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Gastrointestinal Syndromes Due to *Diabetes Mellitus*: A Review

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ABSTRACT

Diabetes mellitus is a clinical syndrome that might result in a diversity of derangements of gastrointestinal structure and function. Disturbances may evident as symptoms and metabolic changes that in turn, might impeach in the management of the patient with diabetes. The present article explains the path physiology, clinical finding options dealing with the main clinical syndromes related to disturbances of gastrointestinal physiology in diabetics. It addresses oesophageal dysfunction, occasionally subclinical, but often a basis of troublesome upper gastrointestinal symptoms, and also, describes the gastroparesis syndrome, possibly the most characteristic form of gastroduodenal dysfunction in the diabetic. It covers the complex issue of diarrhea in diabetic patients as well, often multifactorial and sometimes resulting from a combination of pathophysiological abnormalities related to diabetic sequel and association with common gastrointestinal ailments, such as irritable bowel syndrome. Likewise, some attention is paid to the issue of constipation and fecal incontinence in the patient with diabetes mellitus, a particularly disturbing problem quite common in long-standing diabetics.

1. INTRODUCTION

In a patient with *Diabetes mellitus*, gastrointestinal symptoms may be caused by the same spectrum of disorders as in the general population or by disturbances that arise as a complication of diabetes. The prevalence of gastrointestinal symptoms in diabetics is not well recognized but appears to be considerably higher than in the general population. As many as 60–75% of patients visiting diabetes clinics report significant gastrointestinal symptoms on the basis of a population-based survey of 15,000 adults, which showed that the prevalence of a variety of upper and lower gastrointestinal symptoms and symptom complexes in diabetics was increased[1,2,3]. Abnormalities in gastrointestinal function, mainly motor nerve function, are not consistently symptomatic. Annese *et al.*[4] studied oesophageal, gastric, and gallbladder motor nerve function in a group of patients with type 2 diabetes mellitus (most with autonomic neuropathy) and detected oesophageal motor abnormalities and delayed gastric emptying of solids in about 50% of the group, and impaired gallbladder emptying in two-thirds. In total, 74% of the patients had at least one of the three organs affected though; only 26% had all three involved. About two-thirds had gastrointestinal symptoms, although these could not always be associated with specific organ dysfunction. Sometimes even asymptomatic patients might show confirmation of digestive-tract dysfunction when tested, but again exact prevalence figures are not known because population-based studies have not been done[5]**.** The pathogenesis of gut disturbances that arise as a complication of diabetes mellitus is likely to be multifactorial and is not clearly understood. In 1945, Rundles [6]documented autonomic neuropathy as one of the etiological factors involved. However, other factors such as metabolic abnormalities (hyperglycemia, hypokalemia), vascular changes (microangiopathy), altered hormonal control, and increased susceptibility to infections might play a vital role. Gastro-intestinal complications of diabetes mellitus have become more prevalent as the rate of diabetes has increase enormously. These complications and their symptoms are often caused by gastro-intestinal motility disfunction which is a repercussion of Diabetic Autonomic Neuropathy involving the gastro intestinal tract[7].

The article encompasses all the aspects related to gastro-intestinal diseases due to *Diabetes mellitus.*

2. METHODOLOGY:

Relevant literature regarding the article was collected from the Library of RRIUM, Srinagar, Kashmir University and information also retrieved from published papers on various database like Web of Science, Google Scholar, Researchgate, Springer, and PubMed.

3. OBSERVATION AND DISCUSSION

3.1 Oesophageal Dysfunction

3.1.1 Pathogenesis: Autonomic neuropathy is the chief pathogenetic factor. Neuropathological oesophageal abnormalities, swelling, irregularity of caliber, and disruption of parasympathetic fibers in the oesophageal wall and the extrinsic trunks have been reported. The myenteric plexus appeared normal except for a lymphocytic infiltration within the ganglia. Chronic Persistent hyperglycaemia may also be involved, it will be shown later for some motor gut disturbances[8].

3.1.2 Clinical findings and Evaluation

Oesophageal motor dysfunction is common in patients with diabetes mellitus but is usually asymptomatic. The most common complaints are heartburn and dysphagia, but these symptoms are nonspecific. Nishida et al. [9]reported that 25.3%of a group of 241 patients with diabetes mellitus had symptomatic gastroesophageal reflux disease symptoms against 9.5% of a control group of patients with chronic hepatitis C. This data approximates the 28% prevalence of abnormally elevated gastroesophageal reflux in diabetics, based on pHmetry studies, reported by Lluch *et al.*[10], though most patients in the second group appeared to be asymptomatic. In any case, the presence of abnormal gastroesophageal reflux was related with cardiovascular autonomic neuropathy [10]. However, on the subject of reflux and autonomic neuropathy, there are some contradictory reports. Jackson *et al.*[11]observed that among symptomatic gastroesophageal reflux disease patients, those with diabetes mellitus often have normal 24-hour pH metry, but abnormal autonomic functioning. In contrast to non-diabetics in whom the relationship between gastroesophageal reflux disease symptoms and abnormal oesophageal pHmetry is closer. It is feasible that abnormal oesophageal motility or sensitivity, or both, produce symptoms in diabetics with autonomic neuropathy that imitate acid reflux but are not directly related to acid. This possibility should be considered in patients who do not respond as well as expected to routine pharmacological therapy. These issues were also analyzed by Antwi *et al.* [12]who stated that endoscopic

oesophagitis was more prevalent among diabetics with autonomic neuropathy than without, whereas reflux like symptoms were similar with or without neuropathy. Furthermore, intuition was provided by Kinekawa *et al*. [13]who observed that abnormal acid reflux on the basis of oesophageal pHmetry correlated with motor nerve conduction velocity, although not with the coefficient of variation of R–R intervals on the electrocardiogram. Oesophageal motility disorder usually consists of reduced or absent primary peristaltic waves, sporadic tertiary contractions, and delayed oesophageal clearance. However, Loo*et al*. [14]were more impressed with the finding of multipeaked peristaltic wave complexes than with the earlier mentioned abnormalities, which they regarded as nonspecific. Oesophageal motor abnormality, calculated manometrically, also appears to correlate with test evidence of neuropathy [13]. Holloway et al. [15]explored the association between oesophageal transit and oesophageal dysmotility in patients with long-standing diabetes mellitus. He simultaneously performed oesophageal manometry and radionuclide transit measurement of solids and liquids in the oesophagus. They analyzed a high prevalence of transit hold-ups in diabetics, significantly higher than in controls (both young and elderly, the later being suffered by a higher prevalence of dysmotility on account of presbiesophagus). The main mechanism responsible for oesophageal bolus hold up in diabetics was a peristaltic failure or focal low amplitude pressure waves, confirmed manometrically. Drawbacks in interpreting oesophageal motor dysfunction as a cause of patients symptoms do abound. A report of unsatisfactory symptomatic response to laparoscopic myotomy in a patient with diabetes mellitus having evidence of achalasia cardia diagnosed by manometry should be considered.[16]Psychosomatic factors in the genesis of oesophageal motor dysfunction have also been suggested[17].

3.2 Gastroduodenal Dysfunction (The Gastroparesis Syndrome)

3.2.1 Pathogenesis: Diabetic gastroparesis is an electromechanical motility disorder that in many cases involves not only the stomach, but also the upper small intestine. The molecular pathophysiology of diabetic gastroparesis is not clear. In fact, a number of pathogenetic factors may be implicated in most patients. Animal studies indicate a defect in the enteric nervous system characterized by a loss of nitric oxide signals from nerves to gut smooth muscle [18,19]. Interstitial cells of Cajal might also be disrupted [20]. Impairment of vagal nerve function by autonomic neuropathy, in turn, makes alterations in postprandial hormones including gastrin levels [21]. Prostaglandin overproduction in gastric smooth muscle has been related to gastric slow-wave disruption[22]. In animal models of diabetic gastroparesis there is evidence that homeostatic mechanisms are activated in the enteric nervous system to

compensate for the loss of extrinsic innervation[20]. Acute persistent hyperglycemia might play an important pathogenetic role [23]. Antral motility decreases with postprandial glucose levels more than 9.7 mmol/L [2]. In 10 patients with type 1 diabetes mellitus and sensory-motor neuropathy, Flowaczny and co-workers[24] analyzed that when plasma glucose concentrations were controlled by permanent intravenous administration of insulin; gastric emptying rates were near normal. Although, achieving and sustaining normoglycemia is certainly important, in clinical practice symptomatic patients with gastroparesis still needs prokinetic therapy for satisfactoryresults[2]. However, to further complicate matters, it has been shown that the accelerating effect of prokinetics in turn significantly dampened by hyperglycemia. Thus, strict glycemic control is of paramount importance in successful management of diabetic gastroparesis[25].

3.2.2 Clinical Findings and Evaluation

Both acute and chronic gastroparesis are comparatively common occurrences. Gastric emptying of solids is delayed in 30–50% of patients with diabetes mellitus[23,26,27,28,29]. Another 20% may in fact present increased gastric emptying [29]. Though many such patients experience upper Gastrointestinal symptoms that impair their quality of life, others are asymptomatic. Thus, the conception that symptoms are the direct result of delayed gastric emptying or on the other hand that delayed gastric emptying might be related with clinical symptoms is now recognized as very simplistic. Lack of association between gastric emptying rates and gastro intestinal symptoms has been evidenced by various studies [26]. On the other hand, the potential impact of gastroparesis on oral drug absorption and blood glucose control in diabetics has probably been underemphasized[28].Certainly, gastroparesis should be suspected in patients with poor glucose control[23,30]and timing insulin regarding gastric emptying rates might be helpful. A hypothesis has been projected that improving gastric emptying in diabetics with gastroparesis with the use of prokinetics would normalize duodenal nutrient delivery rates and achieve better glycemic control. Although logical and attractive, experimental studies in human diabetics have not shown enough supportive evidence to justify it as clinically significant [31,32]. Gastropares is affects both types of diabetes mellitus i.e. type 1 and type 2. [13]. Diabetic peripheral neuropathy is present in about two-thirds of gastroparesis patients with type 1 and about one-fifth with type 2 diabetes mellitus[2].One study examined the association between gastric emptying parameters, gastric symptoms, and cardiovascular autonomic function. In addition, they found no significant relationship between the prevalence of Gastro intestinal symptoms and abnormalities in

gastric emptying. Neither there was any significant association between delayed gastric emptying and cardiovascular autonomic neuropathy in their group of patients [33]. This is mostly a controversial issue as other studies results are discrepant. Tomi *et al.* [29]set up a relationship between abnormalities in gastric emptying (delayed or increased) and cardiovascular autonomic neuropathy, although not with symptoms. De Block *et al.* [26]also established an association between delayed gastric emptying and autonomic nerve dysfunction. Likewise, other investigators[34]established a strong relationship between diabetic gastroparesis and cardiac autonomic neuropathy, nephropathy, and retinopathy. Huszno *et al.* [35]also explored the potential accord between diabetic gastroparesis and cardiovascular neuropathy in42 subjects with type 1 diabetes mellitus. Their results showed a trend toward a higher prevalence of recognized cardiovascular neuropathy in patients with diabetic gastroparesis as opposed to those with normal or increased emptying, but the substantial overlap was apparent. These writers concluded that diabetic autonomic neuropathy tends to be scattered and does not always affect and alter the function of a particular organ in the body. Gastric emptying abnormalities, including both solid and liquid components of a test meal, remain rather stable for long periods (mean 12.3 ±3.1 years of follow-up(SD) in one study [36]. There was not much change in the Gastrointestinal symptom pattern during such long follow-up. The prevalence of autonomic neuropathy did increase during the years from an initial 35% at baseline to 80% at follow-up[36]. When it comes to specific abnormalities in upper gut function as responsible for gastroparesis, the thoughts have fluctuated significantly during the decades. Antral hypomotility with failure to grind and propel mixed chyme into the duodenum has been conventionally accepted as a major pathophysiological factor. Though, animal studies, proposed that proximal gastric hypomotility and pyloric hypercontractility are more significant[37]. Indeed, quite early, in the laboratory it was documented that some patients with diabetic gastroparesis presented manometric evidence of hyperactivity at thepylorus[38]. In other patients, delayed gastric emptying might be caused or increased by intestinal dysmotility [39]. Finally, in some patients with chronic nausea, gastric stasis may be due in part to centrally relayed reflexes triggered by gastric dysrhythmia or other visceral afferent signals. When symptomatic, gastroparesis manifests by episodes of nausea and vomiting(fasting as well as postprandial) that is often, but not always associated with upper abdominal pain. Dyspeptic symptoms such as early satiety, frequent eructation as well as bloating might be present. On abdominal examination, a gastric splash might be noted, but it is rare. The occurrence of nausea and vomiting be likely to follow a variable course and might be self-limited or recurrent. In severe cases, the gastroparesis syndrome

may lead to malnutrition or severe complications, like bleeding from upper gastrointestinal tract (Mallory–Weiss tears) secondary to repeated bouts of retching or vomiting. Symptoms are likely to be worsening during the course of diabetic complications and in fact in patient with symptomatic diabetic gastroparesis have poorly controlled long standing, insulin-dependent diabetes. Peripheral neuropathy and other manifestations of autonomic dysfunction (orthostatic hypotension, impotence, bladder dysfunction) are commonly, but not invariably associated. In evaluating a patient with suspected diabetic gastroparesis, gastroduodenoscopy, and at least upper Gastro intestinal radiology should be done first to exclude pyloric or any other type of mechanical obstruction. A careful and detailed history about medications (e.g. psychotropic drugs, anticholinergics, ganglion-blocking agents etc.) should also be obtained. Radiological features of gastric stasis, such as dilatation of the stomach with retained food and secretions are useful if present in the absence of demonstrable mechanical lesion. However, the sensitivity of radiology in detecting Gastro intestinal motor dysfunction is low. Therefore, a normal barium meal does not exclude diabetic gastric dysmotility. Several methods with higher sensitivity to assess gastric motor function are currently available. Gastric emptying time is best assessed using radioscintigraphic techniques that differentiate between emptying of the solid and the liquid phases of a meal(double-isotope scintigraphy). Estimation of gastric emptying rates by a radionuclide study remains the gold standard for assessment of gastroparesis. Other techniques include the 13C-octanoic acid breath test and ultrasonographic measurement of gastric emptying. The 13C-octanoic acid breath test has been compared with the radionuclide emptying test in diabetics [17]and has been shown to constitute a suitable method for diagnostic function with good correlation observed between both tests. Real-time ultrasonographic measurement of gastric emptying of a semisolid meal has also shown a good correlation with the conventional scintigraphic test[40]. The ultrasonographic technique does not actually determine the disappearance of meal from the stomach, but the decline in antral cross-sectional area as the stomach empties. Electrogastrography has also been suggested as a diagnostic tool for gastric motor disorder in diabetics, but the evidence is not sufficiently strong to recommend it asa clinical diagnostic tool at this point[41].Manometry is another useful method in the evaluation of upper intestinal motility disorders[42].

3.3 Mid and Lower Gut Dysfunction (Diabetic Diarrhoea and Constipation)

Diarrhea or constipation, or both, are among the most common gastrointestinal complaints experienced in patients with diabetes mellitus. These disorders of bowel habit reflect, at least in part, small bowel and colonic dysfunction.

3.3.1 Diarrhea

3.3.2 Pathogenesis*:* The pathogenesis of diarrhea in patients with diabetes mellitus is not clearly understood and possibly multifactorial. It may be caused by disorders directly related to diabetes (primary causes) or to late complications (secondary causes). Among primary causes, Diabetic neuropathy is an important factor but other factors probably contribute as well. Functional changes such as accelerated transit time and decreased intestinal tone might be related with increased cholinergic and decreased β-adrenergic receptor activities [43]. Neuroendocrine peptide dysfunction might also be involved. El-Salhy and Spangeu[44]have revealed that in diabetic mice antral vaso active intestinal peptides (VIP) and galanin levels are increased, whereas colonic Peptide YY concentrations are decreased. These particular abnormalities in enteric peptide profile would favour the development of diarrhea, whereas other abnormalities in peptide levels could favour constipation. Low *et al.* [45]examined the association between various gastrointestinal symptoms attributable to autonomic neuropathy (diarrhea among them) and objective autonomic impairment measured by laboratory tests in patients with type 1 diabetes mellitus. Their findings recommend that both symptoms and autonomic dysfunction are common in diabetes. Though, they could not invariably establish a conclusive relation between autonomic dysfunction and the clinical manifestations. Rosa-e-Silva *et al.* [46]observed rapid transit in the distal small bowel of patients with type 1 diabetes mellitus with strong association with the presence of orthostatic hypotension, suggesting that autonomic neuropathy is the common relation between both findings. In patients with a postganglionic sympathetic lesion, Camilleri *et al.* [47]established manometric evidence of intestinal dysmotility in the form of in coordinated bursts of nonpropagated phase III-like activity, although not all of these patients had diarrhea. Among other primary causes of diabetic diarrhea, microangiopathy and functional mucosal abnormalities might also play a role. Secondary causes of diabetic diarrhea include bacterial overgrowth, abnormalities in bile acid enterohepatic circulation, and exocrine pancreatic insufficiency[48.]

3.3.3 Clinical Findings and Evaluation

Diabetic diarrhea was first documented in 1936 by Bargen *et al*. [49]. The diarrhea is watery, often severe, and preceded by abdominal cramps and it occurs particularly at night and may be associated with fecal incontinence. Symptoms are intermittent and might last from a few hours to some weeks. During remissions, patients may shift and complain of constipation, resembling the bowel movement alternance feature of irritable bowel syndrome. Mild steatorrhea, though not common is congruent with the diabetic diarrhea syndrome, whereas weight loss is unusual. Other signs of autonomic neuropathy may be present concurrently. The diagnosis of chronic diabetic diarrhea is basically one of exclusion. The main problem with this move towards remains that some of the main conditions in the differential diagnosis (pancreatic insufficiency, bacterial overgrowth and celiac sprue) can themselves be part of the diabetic diarrhea syndrome. A detailed history should be taken to exclude osmotic diarrhea from excessive ingestion of non-absorbable hexitols (e.g., sorbitol). A48–72-hour stool collection for weight and fat measurement used to be standard approach, but it is troublesome and nowadays tends to be bypassed in favour of other tests, when steatorrhea is found, pancreatic insufficiency should be excluded by carry out a pancreatic function test or, if these are not available, by a trial with oral pancreatic enzymes. The degree of steatorrhea relative to diarrhea might sometimes be a helpful clue in distinguishing pancreatic insufficiency from that caused by other gastrointestinal diseases. Bacterial overgrowth might be established by breath tests. Although a positive response to antibiotics is suggestive, it is not reliable confirmation because diabetic diarrhea often shows spontaneous remissions. Celiac disease might be associated with diabetes and accompanied by features of more severe malabsorption (considerable steatorrhea, hypoalbuminemia, anemia, abnormal Schilling and xylose test, low serum folate) than is characteristic of diabetic diarrhea. Serological tests for celiac disease are advisable. Small bowel biopsies maybe useful but are not specific for gluten enteropathy because blunting of villi might occur in bacterial overgrowth and other conditions. A favourable clinical and histological response to gluten-free diet helps confirm the diagnosis. Sometimes, diabetics may also experience abdominal pain because of thoracolumbar diabetic radiculopathy with no evidence of gastrointestinal pathological findings. A detailed history of the typical burning, sharp dermatomal pain, the chronic course, and the electromyogram and thermoregulatory sweat test findings would point to the correct diagnosis of this syndrome. From a clinical viewpoint, it is important to recognize the incidence of pseudodiarrhea (also denominated low volume diarrhea), which in fact

represents constipation with impaction of hard stools in the lower colon and rectum. These patients often complain to physicians of “diarrhea” because they have recurrent bowel movements expelling small quantities of liquid residue, which leaks around the impacted solid faeces. It is often associated with tenesmus and incontinence. Pseudodiarrhea is in fact constipation, and should be treated as such [50].

3.4 Constipation

3.4.1 ***Pathogenesis:*** Constipation and the use of laxatives are relatively common in patients with diabetes mellitus [51]but the mechanism of constipation remains uncertain. Epidemiological studies in community-based practices suggest that clinicians should not instantly assume that gastrointestinal symptoms in patients with diabetes mellitus represent a complication of diabetes mellitus [52]. Diabetic autonomic neuropathy may be concerned in some patients, but other factors might also be significant. For instance, evacuatory disorder is another key factor [53]. Jung *et al*. [54]showed in a trial involving patients with type 2 diabetes mellitus that those with constipation had longer total colonic transit times than those without constipation. Though, there was no difference in colonic transit times between patients with or without cardiovascular autonomic neuropathy. Another study by Ron *et al*. [55]in elderly, weak patients showed a high prevalence of constipation associated with prolonged colonic transit times. Though, no significant differences were noted between patients with and without diabetes. Iida *et al*. [56] showed in type 2 diabetics a relation between prolonged colonic transit measured by the radiopaque pellet method and autonomic cardiovascular dysfunction. In one trial, constipation in type I diabetics was found to be associated with the use of calcium channel blockers [52]. Poor glycemic control is possibly a key contributory factor [57]. Acute persistent hyperglycemia affects anorectal motor and sensory function [58]. The natural history of constipation in diabetics does not seem to forecast symptom change overtime [59].

3.4.2 Clinical Findings and Evaluation

It is complicated to separate constipation in patients with diabetes from that occurring among the normal population because constipation is such a very prevalent symptom. The depth of diagnostic assessment in a patient with diabetes complaining of constipation depends on the severity of constipation and on the related symptoms. Digital examination, testing of stools for occult blood, proctosigmoidoscopy, and barium enema, full colonoscopy should be done to rule out colonic malignancy. Anorectal manometry might be helpful to evaluate the

anorectal inhibitory reflex which is absent in Hirschsprung's disease. Colonic segmental transit time can be obtained from the mean segmental transit time of radiopaque markers through right colon, left colon, and rectosigmoid area. These tests should assist to distinguish between diffuse colonic hypomotility and rectosigmoid dysfunction (outlet obstruction). Unfortunately, the sensitivity and the specificity of these procedures have not been specifically evaluated in diabetics [60].

3.5 Fecal Incontinence

3.5.1 ***Pathogenesis:*** Faecal incontinence is a challenging clinical situation particularly in elderly diabetics. It has been approximated that up to one-fifth of patients with diabetes have fecal incontinence, although prevalence depends on criteria of incontinence applied. The incidence of fecal incontinence in diabetics appears to associate with duration of the disease [61]. Incontinence is most likely multifactorial and involves-related changes, diabetic neuropathy, co-morbidity, and polymerization [62]. Though, instability of the internal sphincter probably plays a key role in incontinent diabetics [63]. Another important cause is fecal impaction [64]. The huge majority of patients with diabetes with fecal incontinence have normal or only moderately increased daily stool volumes, but also exhibit multiple disorders of anorectal sensory and motor functions. Fecal incontinence might be related with severe diabetic diarrhea or comprise an apparently independent disorder. Diarrhoea might of course, produce stress on the continence mechanisms that are already impaired[65].

3.5.2 Clinical Findings and Evaluation

In evaluating fecal incontinence in patients with diabetes it is important to take a careful history and to assess stool weight. Incontinent diabetics may complain of "diarrhea," although their 24-hour stool weights are within average limits. An anorectal function can be assessed by anorectal manometry and tests of continence for solids and liquids. Anorectal manometry provides information about the maximum basal sphincter pressure, the maximum "squeeze" sphincter pressure, and the rectoanal inhibitory reflex (inflation of a balloon in the rectum causes a reflex relaxation of the internal anal sphincter). Continence for solids and liquids can be assessed by simulating the stress of stools with a solid sphere or with rectally infused saline. Unfortunately, these tests do not appear to be very useful in making therapeutic decisions. Suitable treatment of incontinence in diabetics includes optimizing blood sugar control and biofeedback therapy. Surgical intervention should be reserved for cases refractory to medical treatment or for those patients with rectocele or obstetrical injury.

The clinical outcome of surgical treatment of incontinence is far from uniform and caution is advisable before recommending it [66.]

3.6 CONCLUSION

Gastrointestinal symptoms and dysmotility are frequent in diabetes mellitus but not commonly recognized in clinical practice. The duration of diabetes and extent of glycemic control are main considerations in the incidence and severity of gastrointestinal problems. The entire gastrointestinal tract can be affected including esophagus, stomach, small and large intestines leading to a variable symptom complex. The workup starts with a detailed patient history and suitable laboratory, radiographic and gastrointestinal testing. In addition to pharmacological therapy, strict glycemic control and dietary manipulations plays an important role in managing gastrointestinal disorders in people with diabetes mellitus.

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