. Radiographic medical reports in patients with diabetic diarrhoea-steatorrhea are not typical. The time of barium transit through a small intestine is usually prolonged, the lumen is dilated and the barium meal can be segmented with mucous villous atrophy which may show roughness, irregularity and even obliteration. Barium can produce pools in the small intestine (24).

Diabetic diarrhoea with steatorrhea

Diabetic diarrhoea and steatorrhea manifestations are of the same basic process. In some patients, steatorrhea occurs only when diarrhoea worsens. Some think that this complication is not the consequence of diabetes but of the reduced exocrine function of pancreas (42).

Clinically, diabetic steatorrhea shows intermittent flow. It can last several hours, weeks, as well as several months and years. Symptoms are, more frequently, postpardial and they appear at night when incontinency of the stool is possible. Pain usually does not occur, but the difficulties in the abdomen may precede diarrhoea. The main symptom is 20–50 stools a day during the deterioration. Stools are not typically fatty, but they are rare, watery and abundant. The higher level of fats and nitrogen products is registrated in the stool.

Histological findings

Histologically established changes of intestinal mucosa in both types (diarrhoea with or without steatorrhea) are atrophic, thicker, reduced villi, stromal infiltration in a certain number of patients (40).

In a large number of patients, the medical report was normal, so that it still cannot be stated with certainty whether or not histological changes exist.

The treatment of diabetic diarrhoea-steatorrhea

Since the cause of the appearance of these complications is unidentified, it is not possible to apply a specific treatment. The appropriate control of diabetes is so far the best way to treat these complications (3).

Some authors accomplished prompt remission of diarrhoea in a small number of patients after the use of antibiotics of broad spectrum (36). In the treatment of diarrhhoea-steatorrhea other medicaments were also used (cholinergetics, sympathomimetics, vitamins, folic acid, liver extracts, bismuth, opiates, atropine) with changeable, mostly unfavourable results. Even a diet with fruit and vegetables limitation was recommended. In some patients, after the use of corticosteroids, the improvement was described. On the whole, because of the general characteristic of this complication, the tendency towards spontaneous remissions and exacerbations it is hard to evaluate the results of any kind of treatment objectively.

Diabetes and celiac disease in adults (CDA)

Diabetes and celiac disease in adults or untropical sprue can coexist (3,43). If CDA precedes diabetes, there is no problem with the diagnosis. When a diabetes is initially presented with steatorrhea the diagnosis does not have to be clear. The confirmation of the diagnosis is based on the autopsy of a small intestine which shows villous atrophy and abnormal superficial epithelium as well as a definitive therapeutic response to diet without gluten. Malabsorption in CDA refers to all kinds of food contrary to malabsorbtion in diabetes, which is limited only to fats. In CDA there are signs of vitamin deficit, losing weight and pigmentation. Laboratory studies reveal a wide malabsortive syndrome.

Studies on diabetes and follow-up sprue mainly refer to patients with relatively mild uncomplicated diabetes. There is no neuropathy. Diabetes and celiac disease can be combined more often than expected. (44) The treatment consists in the therapy without gluten.

LARGE INTESTINE

Obstipation is probably the most common gastrointestinal symptom in patients with diabetes (4,36). It was generally accepted that diabetic neuropathy damages the motility of the colon resulting in a significant obstipation. However, obstipation is equally frequent and severe in diabetics without neuropathy. Obstipation can be an extension of diabetic diarrhoea, which happens more often, or it can, less frequently, precede diarrhoea, but it can exist independently of any kind of digestive disorders, particularly in older diabetics. The existence of various gastrointestinal symptoms such as nausea, vomiting, belching, and bloating can be established in a patient with prolonged obstipation.

Megasigmoid syndrome

It is a rare complication of large intestine in diabetics. It is considered that colon dilatation, analogously to gastric dilatation, is causally connected to neuropathy and the paralysis of ganglia in the large intestine wall (45). In patients who were subjected to surgical sympathectomy no similar changes were described.

The autopsy of a patient with megasigmoid syndrome showed erosions and discrete ulcers of sigmoid colon. No pathological changes were observed in the area of mienteric and submucous plexus. Megasigmoid syndrome can clinically imitate an acute intestinal pseudo-obstruction (46). Patients are complaining about the abdominal bloating, diarrhoea or obstipation. An X-ray reveals abnormal dilatation of sigmoid colon. Some authors described an isolated caecum dilatation, less frequently of sigmoid. This complication may occur in diabetics with diarrhoea and obstipation (47,48). The obstipation in these patients is long-standing and refractory to the usual treatment measures. The prognosis is bad and can be fatal.

Very often, in anamnesis of patients with obstipation, there is laxative abuse. The treatment of obstipation in diabetics does not differ from the treatment of the same manifestation in patients who do not suffer from diabetes. Histologically, no changes were observed in mucosa of the large intestine in diabetics with enteropathy, in opposite to the stomach and small intestine mucosa.

PANCREAS

In patients who suffer from diabetes there is a complex relation between exocrine and endocrine pancreas component: pancreatitis can produce diabetes, and diabetes is often combined with deteriorated exocrine pancreas secretion.

Diabetes and pancreatitis

Acute pancreatitis often causes hyperglycemia, glycosuria and the glucose tolerance test will show abnormalities in more than 1/3 of the patients

with this condition. A disorder occurs shortly after manifestations of an acute pancreatitis attacks, though it may even persist for several months. Very small number of patients acquired permanent diabetes as consequence of an acute pancreatitis (49). In general, diabetes can more often be found combined with reccurent or chronic pancreatitis especially when pancreatic classifications are present. Rarely does a pancreatitis episode lead to the occurrence of the permanent diabetes. Diabetes which arises from pancreatitis certainly differs from the genetically determined form. Usually, degenerative complications of diabetes mellitus are less frequently found in pancreatic diabetes. Diabetes which occurs during pancreatitis needs less insulin 30–40 IJ and is generally mild, but, from case to case, it can be as difficult to control as a juvenile diabetes (50).

Any assessment of the incidence of pancreatitis in diabetes or diabetes in pancreatitis is burdened with determination to discover what occurs first. When acute pancreatitis appears in patients with an underlying diabetes, this can be a lethal event. Nair published 100 cases of simultaneous diabetic acidosis and acute pancreatitis in which the results were uniformly bad regardless of whether diabetes clearly preceded pancreatitis.

Tully and Lowenthal published 7 cases of diabetic coma and pancreatitis observed in a year and emphasized that the shock is common and that they can request correction by blood or by plasma (51). Measurement of serum amylase is a natural precaution in all the patients with diabetic acidosis especially in a state of shock, especially if acute pancreatitis, as the cause of diabetic acidosis remained unidentified, though is highly possible that mild episodes of pancreatitis remain unidentified reason of abdominal pain in diabetics.

Exocrine secretion

Recent studies show that there are definite abnormalities of pancreatic secretion in diabetes (52). Chey and associates with their research discovered the reduction of total volume output as well as the enzyme reduction (53).

Carcinoma of the pancreas

A general assessment of cancer incidence in diabetics is burdened with the fact that diabetes mellitus itself is combined with increased mortality rate, so other diseases can occur more often in survivals, but far less when the autopsy material is available (54).

The most frequent malignant lesion in diabetes is carcinoma of the pancreas which must be suspected of in every diabetic with enormous loss of weight and deteriorated glycoregulation. An increased incidence of pancreatic cancer among diabetic patients was found in nationwide population-based cohort studies carried out in Sweden (55).

LIVER

Common complication of diabetes mellitus is fatty liver. Histologically, fatty deposition, nuclear vacuolisation, cellular infiltration and fibriosis are observed in the liver of diabetics. Apart from fatty liver which occurs as a regular complication, it is not noticed that diabetes mellitus and liver cirrhosis are often combined. Diabetes may precede or be the cause of cirrhosis of the liver and vice versa - cirrhosis of the liver may precede or cause diabetes (56,57).

GALL BLADDER

There is an unexplained higher incidence of gall stones in patients with diabetes metillus, although its exact frequency varies widely among studies (58,59). Gall stones may be a significant source of problems in diabetics. Risks combined with acute cholecystitis and a rate of postoperative complications are higher in diabetics. This means that in every diabetic discovering the presence of gall stones is neccesary, as well as timely cholecystectomy as a preventive measure.

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SAŽETAK

Šećerna bolest utiče na svaki organski sistem, pa prema tome i na gastrointestinalni trakt. Precizna učestalost digestivnih poremećaja u sklopu šećerne bolesti nije poznata. Nekoliko mehanizama uzrokuje nastanak ovih poremećaja uključujući autonomnu neuropatiju, dijabetičnu mikroangiopatiju, lošu glikoregulaciju, poremećaj lučenja insulina i glukagona i povećanu osetljivost na gastrointestinalne infekcije. Ezofagealni poremećaji kao smanjena amplituda ezofagealnih kontrakcija, smanjen pritisak donjeg ezofagealnog sfinktera i refluks kiselog želudačnog sadržaja su česti kod pacijenata sa šećernom bolešću. Dijabetes je uključen u određen broj poremećaja želuca i smatra se odgovornim za neodređene dispeptične simptome. Nasuprot manifestacijama u želucu koje su obično asimptomatske, manifestacije na tankom crevu u okviru dijabeta su od većeg simptomatskog značaja za pacijenta. Dijareja i steatoreja su česte kod dijabetičara. Opstipacija je verovatno najčešća gastrointestinalna tegoba kod pacijenata sa dijabetom. Opstipacija se može javiti nakon dijabetične dijareje, što se događa češće, dok ređe prethodi dijareji, mada može postojati nezavisno od bilo kojih probavnih poremećaja naročito kod dijabetičnih bolesnika starije životne dobi. Kod pacijenata koji imaju dijabetes postoji kompleksan odnos između egzokrine i endokrine komponente pankreasa. Pankreatitis može produkovati dijabetes, a dijabetes je često udružen sa pogoršanom egzokrinom pankreasnom sekrecijom. Uobičajena komplikacija kod pacijenata sa dijabetesom je i masna jetra. Šećerna bolest je često kombinovana i sa cirozom jetre. Dijabet može prethoditi ili biti uzrok ciroze i obrnuto, ciroza može prethoditi ili izazvati pojavu dijabeta. Postoji neobjašnjivo povećanje incidence žučnih kamenaca kod pacijenata sa šećernom bolešću.

Adekvatno i pravovremeno prepoznavanje gastrointestinalnih manifestacija šećerne bolesti je od izuzetnog značaja u tretmanu ovih pacijenata.

***Ključne reči*: šećerna bolest, digestivni poremećaji**