Diabetes Mellitus and Gastrointestinal Disorders

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1 Introduction

Diabetes mellitus has been described as a metabolic disorder usually associated with hyperglycemia, which brings about complications, that affects multiple organs particularly if it persists for a long time either in type 1 or type 2 diabetes mellitus (Rodrigues & Motta, 2012). Although there are many differences in both types (Table 1), studies have shown that the gastrointestinal tract function is compromised, affecting the digestive processes, the motility and nervous control of the entire system (Bener et al., 2012; Bernstein, 2000). These complications manifests in various forms and affecting about 75 % of long standing diabetics worldwide (Zhao et al., 2006). The symptoms of this disorder seen in both the lower and upper gastrointestinal tract are caused by functional and/or structural changes. They may include gastroparesis, anorexia, vomiting, early satiety, intestinal enteropathy, diarrhea, constipation or fecal incontinence (Bytzer et al., 2002; Bytzer et al., 2001, Ko et al., 1999; Feldman & Schiller, 1983). Hyperglycemia injures the nerves directly and also disrupts blood supply to the nerves in the gastrointestinal tract (Kashyap & Farrugia, 2010; Ordög et al., 2009). The disruption of the nerve functions consequently affects the motility of the gut causing incomplete emptying of the different sections of the gastrointestinal tract. This could lead to gastroentropathy, a disorder of the esophagus, stomach and the colon. The effect of diabetes on digestive system can also cause malabsorption. Diabetics are reported to be at risk of developing gallstone due to decreased motility of the gallbladder as well (Yang et al., 1984).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
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<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Immune mediated with weak family influence (Vinik et al., 2005)</td>
<td>Metabolic disorder with strong family influence (Kota et al., 2012)</td>
</tr>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Loss of pancreatic β-cells leading to absolute insulin deficiency (Sparre et al., 2005)</td>
<td>Complex but due to inadequate insulin secretion, insulin resistance or both (Sparre et al., 2005)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Autoimmune diseases and environmental factors (Peng &amp; Hagopian, 2006)</td>
<td>Obesity, familial and ethnic variations (Kota et al., 2012)</td>
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<td><strong>Prevalence</strong></td>
<td>5-10 % of diagnosed cases (Daneman, 2006)</td>
<td>Over 90 % of diagnosed cases (Kota et al., 2012)</td>
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<td><strong>Onset</strong></td>
<td>Abrupt. Symptoms usually start in childhood or adolescence</td>
<td>Slow. The disease is mostly discovered in adulthood, but an increasing number of children are being diagnosed with the disease</td>
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<td><strong>Clinical signs</strong></td>
<td>Weight loss, and ketoacidosis (DiMeglio et al., 2003)</td>
<td>Overweight (Kota et al., 2012)</td>
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<tr>
<td><strong>Management</strong></td>
<td>Exogenous insulin</td>
<td>Exercise and diet plus medication e.g., oral hypoglycemics</td>
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Table 1: Differences between Type 1 and Type 2 Diabetes Mellitus.

Gastric mucosal damage has also been associated with diabetes (Morsy et al., 2010). Diabetic patients are prone to acute gastric injury and impaired ulcer healing which could aggravate to acute stress-induced gastric lesion (Konturek et al., 2010; Harsch et al., 2003). It is reported that severe gastric inflammation or ulcer can affect gastric motility in diabetic patients (Boehme et al., 2007). Healing impairment of chronic ulcers in diabetes mellitus has been attributed to release of proinflammatory cytokines such as tumor necrosis factor-α and the diminished activity of the mucosal antioxidative system (Brzozowska et al., 2004). *Helicobacter pylori*, an organism implicated in ulcer has been noted to have a high prevalence amongst diabetics (Tseng, 2012).
2 Pathogenesis of Gastrointestinal Disorders in Diabetes Mellitus

It is well established that autonomic nervous supply to the gastrointestinal tract is affected in a chronic diabetic state (He et al., 2001). The enteric system is the intrinsic nervous system of the gastrointestinal tract. This system, also termed "the brain of the gut", exerts a profound effect on the functions and activities of the gastrointestinal tract. It influences the digestive processes, whose actions include, motility, secretions, absorption, and gastrointestinal tract blood flow. The gastrointestinal tract function is mediated by both the extrinsic and intrinsic nerve fibers. The extrinsic neurons are controlled by the central nervous system and mediated via the parasympathetic and sympathetic nervous system (Figure 1), whereas the intrinsic nerves are found within the enteric nervous system where they originated from (Spångéus & El-Salhy, 2001; Spångéus et al., 2000). The control of these systems and the balancing of their activities modulate gastrointestinal tract normal function (Kashyap & Farrugia, 2010). Embedded in the walls of the gastrointestinal tract are two nerve networks of the enteric nervous system called plexuses, which also run from the esophagus to the anus. The plexus comprises of three types of neurons namely sensory, motor and interneurons that elaborate an array of neurotransmitter substances. The major neurotransmitters are acetylcholine, norepinephrine, serotonin (5-HT) and vasoactive intestinal peptide. Current evidence indicates that there are various types of neurotransmitters involved in the nervous network of the gastrointestinal tract, while some are primary others are subsidiary neuromodulators. They include peptide and non-peptide neurotransmitters found within the enteric neurons. Studies have identified and located these neurotransmitters to specific neurons using specialized staining method. In the myenteric plexus, γ-aminobutyric acid is found to be involved in regulating muscle contraction, whereas 5-HT within the same location functions as interneuron transmitter. Adrenergic neurons are said to emanate from autonomic ganglia and are connected via synapses to enteric nervous system. Report indicates that neuropeptide Y secreted from adrenergic neurons is inhibitory in nature (Spångéus & El-Salhy, 2001).

The parasympathetic innervation produces excitatory effects, stimulating smooth muscle contraction as well as increasing blood flow, secretions and release of enteric hormones (Frøkjaer et al., 2007). On the other hand the sympathetic nerve stimulation provides inhibition of gastrointestinal tract secretions, motor activities and decrease of blood flow. The submucosal plexus, an integral part of the enteric nervous system, is stimulated by the release of acetylcholine and inhibited by vasoactive intestinal peptide via the cholinergic neurons (Spångéus & El-Salhy, 2001; Tonini et al., 2000). Also, the sympathetic neurons by the release of norepinephrine modulate the secretory responses and blood flow (Lomax et al., 2010). The myenteric plexus neurons mediate contractile responses via the cholinergic system and these responses are inhibited by vasoactive intestinal peptide and nitric oxide by provoking relaxation responses (Iwasaki et al., 2006). On the other hand, epinephrine/norepinephrine mediates vasoconstriction, reduces gastrointestinal tract secretions and relaxation in addition to the contraction of sphincters (Lomax et al., 2010; Sarna, 2006). There is evidence that combined effect of the sympathetic system and activities of the dopaminergic inhibitory system is geared to reduce acetylcholine elaboration which consequently reduces gastrointestinal tract contractility (Eshraghian & Eshraghian, 2011).

There are abnormalities of neurotransmitters in the neurons of enteric nerve fibers in diabetic animal model. These abnormalities are seen from the esophagus to the anal region of the gastrointestinal tract (Spångéus & El-Salhy, 2001). Studies have shown that reduced vagal activity in acute hyperglycemic state decreases release of nitric oxide from the myenteric plexus and results in impaired gastric relaxation and delayed gastric emptying (Ishiguchi et al., 2001). The enzyme responsible for the elaboration of nitric oxide, nitric oxide synthase, is found to be reduced in diabetic patients and experimental diabetic
animal models. This is said to be critical in development of gastric dysmotility because the expression of neuronal nitric oxide synthase is found to be decreased in diabetic gastroparesis. The damaging effects of hyperglycemia on gastric motility stress the importance of rigorous metabolic control in the management of diabetic patients. There are indications that changes in the excitatory and inhibitory neurons or contents of the neurotransmitter in diabetes will lead to gastrointestinal tract dysfunction and these have been demonstrated in diabetic patients (Chandrasekharan & Srinivasan, 2007). This is seen as a significant decrease in the density of these inhibitory neurons. Since diabetes produces a state of oxidative stress precipitating conditions of advanced glycosylation end products, there is evidence that inhibitory neurons such as vasoactive intestinal peptide, nitric oxide and neuropeptide are mostly affected when compared to excitatory neurons (Iwasaki et al., 2006; Sheetz & King, 2002). The decrease and/or increase in the density of these neurons is believed to be responsible for altered gastrointestinal tract motility and gastric emptying observed in diabetic patients, while the loss of neurons could be due to apoptosis or necrosis in hyperglycemic state (Guo et al., 2004; Wautier & Guillausseau, 2001). Thus the diabetic state affects the innervation of gastrointestinal tract in both animal model and diabetic patients.

Figure 1: Gastrointestinal Tract Innervations and Neurotransmitters

The key to the pathogenesis of gastrointestinal tract disorders in diabetic patients is reported to be related to autonomic neuropathy (Shakil et al., 2008). The pathogenic mechanism of this abnormality appears to be multifactorial, manifesting in one or more of the gastrointestinal tract segments as form of demyelination of enteric neurons, decreased neuronal size, reduction in hormonal secretions and degeneration of axons in the submucous plexus (Bernstein, 2000). The theories proposed by scientists in the pathology of diabetic gastric dysfunction include, oxidative stress within the cells, impaired fatty acid metabolism, synthesis of advanced glycosylation end products in hyperglycemic state, increased sorbitol
production by aldose reductase enzyme and reduction of blood flow in the gastrointestinal tract (Chandrasekharan et al., 2011).

3  Affected Signaling Pathways in Diabetic Gastrointestinal Tract Disorders

The pathophysiology of gastrointestinal tract disorders in diabetes involves signaling pathways and disruption to any one of these could lead to autonomic neuropathy. In the presence of persistent high blood glucose, non enzymic glycosylation occurs resulting in excess glycosylation of proteins, particularly hemoglobin and cellular structures (Brownlee et al., 1988). Advanced glycosylation end products are protein and lipids that have been converted to glycated products upon exposure to sugars. They are predominant in diabetics and affect cellular structure and functions. The development of advanced glycosylation end products in diabetes, will affect the cell function, especially membrane cells (Bernstein, 2000). Advanced glycosylation end products impair nitric oxide production by reducing the half-life of neuronal nitric oxide synthase (Xu et al., 2003; Rojas et al., 2000). Polyol signaling pathway activity is also enhanced in a high blood glucose level condition where glucose is converted to sorbitol by the enzyme aldose reductase and is involved in autonomic neuropathy (Bernstein, 2000). Sorbitol may also glycate protein thus producing advanced glycosylation end products. Because this compromises the cell integrity, cellular information is disrupted and hence, nerve transmission is affected and morphological changes occur, altering nerve fibers within the enteric nervous system. Also excess sorbitol is known to decrease nitric oxide concentration in diabetic condition. This decrease in concentration of nitric oxide is reported to reduce gastrointestinal tract relaxation responses to non-adrenergic non-cholinergic nerves (Jenkinson & Reid, 1995).

4  Morphological and Functional Changes in Gastrointestinal Tract of Diabetic Patients

Impairment of nervous system function by diabetic neuropathy can occur anywhere in the body. Along the gastrointestinal tract, it produces conditions that are akin to vagotomy (Vittal et al., 2007; Kong & Horowitz, 2005). In diabetic conditions, advanced glycosylation end products are produced and this brings about morphological changes which occur in the presence of hyperglycemia. These changes, lead to biomechanical remodeling of the gastrointestinal tract (Zhao et al., 2010; Zhao et al., 2006). It is the accumulation of advanced glycosylation end products in the diabetic cells that causes the modification of structure and function of protein matrix. This has been demonstrated in animal models of diabetes mellitus and found to be one of the key mechanisms involved in gastrointestinal tract alterations in diabetes mellitus (Suzuki et al., 2012). A significant number of long standing diabetics exhibit different forms of symptoms due to disruption of function or changes in the gastrointestinal tract structure (He et al., 2001). Mandelstam and Lieber (1967) was the first to satisfactorily describe the relationship between esophageal dysfunction and diabetes mellitus. Several studies have since shown that esophageal motor dysfunction is common in patients with associated diabetic neuropathy (Kim et al. 2012; la Roca-Chiapas & Cordova-Fraga, 2011; Shakil et al., 2008; Frokjaer et al., 2007; Chandran et al. 2003). Findings have now revealed swelling, irregularity of caliber and disruption of parasympathetic fibers both within the myenteric plexus
and in the extrinsic trunks in the walls of the esophagus (Ordög et al., 2009; Bernstein, 2000). In the esophagus, distress may be described as dysphagia, chest pain and odynophagia (Kotler & Hsu, 2010). It is postulated that hyperglycemia which affects the vagal control of the esophagus, increases the relaxation of the esophageal sphincter (Ordög et al., 2009). It usually results in the delay of esophageal transit and seen in about 50% of the chronic diabetic cases (Kotler & Hsu, 2010). This effect is attributed to either peristaltic failure or development of focal low amplitude waves which consequently leads to gastroesophageal reflux (Holloway et al., 1999). Studies have shown that esophageal motor dysfunction in diabetes is more prevalent in the presence of neuropathy (Ordög et al., 2009; Shakil et al., 2008). Therefore changes are seen in both the structure and function of part or whole of the gastrointestinal tract. The structural changes are described as demyelination of the enteric nerves and loss of Schwann cells in the parasympathetic fibers, both in the wall and extrinsic nerves. The observed loss of function is as a result of reduced cholinergic stimulation. The parasympathetic innervation controls the peristalsis and relaxation of the esophagus and hence this loss will lead to distinctive alteration of both morphology and function. It is convenient to describe the clinical picture as loss of contraction amplitude, or reduced velocity in peristaltic movement and/or delay in esophageal emptying time (Zhao et al., 2006).

The stomach has two parts namely proximal and distal segments with two ends, cardiac and pylorus. The movement of food out of the stomach into duodenum is controlled by two processes, peristaltic and gastric emptying process (la Roca-Chiapas & Cordova-Fraga, 2011). Morphologically, the stomach is well suited in receiving and grinding food particle and stretching. The myenteric plexus is said to be responsible for gastric motility and in maintaining muscular tone of the stomach. In the presence of hyperglycemia, the stomach experiences cellular anatomic disruption in form of swelling of nerve cells with a consequent loss of myelin fibers, and smooth muscle are observed to be rounded and hyalinized (Bernstein, 2000). The diabetic stomach is reported to have a reduced ability to distend in response to food due to morphological structural changes in the musculature. Ordög et al. (2009) reported the presence of eosinophilic bodies and smooth muscle atrophy with accumulation of collagen in diabetic affected cells. While other workers reported diffuse smooth muscle atrophy and fibrosis of the stomach in diabetes mellitus (Pasricha et al., 2008). Abnormalities of gastric motility is said to occur in 20-30% of diabetic patients and, like esophageal motor dysfunction, they are often without clinical symptoms or manifestations (Shakil et al., 2008).

From human studies, disorders of gastric emptying is said to occur frequently in diabetes and acknowledged as disordered gastric contractile activity (Chandrasekharan et al., 2011; Bernstein, 2000). This motility dysfunction is said to manifest in amplitude and frequency of contractions and pyloric dysfunction (Zhao et al., 2006). Kassander in 1958 first recognized gastroparesis which he termed "gastroparesis diabeticorum" signifying delayed gastric emptying seen in diabetic patients. Delayed gastric emptying or gastric retention may present as nondescript abdominal discomfort. The cause of delayed gastric emptying is suggested to be because of vagal neuropathy, since the vagi are responsible for regulating gastric motility and transit. Support for this hypothesis is that there is a constant intragastric pressure within the normal stomach, despite receiving large volumes of food. This receptive relaxation, which the vagal nerves mediate has been shown to be impaired after vagotomy and is similar as seen in patients with diabetes mellitus (Vittal et al., 2007). In all, there is motor dysfunction of the stomach resulting in irregularity and uncoordinated motor activity as a consequence of diabetic neuropathy. Therefore in diabetic patients with gastric dysfunction, the activities of the stomach are grossly hampered. Studies have shown a decrease in the density of myenteric neurons caused by prolonged hyperglycemia in diabetic patients (Spångéus & El-Salhy, 2001). Evidence suggests that the condition of a hyperglycemic state will
cause autonomic neuropathy, which is a causal factor that precipitates disturbances of gastric motility (Ordög et al., 2009; Tieppo et al., 2009). This phenomenon has been reported in both animal and human studies (Kashyap & Farrugia, 2010). It can be argued that loss of myenteric neurons whether sensory or motor will mean a decreased innervation and motility of the stomach. Studies have provided evidence that increased production of fructose in hyperglycemic conditions will result in edema and rupture of nerve sheath, ultimately reducing nerve impulse conduction (De Freitas et al., 2008). The proposed mechanism is described as decrease in inositol metabolism, which reduces the activation of protein kinase C. The resultant excess intracellular sodium causes edema and rupture of myelin sheath, affecting transmission of nerve impulses (De Freitas et al., 2008). This will in turn affect the functions of the stomach as evidenced by the slowing of gastric emptying seen in diabetic patients and has also been demonstrated in animal models (Liu et al., 2004; Mehta et al., 2002). The slowing of gastric emptying is observed as slowing transit with food retention and loss of motility of the gastric wall (Smith & Ferris, 2003). The abnormalities of the fundus and pylorus were demonstrated also in diabetic animals by James et al. (2004) as seen frequently in patients with diabetes mellitus of either type 1 or 2 or both. Interestingly, studies that show the link with diabetes, also demonstrated that induced hyperglycemia in healthy subjects lead to slowing of gastric transit and food retention (Samsom et al., 1997; Abrahamsson, 1995).

Small intestinal dysfunction appears to be more common in diabetes when compared with esophageal or gastric dysfunction and with more severe symptoms. Like in the esophagus and stomach, the small intestine may be extensively affected in conditions of diabetes mellitus. The diabetic effect on the small intestine usually manifests with many symptoms when compared with the disorders involving the esophagus and stomach which may go unnoticed. A decrease in the intestinal tone of diabetic patients has been attributed to an increase in cholinergic activities and a decrease in adrenergic receptor activation (Anjaneyulu & Ramarao, 2002). The effect is seen as both slowing and rapid transit of the small intestine and is well documented also in animal studies (De Freitas et al., 2008). The small intestine of diabetic patients undergoes structural and functional changes. These changes are responsible for the impairments of motility, slowing of transit time, and affecting both secretory as well as absorptive functions. Evidence show that increase in the sorbitol production causes changes in the intracellular osmolality, which leads to neuronal death (Zanoni et al., 2002). This effect will deplete the small intestine of neurons and thereby decrease its neuronal stimulatory actions. From animal studies, diabetes induced rats will present with hyperplasia and hypertrophy of the mucosa and submucoosa of the layers of the small intestine (De Freitas et al., 2008). Clinical examinations have revealed a number of histological changes due to angiopathy in the intestinal mucosa of diabetic patients and are therefore associated with autonomic neuropathy. These changes which are strongly associated with reduced mesenteric perfusion are atrophic in nature with thick walls, reduced villi and possibly change in permeability (De Las Casas & Finley, 1999; Kandemir et al., 1995). The disruption of the intestinal mucosal cell integrity will compromise its functional ability as a surface barrier to prevent the passage of possible harmful agents. The observed increase in permeability of the small intestine to potentially dangerous substances in diabetic patients has also been documented in human studies and is related to its functional abnormality as well (de Kort et al., 2011).

The diabetic colon is more susceptible to damage when exposed to hyperglycemia (Rodrigues & Motta, 2012; Chandrasekharan et al., 2011). This damage can manifest as apoptosis of the enteric neurons and reduction in the size of the ganglionic neurons in the colon. The consequent development of this disorder is due to the creation of an oxidative state (Kashyap & Farrugia, 2011). Functional disorders will follow when there is a profound structural disruption in tissues. Evidence abound that show a delayed transit in the diabetic colon (Unal et al., 2008; Jung et al., 2003). As with the small intestine, these
Changes have been demonstrated in both human and animal models of diabetes mellitus in form of neuronal necrosis and hyperplasia resulting in increased thickness of the epithelial layers with reduced cell density (Unal et al., 2008). The development of morphological changes due to diabetes has been shown to bring about functional changes also in the colon. These functional changes could significantly affect the total colonic transit time due to a marked alteration in motility as a result of the loss and injury to interstitial cells of Cajal in the colonic submucosal cells (Forrest et al., 2008). Evidence from studies in humans show that the dysfunctional diabetic colon is related to the development of diabetic neuropathy, with absent postprandial response (Mirakhur & Walshaw, 2003). Also the prolonged diabetic conditions will blunt receptor-mediated responses and reduce contractions. This is said to be attributable to decreased ganglion size and increased enteric neuron apoptosis in a diabetic colon (Chandrasekharan et al., 2011).

The functions of anorectal region of the gastrointestinal tract are also affected in long standing diabetes mellitus. Changes are seen as alterations in evacuation and continence mechanisms (Tieppo et al., 2009). Fecal incontinence is the main sign seen in patients with anorectal dysfunction in patients with diabetes mellitus (Weiss & Sumpio, 2006). It is characterized by involuntary release of flatus's and/or liquid or solid feces, causing both hygienic and social problems. These social problems could lead to stigmatization and can cause serious psychological depression. This anorectal dysfunction is attributable to conditions of hyperglycemia which cause the impairment of the sphincter muscle function, altering the anal pressure (Tieppo et al., 2009). There is clinical evidence from diabetic neuropathy studies to show that the dysfunction of the anal sphincter in long standing diabetes mellitus is common (Ricci, et al., 2000). Diarrhea is usually accompanied by accidental passage of feces which is described as fecal incontinence. In these patients, the diarrhea is protracted with the presence of diabetic neuropathy occasioned by abnormal anal sphincter motor function (Bjelaković et al., 2005). This is said to be as a result of a defective autonomic nervous system regulation of the internal sphincter and/or abnormal intrinsic sphincter smooth muscle (Yang et al., 1984). Evidence from animal studies show that this is brought about by decrease in sphincter pressure and contraction of anorectal muscle (Tieppo et al., 2009). The alteration in function and structure of this region of gastrointestinal tract has been attributed to hyperglycemia. The state of hyperglycemia is known to induce an increase in apoptosis and causes the reduction of phosphatidyl inositol-3-kinase signaling in the enteric neurons (Chandrasekharan et al., 2011).

5 Consequences of Diabetic Neuropathy on the Gastrointestinal Tract

Poor glycemic control in diabetes mellitus has been suggested to be responsible for the many complications observed in gastrointestinal tract disorders (Ordög et al., 2009). Demonstrations of this disorder in both human and animals show that it is evident in type 1 as well as type 2 diabetes mellitus and that they are equally affected (Mishima et al., 2009). Previous studies show that diabetic neuropathy has an enormous influence on the sensory and motor functions from the esophagus to the terminal portion of the gastrointestinal tract (Chandrasekharan et al., 2011). It is believed that chronic hyperglycemic state in diabetic patients will create a condition of oxidative stress which is known to play a critical role in cellular injury. This condition is said to stimulate the generation of free radicals which are very reactive chemically and can impose a damaging effect on tissues causing injury to cell membrane and DNA (Kim et al., 2012). Both animal and human have shown the attenuation of vascular dysfunction seen in diabetes with antioxidant (Zhao et al., 2010). Increased oxidative stress is related to loss of hemeoxygenase-1 which in
turn leads to loss of the interstitial cells of Cajal and reduced expression of neuronal nitric oxide synthase and initiation of apoptotic process within the cells (Suzuki et al., 2012; Forrest et al., 2008). Oxidative stress in diabetes mellitus is reported to be activated by hyperglycemia (Rösen et al., 2001). In diabetes mellitus, the production of reactive oxygen species causes the activation of several metabolic reactions within the cells. In high glucose concentration, the enzyme aldose reductase converts glucose to sorbitol which is the first step in the polyol pathway, eventually converting it to fructose. The continuous activation of this pathway is reported to affect other oxidative reactions within the cells such as reduced levels of glutathione due to shunting of glucose through the polyol pathway critically reducing NADPH (King & Loeken, 2004). There is the likelihood of reduction of antioxidant potentials, which will critically expose cells to oxidation and damage compromising their function and integrity. In these conditions the activities of other stress sensitive intracellular signaling pathways are altered. There is an increase in the mitochondrial superoxide and hydroxyl radical formation precipitated also by these reactions. Again this is responsible for the high oxidative state in which protein cellular structures and membrane lipids are modified. Kasznicki et al. (2012) reported that hyperglycemia decreased plasma nitric oxide content in diabetic subjects because superoxide anion can inhibit endothelial nitric oxide synthase by reacting with nitric oxide. The decrease of nitric oxide by hyperglycemia is suggested to be the major cause of endothelial dysfunction seen in diabetic conditions. The development of oxidative stress leads to diabetic neuropathy and has been documented in animal models of diabetes mellitus and reported also in diabetic patients (Chandrasekharan et al., 2011). Due to overproduction of reactive oxy and hydroxyl radicals in the presence of hyperglycemia in diabetic conditions, the created high oxidative state causes endothelial injury (Kim et al., 2012). The non enzymic reaction of glucose with protein forms advanced glycosylation end products in which various reports have shown to promote other complications of gastrointestinal tract disorders (Chandrasekharan et al., 2011; Kashyap & Farrugia, 2010; De Freitas et al., 2008).

6 Symptoms of Gastrointestinal Disorders in Diabetes Mellitus

Symptoms of gastrointestinal tract disorders in diabetic patients are diverse and can be related. These have also been reported to be observed in various sections of the gastrointestinal tract, from the esophagus to the anorectal region either in part or as whole (Hasler, 2007; Bjelaković et al., 2005; Kong and Horowitz, 2005). The role of hyperglycemia in the disorders of gastrointestinal tract is well documented (Onitilo et al., 2012; Marmuthu et al., 2011; Stacher, 2001). These effects are either acute or chronic, however both conditions produce similar outcome. According to reports, acute glycemia decreases the tone of the fundus and contractile activities of the stomach and intestine (Rodrigues & Motta, 2012). The decrease in gastric motility and impaired emptying by hyperglycemia has been demonstrated in animal experiments. In the colon, it affects muscular contractility and alters emptying time with attendant hypotonia of the sphincter muscle of the anus. These are clinically described as esophageal enteropathy and gastroentropathy which are associated with autonomic neuropathy. The main disorders of the esophagus are described as peristalsis abnormality and dysfunction of the lower esophageal sphincter (Ebert, 2005). These disorders are said to be due to dysfunctional vagus nerve. The resultant consequences of this in both type 1 and type 2 diabetes are impaired esophagus transit and abnormal gastric acid reflux (Bjelaković et al., 2005). Symptoms experienced by diabetics are heartburn, dysphagia and sometimes regurgitation. From animal studies it is revealed that gastroesophageal reflux could lead to the development of oxidative stress which is capable of causing epithelial mucosal damage (Kim et al., 2012; Zhao et al.,
However these symptoms observed in the esophagus might be also a direct effect of a developed dysfunctionality in the gastric section of the gastrointestinal tract.

In the diabetic stomach, symptoms of dysfunction are commonly seen in both types of diabetes (Hasler, 2007). It is dynamic in development particularly with the presence of prolonged hyperglycemia and described as gastroparesis. Gastroparesis is increasingly becoming a significant health issue as the problem of diabetes mellitus increases across nations. Gastroparesis is reported to be the outcome of a variety of potentially disabling upper gastrointestinal tract. Some diabetic patients with impaired gastric motility do not show any symptoms of gastroparesis (Shakil et al., 2008; Zochodne, 2007; Carnethon et al., 2006). The impairment of gastrointestinal tract function as in delayed gastric emptying seems to be closely related to parasympathetic insufficiency (Jørgensen et al., 1991). Delayed gastric emptying is a common feature of gastroparesis. About 90% of ingested food in healthy subjects and non-diabetic patients are emptied after 4 hours from the stomach which allows for gastric accommodation (Tougas et al., 2000). This is a form of physiological response that permits the stomach to stretch and accommodate the ingested food without increasing intragastric pressure or cause discomfort. However, long standing diabetic patients with gastroparesis, have delayed gastric emptying, which is attributed to antral hypomotility and recognized as a major pathophysiologic mechanism underlying the symptoms of gastroparesis with impaired gastric accommodation. Because the accommodation reflex is mediated by the vagal pathway, therefore this results from impaired autonomic nervous system. This impaired gastric accommodation plays a critical role in the generation of certain symptoms seen in patients with gastroparesis (Yin et al., 2010). Gastroparesis may enhance bezoar formation and acute gastric dilatation, intestinal obstruction, vomiting, respiratory aspiration, and affect the glycemic control in diabetes mellitus by impeding the absorption of oral medications (Kashyap & Farrugia, 2010; Bernstein, 2000). This may lead to inconsistent blood glucose readings and will further aggravate the hyperglycemic situation and worsens the gastroparesis condition. Gastroparesis symptoms are nonspecific and because of this the diagnosis is often missed and so the degree of diabetic neuropathy does not show any relationship with the symptoms no matter how severe the presentation (Grover et al., 2011). In the condition of gastroparesis, gastric emptying could be fast, due to impaired relaxation and autopyloroduodenal coordination or slow emptying due to reduced motility. In some patients with type 2 diabetes, both accelerated and retarded gastric emptying has been reported (Intagliata & Koch, 2007). The activity of gastric emptying is dependent on the function of the vagus nerve which has been said to be affected in a persistent hyperglycemic state. It is established that hyperglycemia can have a profound effect on sensory and motor functions of the gastrointestinal tract (Kim et al., 2011).

The relationship between hyperglycemia and gastric dysfunction is unequivocal in that it causes the relaxation of the fundus and abolishes impulse propagation. This situation is capable of precipitating ketoacidosis and a condition of acute gastroparesis (Kotler & Hsu, 2010). Other factors which may be secondary can include damage to cells of interstitial cells of Cajal and lack of nitric oxide inhibitory actions due to oxidative stress. The interstitial cells of Cajal are known to serve a variety of functions within the gastrointestinal tract. The slow wave generated by interstitial cells of Cajal is transmitted to the smooth muscles initiating membrane depolarization (Ordög et al., 2009). Therefore loss of interstitial cells of Cajal as seen in gastroparesis will affect slow wave generation and transmission causing gastric dysmotility (Horváth et al., 2006). The consequence of disrupted gastric motility is the development of delayed gastric emptying. Studies in animals show that high oxidative state in diabetes ultimately leads to the emergence of diabetic gastroparesis which procures the loss of interstitial cells of Cajal (Forrest et al., 2008; Choi et al., 2007; Forster et al., 2005). The interstitial cells of Cajal are known to mediate neuronal
activities within the gastrointestinal tract and therefore play crucial role in its motility (Kim et al., 2011). There is an abundance of evidence showing that in diabetic state, interstitial cells of Cajal network is depleted causing a condition of neuropathy and this has been demonstrated in both human and animal experiments (Forrest et al., 2008). Therefore, delayed gastric emptying in diabetes is suggested to be a feature of gastroparesis caused by poor glycemic control. Clinically, gastroparesis is said to be difficult to diagnose, however, features like anorexia, bloating, epigastric discomfort/pain, early satiety, distention, nausea and vomiting are common (Aljarallah, 2011). Gastroparesis is reported to be common amongst diabetes and leads to gastric stasis affecting other sections of the gastrointestinal tract and causing the deterioration of gastroesophageal reflux with all the associated symptoms. Koch and Uwaifo (2008) described gastroparesis as the dysfunction of the enteric nervous system as well as muscular and hormonal activities of the gastrointestinal tract. The presence of gastroparesis is common amongst diabetes suffering patients affecting their intestinal functions (Camilleri et al., 2012). Manifestations can be described as diarrhea and constipation due to impaired motility and secretory activities related to development of diabetic neuropathy (Camilleri et al., 2011, Ma et al., 2009).

Intestinal and colonic motility disorders in both types of diabetes mellitus can lead to diarrhea. Diabetic diarrhea can be described as the presence of chronic diarrhea which usually is brown, watery, profuse stool and might be associated with tenesmus. The diarrhea is long lasting, typically episodic, and consistent with hyperglycemia and the presence of diabetic neuropathy. Diabetic diarrhea has been described as a worrying debilitating gastrointestinal tract complication seen in about 10-22 % of diabetic patients (Wolosin & Edelman, 2000; Ogbonnaya & Arem, 1990). It is seen in patients with long standing history of diabetes mellitus and accompanied with abnormal rapid transit of fluids, increased frequency and urgency (Wolosin & Edelman, 2000). Due to altered absorptive process, volume of stool may also increase. It appears to be episodic and can last for several days to weeks or months. The pathogenesis of diabetic diarrhea is difficult to predict. However, the proposed mechanism is thought to be as a result of autonomic neuropathy (Murao & Hosokawa, 2010). A body of evidence has shown that disordered gastrointestinal tract motility coupled with abnormal intestinal secretions, reduced fluid absorption and sometimes bacterial overgrowth are among causative factors (Rodrigues & Motta, 2012; Ebert, 2005; Lysy et al., 1999; Virally-Monod et al., 1998; Keshavarzian & Iber, 1986). Particularly, studies have revealed the association between Clostridium difficile infection and its role in diabetic diarrhea (Shakov et al., 2011). These conditions are also said to exacerbate fecal incontinence (Rodrigues & Motta, 2012). Rayner et al. (2001) reported that stasis syndrome, a condition of altered motility, is also associated with diarrhea. These episodes are often followed by an occasional constipation with intervals of weeks to months of normal movements. The pathogenic mechanism is said to be related to decrease adrenergic receptor activity, abnormal gastrointestinal tract motility and delayed transit time.

The enteric neurons in concert with autonomic nervous system regulate the gastrointestinal tract motility. Excitatory neurons like cholinergic and serotonergic nerves are known to stimulate the gastrointestinal tract, whereas the sympathetic, nitrergic and vasoactive intestinal peptide nerves mediate relaxation response (Chandrasekharan & Srinivasan, 2007). Therefore neuronal changes either morphological or functional due to diabetes mellitus will affect the excitatory and inhibitory responses. Studies in both human and animal models of diabetes have shown loss of inhibitory neurons (Murao & Hosokawa, 2010). The reported loss of inhibitory responses to sympathetic relaxation and loss of nitric oxide neurons in diabetic patients is said to be responsible for the intestinal hypermotility. Also implicated in diabetic diarrhea is the loss of interstitial cells of Cajal (He et al., 2001). They are identified as enteric neuron pacemaker cells, involved in the regulation of intestinal motility (Sanders et al., 2000). Their role in this re-
gard has been demonstrated in patients with diabetes mellitus (Iwasaki et al., 2006). Therefore the balance between excitatory and inhibitory stimulation in the enteric neurons hold the key to the control of this complex motor function. Critically the disturbance of this balance regulation in diabetic state is said to cause dysmotility function. This phenomenon has been described in experimental diabetic models as lack of inhibitory responses (Chandrasekharan & Srinivasan, 2007).

The intestinal symptoms in experimentally-induced diabetes in rats are very similar to those observed in human diabetes, thus the results of experimental models might be applied to the study of the illness in humans, in order to gain a better knowledge of the alterations caused on the nerves of the enteric system by this illness. Recent studies on experimental diabetes have shown alterations in the adrenergic, cholinergic and peptidergic innervation in the gastrointestinal tract of streptozotocin-induced diabetic rat (Belai et al., 1988; Schmidt et al., 1988; Lincoln et al., 1984) suggesting autonomic dysfunction (Cuervas-Mons et al., 1990). About 17 % of diabetic patients were associated with ischemic colitis (Cubiella Fernández et al., 2010; Longstreth & Yao, 2010; Longo et al., 1992). This condition is said to affect all segments of the colon where it is transitorily deprived of blood supply. Persistent hyperglycemia affects arteries supplying the bowel which could cause hardening and narrowing, effectively precipitating ischemic colitis in which mesenteric microcirculation deteriorates considerably (Karayiannakis et al., 2011; Nagai et al., 1998; Sharieff et al., 1997; Spotnitz et al., 1984).

Constipation is seen as a major gastrointestinal tract complaint in patients with diabetes than in non-diabetics. It is estimated that 44 % of diabetic patients are affected by constipation and is the most common gastrointestinal complication resulting from diabetic neuropathy (Kotler & Hsu, 2010; Shakil et al., 2008). Gastrocolic reflex is altered with a diffuse disorder of colonic motility. The pathophysiology of colonic dysmotility in diabetes is believed to be due to delay or absent postprandial motility caused by dysfunction of autonomic nervous system. Clinical examination usually reveals occasional massive amount of fecal material found in the large atonic and dilated colon of diabetic patients (Taub et al., 1979). This condition may present as intestinal obstruction or fecal impaction capable of causing stercoral ulcerations associated with colonic distension and consequent mucosal erosion in patients (Taub et al., 1979). It might be due to loss of intestinal nervous control attributed to dysfunction of intrinsic and extrinsic intestinal neurons and decreased or absent of postprandial gastrocolic reflex (Vinik et al., 2003). It is the most definable symptom of the gastrointestinal tract disorders in both type 1 and type 2 diabetes mellitus.

Diabetic patients may present with several different symptoms of gastrointestinal tract motor dysfunctions whose clinical features may differ from patient to patient (Nowak et al., 1995). Clinical features are suggestive of gastroparesis and enteropathy as mentioned earlier which is termed gastroenteropathy because it reflects a similar wide range of symptomatologic spectrum (Quigley, 1999). Different evaluation methods are currently been used by clinicians to assess gastric emptying, antral contractility, colonic segmental transit time, sphincter tone and the rectal anal inhibitory reflex (Vinik et al., 2003; Quigley, 1999). These evaluations employ different investigative tools for the detection of gastrointestinal tract dysfunction in diabetics like breath test based on 13C-octanoic acid, electrogastrography, ultrasonography, magnetic resonance imaging and manometry for effective management (Vinik et al., 2003; Quigley, 1999).

### 6.1 Treatment of Diabetic Gastroparesis

Gastroparesis has the potential to cause a wide range of health problems among diabetics that is often times very difficult to assess and treat. By the time symptoms of diabetic autonomic neuropathy begin to
appear, nerve damage would have been evident, irreversible and most likely to be advanced with poor prognosis. Hence, the best form of treatment would be to aim at preventing the progression of diabetes mellitus. This will limit the progression to autonomic neuropathies seen in chronic diabetes. Therefore adequate glycemic control, diet monitoring and prompt medication needs will decrease the development of gastroparesis and its debilitating consequences. For this reason, management of gastroparesis, is often a challenge and mostly dependent upon patients glycemic control and frequency and severity of symptoms presented (Forgacs & Patel, 2011). However, the early recognition of gastrointestinal motility disorders may be important for the better long-term management of patients. Sometimes the patient’s nutritional status becomes a factor in considering mode of treatment. Despite the fact that glycemic control and dieting are important aspect of treatment, they cannot suffice particularly where symptoms are debilitating. Definitive and individualized management of patients is likely to improve functionality, quality of life and ensure glycemic control. Therefore, a better understanding of the nature and pathophysiology of the diseased condition in animal models and human as well as a confirmed symptom evaluation, will help to guide management decisions. Drugs acting on central and peripheral satiety centres may possibly improve nutrition and prevent excessive weight loss. However, agents that are prokinetic are useful in the control of symptoms and treatment of gastroparesis. Therefore, several drugs used in the management of gastroparesis has prokinetic activity. The dopamine receptor antagonists and 5-HT receptor antagonist like metoclopramide, domperidone and cisapride are currently been used as form of management which act locally to increase released acetylcholine at the myenteric plexus (Table 2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Effects</th>
<th>Adverse reactions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>Antagonist of dopamine (D2) and 5-HT3 receptors</td>
<td>Impects gastrointestinal tract contractions</td>
<td>Extrapyramidal symptoms and hyperprolactinemia</td>
<td>Parkman et al., 2004</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Dopamine antagonist</td>
<td>Increases antral contractions and decrease receptive relaxation of the proximal stomach</td>
<td>Hyperprolactinemia such as gynecomastia</td>
<td>Talley, 2003</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Partial agonist on 5-HT4 and 5-HT3 receptors</td>
<td>Beneficial effects on small bowel motility</td>
<td>Arrhythmia and diarrhea</td>
<td>Chandran et al., 2003</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Motilin agonist</td>
<td>Improves symptoms and gastric emptying</td>
<td>Abdominal pain and antibiotic resistance</td>
<td>Maganti et al., 2003</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Nonspecific cholinergic muscarinic receptor agonist</td>
<td>Increases amplitude of contractions</td>
<td>Abdominal cramps, salivation, blurred vision and bladder spasm</td>
<td>Parkman et al., 2004</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>A potent inhibitor of neuromuscular transmission</td>
<td>Improves both symptoms and gastric emptying</td>
<td>Swallowing difficulties and muscle weakness</td>
<td>Miller et al., 2002</td>
</tr>
</tbody>
</table>

**Table 2:** Pharmacological Treatment of Diabetic Gastroparesis.

Metoclopramide is a derivative of benzamide which has been used for years in the treatment of gastroparesis as a prokinetic agent. It releases acetylcholine from intrinsic myenteric cholinergic neurons by activating 5-HT4 receptors as well as acting as a dopamine receptor antagonist in the stomach with a weak 5-HT3 receptor antagonism (Parkman et al., 2004). Metoclopramide increases lower esophageal sphincter pressure and it improves symptoms of postprandial fullness and nausea. The prokinetic proper-
ties of metoclopramide are felt more in esophageal and fundus. However, it crosses the blood-brain barrier to cause extrapyramidal symptom, drowsiness and irritability. These adverse effects are dose-related and may be irreversible (Parkman et al., 2004).

Domperidone is a substituted prokinetic benzimidazole derivative and a specific dopamine (D₂) receptor antagonist that is similar to metoclopramide in action. However, it does not readily cross the blood-brain barrier and less likely to cause extrapyramidal side effects like metoclopramide. Apart from its prokinetic effects on the stomach, domperidone possesses centrally mediated antiemetic properties by its action on the area postrema. Because of reduced side effects, dose increases can be employed although tachyphylaxis has been reported in patients (Horowitz et al., 1985). Other side effects noted from using domperidone include hyperprolactinemia, menstrual disturbance and galactorrhea due to its antidopaminergic activity.

Cisapride is among prokinetic agents used by practitioners to treat patients with gastroparesis. It is an agonist of 5-HT₄ receptor and through this facilitates the release of acetylcholine in the gut. Cisapride is said to stimulate contractile responses to acetylcholine and improves antroduodenal coordination, and accelerates gastric emptying (Braden et al., 2002). It increases the rate of gastric emptying time and decreases symptoms associated with gastroparesis. However, it causes cardiac arrhythmias which could lead to sudden death (Rabine & Barnett, 2001). Therefore, its use is contraindicated in individuals with underlying cardiac disease.

Erythromycin, a macrolide antibiotic, is a motilin receptor agonist which has a powerful prokinetic action and stimulates the contractility of the antrum and gastric emptying. In the process, smooth muscle and enteric nerves are also stimulated (Galligan & Vanner, 2005). Erythromycin has been shown to stimulate gastric emptying in diabetic gastroparesis and idiopathic gastroparesis. It is used to relieve symptoms associated with gastroparesis with a good safety profile. It has been reported that hyperglycemia attenuates the stimulation of antral contractility and gastric emptying by erythromycin (Parkman et al., 2004).

The effect of erythromycin is said to diminish with time due to tachyphylaxis caused by downregulation of motilin receptors (Frazee & Mauro, 1994). The most common side effects exhibited by erythromycin are abdominal pain, nausea and skin rashes.

Bethanechol is a nonspecific cholinergic muscarinic receptor agonist which has been shown to enhance the amplitude of contractions throughout the gut. It lacks coordinated contractions and therefore gastric emptying is not demonstrable. It is however used as an adjunct with other agents. It exhibits cholinergic side effects.

For patients who are refractory to pharmacotherapy, botulinum toxin type A injection into the pylorus, or surgery can be considered. Botulinum toxin A is a bacterial toxin that causes muscle paralysis by inhibiting acetylcholine release. It has been shown to improve both symptoms and gastric emptying (Lacy & Zayat, 2002). Pylorospasm has been reported to occur in diabetic patients with gastroparesis.

6.2 Treatment of Diabetic Diarrhea

The treatment of diabetic diarrhea begins with non-pharmacological measures of fluid and electrolyte replacement, glycemic control and then symptomatic treatment. Octreotide a somatostatin analogue has been used in both normal and diabetic subjects to treat several types of refractory diarrhea (Table 3). It delays gastric emptying by prolonging intestinal transit, improves fluid and electrolyte absorption and directly suppresses gastrointestinal motility together with splanchnic vasoconstriction (Mourad et al., 1992; Dudi et al., 1987).
Table 3: Pharmacological Treatment of Diabetic Diarrhea.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Effects</th>
<th>Adverse reactions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>Somatostatin analogue</td>
<td>Reduce intestinal mucosal secretions and enhance absorption</td>
<td>Gallstones, allergic skin reactions, hair loss and inflammation</td>
<td>Dudl et al., 1987</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>Selective 5-HT₃ receptor antagonist</td>
<td>Prolongs colonic transit time, inhibit intestinal bowel secretion and ameliorates fecal incontinence</td>
<td>Hard stools</td>
<td>Murao &amp; Hosokawa, 2010</td>
</tr>
<tr>
<td>Clonidine</td>
<td>α₂ receptor agonist</td>
<td>Inhibits intestinal secretions</td>
<td>Hypotension, dry mouth, dizziness and constipation</td>
<td>Chang et al., 1986</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Opioid-receptor agonist</td>
<td>Slows intestinal transit time and increases the internal anal sphincter tone</td>
<td>Toxic megacolon, bloating, nausea, vomiting and constipation</td>
<td>Vinik &amp; Erbas, 2001</td>
</tr>
<tr>
<td>Antibiotics (metronidazole &amp; tetracycline)</td>
<td>Decreases ability of bacteria to make protein</td>
<td>Inhibit and kill intestinal bacteria growth</td>
<td>Nausea and diarrhea</td>
<td>Dukowicz et al., 2007</td>
</tr>
</tbody>
</table>

Ramosetron a 5-HT₃ serotonin receptor antagonist has also been employed in the treatment of diabetic diarrhea. It enhances absorption, prolongs colonic transit time, inhibits intestinal bowel secretion and ameliorates fecal incontinence (Murao & Hosokawa, 2010). However, because of the risk for constipation its use is reserved for severe cases. Studies have shown that loss of adrenergic innervation may play a role in autonomic neuropathy-induced intestinal fluid and electrolyte malabsorption in diabetic patients. Stimulation of α₂-adrenergic receptors on enterocytes promotes fluid and electrolyte absorption and inhibits anion secretion (Ogbonnaya & Arem, 1990). Clonidine, an α₂-adrenergic agonist, has been used to treat patients with diabetic diarrhea when other treatments had failed. It exhibits antisecretory and antimitotility effect (Chang et al., 1986). Loperamide, a drug used for symptomatic treatment of diabetic diarrhea, is known to slow intestinal transit time and increases the internal anal sphincter tone. However, it can be associated with abdominal pain and bloating, nausea, vomiting and constipation (Vinik & Erbas, 2001). In healthy subjects, there are usually normal intestinal flora in the small intestine. Diabetic conditions change the nature of these bacteria leading to overgrowth causing bloating and diarrhea. Sometimes the use of antibiotic therapy like tetracyclines and metronidazole is employed in such patients (Dukowicz et al., 2007).

6.3 Treatment of Diabetic Constipation

Management of constipation in diabetic patients is similar to non-diabetic patients. Constipation may alternate with diabetic diarrhea and is one of the most common complications of diabetes mellitus. However, apart from conventional treatment methods of employing the use of laxatives, treatment might include good hydration, regular physical activity, and increased fiber intake. Sorbitol or lactulose can also be used to treat constipation (Shakil et al., 2008). Lactulose and sorbitol are poorly absorbed sugars in the intestine and work by increasing the amount of water that is secreted within the intestines. Lactulose is effective in increasing stool frequency, volume and weight in chronic constipated patients. Also sorbitol has been shown to be equally effective as lactulose in increasing bowel movements and good stool consistency with similar side effects like abdominal bloating and flatulence (Foxx-Orenstein et al., 2008; Rayner et al., 2001). Acarbose is another useful agent that has been found to be valuable in the treatment of consti-
pating diabetics (Hücking et al., 2005). It reduces prolonged colonic transit times in addition to its beneficial effect in controlling diabetes (Ron et al., 2002). Prucalopride, a 5-HT$_4$ agonist, has been shown to increase small bowel and colonic transit time and thereby improving the symptoms of constipation (Lacy & Weiser, 2006; Bouras et al., 2001). It also accelerates orocecal transit and increases stool frequency in patients with chronic constipation (Coremans et al., 2003) (Table 4).

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Effects</th>
<th>Adverse Reactions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitol/lactulose</td>
<td>Osmotic laxatives</td>
<td>Increase intestinal bulk</td>
<td>Abdominal bloating and flatulence</td>
<td>Rayner et al., 2001f</td>
</tr>
<tr>
<td>Acarbose</td>
<td>α-Glucosidase inhibitor</td>
<td>Impairing carbohydrate absorption</td>
<td>Abdominal pain, diarrhea and flatulence</td>
<td>Hücking et al., 2005</td>
</tr>
<tr>
<td>Prucalopride</td>
<td>Selective 5-HT$_4$ agonist</td>
<td>Increases stool frequency and colonic transit time</td>
<td>Abdominal pain, nausea and diarrhea</td>
<td>Lacy &amp; Weiser, 2006</td>
</tr>
</tbody>
</table>

Table 4: Pharmacological Treatment of Diabetic Constipation.

7 Symptoms of End Stage Disease of the Gastrointestinal Tract in Diabetes Mellitus

There have been speculations in the past linking diabetes mellitus to several cancers of the gastrointestinal tract. Risk factors associated with diabetes mellitus and gastrointestinal tract cancers are shared by many other cancers linked with it. Evidence is emerging from assessments conducted studies by various workers, who have demonstrated a possible association between diabetes and gastrointestinal malignancy of the esophagus, stomach, colon and rectal (Onitilo et al., 2012; Marimuthu et al., 2011; Omran & Ismail, 2010; Larsson et al., 2005). Epidemiological evidence has shown that the development of hypomotility in the stomach could lead to Barrett’s esophagus and eventually adenocarcinoma (Sun & Yu, 2012). It is estimated that significant numbers of diabetics have increased risks of developing colorectal cancer and esophageal cancer compared with non-diabetic patients (Huang et al., 2012; Sun & Yu, 2012). These associations were observed more in type 2 than that in type 1 and in both sexes. A state of hyperglycemia and increased oxidative stress may act together to contribute to the increase in cancer risk among diabetics. Similar mechanisms have been postulated for the etiology of diabetes induced cancers (Giovannucci et al., 2010). This may be due to common fundamental pathophysiological mechanisms which include hyperinsulinemia, poor glycemic control, presence of advanced glycosylation end products and oxidative stress (Onitilo et al., 2012). Reports from studies have shown that hyperglycemia in diabetes is implicated with increased incidence and mortality for a range of cancers of the gastrointestinal tract (Deng et al., 2012; Onitilo et al., 2012; Jee et al., 2005). This is associated with systemic inflammation, which could explain the role of oxidative stress. Because glycolysis is essential for cancer cells energy metabolism, hyperglycemia can promote carcinogenesis via the generation of reactive oxygen species within the cells (Sun & Yu, 2012). Oxidative radicals can damage the DNA directly or inhibit DNA repair mechanism (Onitilo et al., 2012). It is reported that oxidative stress can influence the expression of gene signaling molecules (Reuter et al., 2010). Anitha et al. (2006) demonstrated that hyperglycemia caused a dose-dependent increase in enteric neuronal apoptosis by inhibiting the glial-derived neurotrophic factor which promotes enteric neuron survival (Srinivasan et al., 2005). Glial-derived neurotrophic factor mediates its
activity by the expression of phosphatidylinositol-3-kinase signaling (Kashyap & Farrugia, 2011). There is strong evidence that hyperglycemia decreases phosphatidylinositol-3-kinase signaling by its inhibitory action on derived neurotrophic factor (Anitha et al., 2006). It is believed that alteration in the phosphatidylinositol-3-kinase pathway can contribute to loss of gastrointestinal motility in both acute and chronic hyperglycemia. The regulations of the phosphatidylinositol-3-kinase pathway may be altered in a hyperglycemic state therefore suggesting that the expression of phosphatidylinositol-3-kinase plays a critical role in development of cancer associated with diabetes.

Clear understanding of the various mechanisms of hyperglycemia-induced enteric neuronal damage may provide a better management option of gastrointestinal disorders. It will also help in identifying potential therapeutic targets that will aid the development of new agents which will improve the disease burden of diabetic neuropathy in long standing diabetic patients.

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References


