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Gastric Mucosal Changes in Type 2 Diabetic Patients

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Abstract: Diabetes mellitus (DM) is a chronic disease requiring lifelong medical attention in order to limit the development of potentially devastating late complications.. Diabetic autonomic neuropathy as well as acute suboptimal control of diabetes has been shown to impair GI motor and sensory function. *Aim*: Study the pattern and prevalence of gastric antral mucosal changes in chronic type 2 DM**.** *Material and Methods*: A detailed history and physical examination was done in all diabetic patient. Patients were counselled and after obtaining an informed consent patients were subjected to endoscopy and in the absence of gross morphological /anatomical abnormalities a biopsy of the gastric antrum was taken and the specimen sent for histopathological examination. *Results:* Of the 32 patients finally subjected for biopsy,25% were found to have normal mucosal layer, 40.6% were found to have superficial erosion and 34.4% were found to have mucosal erosion. Histopathological examination revealed that 40.6% was found to have no evidence of glandular atrophy and 59.4% were found to have glandular atrophy to varying degree. *Conclusions*: The results show that glandular atrophy was found to be more associated with uncontrolled DM. Subjects with HbA1C > 7% had more mucosal layer changes than when compared to subjects with HbA1C< 7%. Females were found to be 2.2 times higher at risk to develop glandular atrophy when compared to males.

Key words: Diabetes Mellitus · Gastric Antrum · Glandular Atrophy · Hba1c

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease requiring lifelong medical attention in order to limit the development of potentially devastating late complications. Gastrointestinal [1] sensory-motor abnormalities are common in patients with diabetes mellitus and may involve any part of the GI tract. Abnormalities are frequently sub-clinical and only rarely do severe and life-threatening problems occur. Common complaints include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting and diarrhoea.

Around 75% of patients attending diabetic clinic reported gastrointestinal symptoms [2]. Diabetic autonomic [2] neuropathy as well as suboptimal control of diabetes has been shown to impair GI motor and sensory function. Morphological and biomechanical remodelling of the GI wall develops during the duration of diabetes and may contribute to motor and sensory dysfunction.

Aim & Objectives: To study the pattern of gastric antral mucosal changes in Type 2 diabetic patients on treatment for more than 5 years.

To study the prevalence of glandular changes in Type 2 diabetic patients.

MATERIAL AND METHODS

Inclusion Criteria: Study subjects were selected from the type 2 diabetic patients being treated in a tertiary medical centre without other comorbid illness for over a period of 5 years.

Exclusion Criteria: Patients having any gastric complaints, alcohol consumers, regular/recent use of analgesics, coronary artery disease, pulmonary tuberculosis or extrapulmonary tuberculosis, GI surgeries and subjects over the age of 60 years. A total of 35 patients were enrolled for the study.

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Patients demographic and anthropometric details were recorded and a detailed history which included age, sex, duration of diabetes, drug history, compliance to therapy.

Patients were counselled and informed consent was obtained and were subjected to endoscopy. In the absence of gross morphological abnormalities in the stomach, a biopsy of the gastric antrum was taken and the specimen subjected to histopathological examination.

RESULTS

Out of 35 patients subjected to endoscopy, 3 patients were found to have abnormal findings and hence were not subjected to further biopsy procedures and excluded from the study.

16 men and 16 women were enrolled in the study.

Among the 32 patients studied 46.9% were diabetic for duration in between 5-10 years and 53.1% were diabetic for duration over 10 years.

15.6% had HbA1C below 7 and the remainder 84.4% had HbA1C more than 7.

On histopathological examination of gastric mucosa, 25% were found to have normal mucosal layer, 40.6% were found to have superficial erosion and 34.4% were found to have mucosal erosion. Among the females enrolled in the study, 25% had normal mucosa, superficial erosion was found in 50% and erosion was found in 25%. Among the males 25%had normal mucosa, 31.3% were found to have superficial erosion and 43.8% were found to have mucosal erosion.

Of the total 32 patients,40.6% were found to have no evidence of glandular atrophy and 59.4% were found to have glandular atrophy of varying degree. Among the females glandular atrophy was found in 50% and among the males 68.8% had glandular atrophy.

Data collected showed that females were at a 2.2 time risk to develop glandular atrophy when compared to the male patients.

Among subjects with HbA1C less than 7, 80% had normal gastric mucosa and 20% had mucosal erosion. Of the 20% of subjects with abnormality most of them (92%) hadglandular atrophy. Among subjects with HbA1C more than 7, 66.7% were found to have glandular atrophy. Subjects with HbA1C >7% were found to be 8 times the risk of developing glandular atrophy.

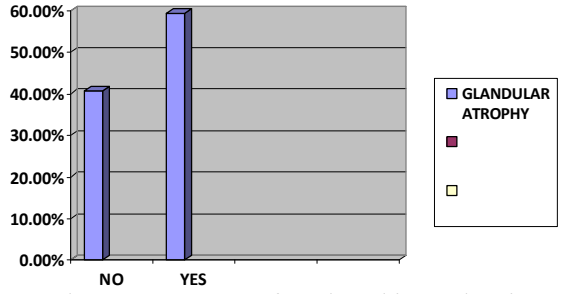

Fig. 1: Shows percentage of study subjects showing of glandular atrophy.

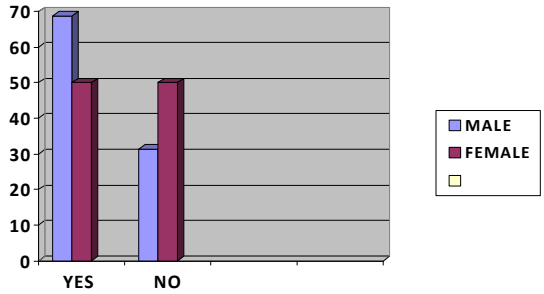

Fig 2: Shows comparative percentage of glandular changes seen in antral biopsies of both the males and females.

The mean age of the study group was 48.59 years and the mean duration of disease was 10.97 years.

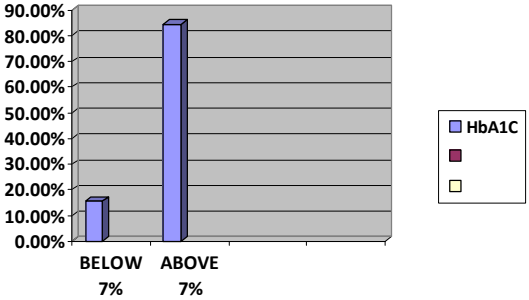

Fig 3: Shows the percentage of those patients who had their HbA1C within 7% and those who had above 7%.

The mean HbA1C value of the study group was found to be 9.054%.

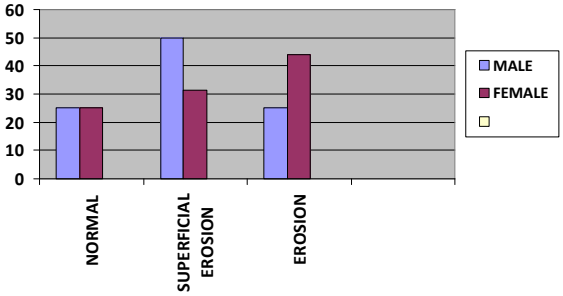

Fig 4: Shows comparative percentage of changes seen antral biopsies of both the males and females.

DISCUSSION

Gastrointestinal disorders are common in diabetic patients [1]. As many as 75% of patients attending diabetic clinics report significant GI symptoms [2]. The entire GI tract from the esophagus to the anorectal region may be affected. Common complaints include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting and diarrhoea. The symptoms may be severe and substantially decrease the quality of life. The pathogenesis of the GI abnormalities is complex of nature, multi-factorial (Motor dysfunction, autonomic neuropathy, glycemic control, psychological factors, etc.) and is not well understood. A number of abnormal conditions have been described in different segments of the GI tract in patients with diabetic autonomic neuropathy (DAN): esophagus (Dysmotility), stomach (Dysmotility, delayed emptying) and small and large bowel (dysmotility, delayed transit, bacterial overgrowth and diarrhoea) [3]. Only a few studies have addressed the visceral sensory function in diabetes [4] and have demonstrated abnormalities in perception thresholds, vagal tonus and evoked brain potentials in patients with DAN. This indicates that diabetes related neuronal changes may be located both in the peripheral and in the central nervous system (CNS).

Many studies have demonstrated prominent morphological changes of the small intestine and esophagus in diabetic patients [5]. Recently, Frokjaer [6] have shown that both the neuronal function of the contractile system as well as the structural apparatus of the GI tract may be affected in patients with longstanding DM and DAN. Hence along with DAN and glycemic control, the structural and biomechanical changes play important roles in the symptomatology of GI abnormalities in long-standing DM. The prevalence of upper GI symptoms is high in both insulin dependent diabetic patients and non-insulin dependent diabetic patients [7]. The symptoms relating to the esophagus, stomach and small intestine are as follows: (1) Esophagus: Heartburn, dysphagia and chest pain; (2) Stomach: weight loss and abdominal pain; (3) Small intestine: Diarrhea, discomfort, pain and pseudo-obstruction. Most symptoms are non-specific of nature and may relate to other GI disorders not necessarily related to diabetes. A number of other incidental conditions must be excluded when diabetic gastroparesis is suspected: gastric outlet obstruction caused by tumors and ulcer disease; metabolic abnormalities such as diabetic ketoacidosis or uremia and side effects of pharmacotherapy. A gastroscopy and biochemical screening followed by physical examination are obligatory requisites to reach the correct diagnosis. The symptoms of diabetic gastroparesis tend to increase in intensity and frequency over the duration of diabetes in patients affected. Most often symptoms are vague and nonspecific such as early satiety, slight abdominal discomfort and perhaps bloating. Abdominal pain can also be seen in diabetic ketoacidosis and severe metabolic acidosis [8]. These conditions are followed by other symptoms as well and therefore distinguishable from gastroparesis. Diabetic patients with thoracic polyradiculopathy, a rare condition, may also suffer from abdominal pain [9]. Although both the afferent and efferent nerves are affected in diabetes, the data related to the sensory dysfunction of the GI tract are sparse compared with those relating to the motor dysfunction of the upper GI tract. Elevation of perception thresholds to esophageal electrical stimulation has been observed in patients with DAN and different severity of GI symptoms [10]. Increased vagal tonus and abnormal evoked brain potentials to mechanical and electrical stimulation of the esophagushas also been shown in studies. To study mechanisms behind postprandial symptoms in patients with diabetes, the gastric accommodation of the meal was assessed by abdominal ultrasound [11]. In DM patients, a large proximal stomach was associated with perception of fullness and a large antrum was associated with perception of pain after a meal. More recently, Frokjaer used a multimodal stimulation device to investigate the visceral sensitivity to mechanical, thermal and electrical stimulation in the esohagus and duodenum in IDDM patients with DAN and GI symptoms. This study demonstrated that the patients had decreased sensitivity to the stimulations of the esophagusand duodenum. This indicates that the affection of the sensory nerves is widespread in the GI tract. As the multimodal approach is thought to stimulate the mucosa, submucosa and muscle layers differentially, the disease seems to be generalized.

Several animal studies reported a slowing gastric emptying in IDDM and NIDDM rats [12]. Using radionuclide measuring techniques it has been demonstrated that gastric empting of solid, or liquid meals was abnormally slow in 30%-50% of patients with long-standing IDDM and NIDDM [13]. The gastroparesis in DM has been known clinically for more than 50years. It is not surprising that the gastric emptying delay in DM is related to both slow transit with increased retention of food in the proximal and distal stomach [14] and abnormal motility of the gastric wall.

In the human studies, it is recognized that disordered gastric contractile activity as assessed by manometry and gastric emptying occurs frequently in DM. The motility disorders may include three aspects: Inter-digestive migrating Disordered GI function in DM has been attributed to irreversible DAN but it is now clear that acute high blood glucose concentration per se have a major reversible influence on upper-GI tract motility and sensory function. Rayner [15] performed isovolumetric and isobarbic distensions of the proximal stomach in ten randomly selected patients with IDDM. They demonstrated that the perception of gastric distension during euglcemia was increased compared with healthy controls. This study demonstrated that the correction of hyperglycemia to euglycemic levels restores the delayed transit [15]. Several studies in both healthy subjects and DM patients have shown that the GI motor function is impaired during acute hyperglycemia]. Marked acute hyperglycemia affects the motility in every region of the GI tract [16]. This may indicate that cholinergic activity is affected during hyperglycemia. Hyperglycemia may also affect the perception of sensations arising from the GI tract. However, much of the data have been observational and there is relatively little information relating to potential mechanisms by which these effects are mediated. Because both stimulatory and inhibitory effects occur during the hyperglycemia, the effects of glucose are likely to be mediated by neural or humoral mechanisms, rather than a direct effect on the smooth muscle of the GI tract. The secretion of pancreatic polypeptide, which is under vagal cholinergic control, is diminished during acute hyperglycemia in healthy control subjects. Considering the effects of systemic changes in blood glucose concentrations, animal studies have revealed the presence of glucose-responsive neurons in the central nervous system, which may modify vagal efferent activity. Neurons responsive to glucose have recently been identified in the rat small intestine, but their response to systemic rather than luminal glucose is unclear. Much work is required to elucidate the neural, humoral and cellular mechanisms by which systemic glucose levels affects GI motility and sensation motor complex (IMMC), amplitude and frequencyof contractions and pyloric dysfunction. DAN is seen as a major factor in the pathogenesis of disordered GI motor and sensory functions in DM [17]. Although GI manifestations related to DAN are diverse, many GI complications of DM seem to be related to DAN.

The best-characterized signs of damage to the autonomic nervous system during DM are morphological animal studies [18]. The number of myelinated axons in the vagosympathetic trunk is decreased in diabetic rats. In the GI tract, many changes of nerves and ganglia were observed i.e. (1) dystrophic axonopathy; (2) degeneration of mesenteric nerves and ganglia [19]; (3) number of vasoactive intestinal peptide (VIP)-IR neurons in myenteric ganglia [20]; (4) relative volume density in myenteric plexus [21]; (5) number of adrenergic and serotonergic neurons [19]. In addition, the surrounding tissue is also often disturbed. There is a thickening of the endothelium [21] which may sensitize axons to damage from increased pressure or decreased oxygen and glucose availability. It is thus possible that axonal damage may be secondary to disorders in tissue surrounding the neurons. Nitric oxide (NO) is a key neurotransmitter in the regulation of GI motor function [22]. In rodents with streptozotocin (STZ)-induced diabetes, NO synthase expression in the gastric myenteric neurons is diminishedand associated with delayed gastric emptying. The results of morphologic studies of the vagal nerves in diabetic patients are less consistent. One study demonstrated a decrease in unmyelinated axons in the abdominal vagus, another study found no abnormalities. Frokjaer *et al*. demonstrated that IDDM patients had decreased sensitivity to the stimulations of the esophagus and duodenum.This was accompanied by an increase in somatic referred pain areas to the gut stimulation. As the referred pain is a result of convergence between visceral and somatic afferents on central neurons, the findings are indirect evidence for central hyperexcitability and neuroplastic changes. Altogether, this indicate that the neuronal changes can be located both peripherally (Receptors, nerve fibers, ganglions) and in the CNS. Sensory nerve dysfunction in the gut may explain why diabetic patients with severe GI motility disorders often do not suffer from the GI symptoms expected from the abnormal motility and motor function. On the another hand a large subgroup of patients with longstanding DM suffers from severe GI symptoms.This overall hyperalgesia/hypersensitivity is in contrast to the peripheral autonomic afferent neuropathy that most likely impairs the perception from the GI tract. The mismatch between hypo-and hypersensitivity can likely be explained by an impaired balance between peripheral and central neuronal changes. Hence, the impaired function of the peripheral afferent nerves is likely

counterbalanced (Or even overruled) by increased central (Spinal and/or brain) neuronal excitability and this balance may determine the symptoms in individual patients.

It is likely that different pathophysiological mechanisms contribute to the peripheral and central neuronal changes in DM, including metabolic alterations, microvascular changes and inflammatory changes. Hypoxia, hyperglycemia and increased oxidative stress in DM contribute directly and indirectly to Schwann cell dysfunction. This will result in impaired paranodal barrier function, damaged myelin, reduced antioxidative capacity and decreased neurotrophic support for axons. Furthermore, the direct effects of prolonged hyperglycemia through the glycation on nervous tissue are alsAlthough the hyperglycemia and neuropathy seem to be the main mechanisms to the motor-sensory dysfunction in the upper GI tract in DM, the question remains whether the disordered motor and sensory functions of the GI tract are only due to the neuronal changes and dysfunction or if primary diabetes-induced structural and biomechanical changes in the GI tract also play a role? Data on the biomechanical properties are crucial for the understanding of the motor function of the GI tract because, (1) peristaltic motion that propels the food through the GI tract is a result of interaction of the passive and active tissue forces and the hydrodynamic forces in the food bolus and (2) remodeling of the mechanical properties reflects the changes in the tissue structure that determine a specific motor dysfunction. Therefore, the morphological and biomechanical remodeling of the GI wall may also be an important factor in the pathogenesis to the GI motor-sensory dysfunction in the diabetic patients important in the development of DAN.

A morphological study in DM rats demonstrated that the gastric mucosa thickness increased in DM rats compared with controls. Remodeling of the interstitial cells network of Cajal in the stomach were found both in animals and humans with DM. A histopathological study of the human stomach in DM patients with severe gastroparesis showed prominent collagenization and smooth muscle atrophy of the muscle layer. Regarding the biomechanical remodeling of the stomach only one report by Liao *et al* is available. The rat stomach was distended *in vitro*. Gastric compliance, the surface tension and circumferential and longitudinal deformation-pressure curves were calculated based on three-dimensional ultrasound reconstructions of non-diabetic and diabetic stomach models. In experimental DM, gastric compliance was lowered both in the non-glandular stomach (proximal part) and the whole stomach. Furthermore, the circumferential stiffness in the non-glandular part increased. The structural changes of the stomach due to DM may together with the sensory and motor nerve dysfunction contribute to the delayed gastric emptying and the symptoms in diabetic patients. In conclusion, GI symptoms are frequent in the diabetic patients and are associated with sensory-motor abnormalities, such as impaired perception and motility of the GI tract. The pathogenesis of abnormal GI sensory-motor function in DM is clearly multi-factorial. DAN seems to be the major factor in the pathogenesis of disordered GI motor and sensory functions in DM. Hyperglycemia has also been shown toimpair GI motor and sensory function. Furthermore, the morphological changes and biomechanical remodeling of the GI wall may compromise the GI motor function and affect the function of the mechanosensitive afferents in the GI wall.

CONCLUSION

The study clearly demonstrated the incidence of gastric mucosal and glandular changes and the comparison of these chances between the male and female subjects, the relation between the duration of the disease and the status of DM to gastric changes in chronic type 2 DM patients

The results show that glandular atrophy was found to be more associated with uncontrolled DM.

Subjects with HbA1C > 7% had more mucosal layer changes than when compared to subjects with HbA1C< 7%.

Females were found to be 2.2 times higher at risk to develop glandular atrophy when compared to males.

Scope for Further Research:

Further studies of the relation between the GI motor-sensory dysfunction, morphological changes and biomechanical remodeling in the diabetic GI tract may shed of more light to understand the mechanism of GI motor-sensory dysfunction in the diabetic patients. This knowledge may prove to be valuable in the development of new treatment strategies, which can also be evaluated with the developed methods. New treatments that may be based on the present knowledge and methods are: (1) neurostimulation of

afferent visceral nerves, i.e. gastric electric stimulation, (2) agents which can break down already formed glycation end product protein-protein crosslinks and (3) modulation of the central nervous system excitability by drugs.

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