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Diabetes-induced mechanophysiological changes in the small intestine and colon

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Abstract

The disorders of gastrointestinal (GI) tract including intestine and colon are common in the patients with diabetes mellitus (DM). DM induced intestinal and colonic structural and biomechanical remodeling in animals and humans. The remodeling is closely related to motor-sensory abnormalities of the intestine and colon which are associated with the symptoms frequently encountered in patients with DM such as diarrhea and constipation. In this review, firstly we review DM-induced histomorphological and biomechanical remodeling of intestine and colon. Secondly we review motor-sensory dysfunction and how they relate to intestinal and colonic abnormalities. Finally the clinical consequences of DM-induced changes in the intestine and colon including diarrhea, constipation, gut microbiota change and colon cancer are discussed. The final goal is to increase the understanding of DM-induced changes in the gut and the subsequent clinical consequences in order to provide the clinicians with a better understanding of the GI disorders in diabetic patients and facilitates treatments tailored to these patients.

Key words: Diabetes; Intestine; Colon; Biomechanics; Motor-sensory; Gut microbiota; Symptoms

Core tip: The disorders of intestine and colon are common in patients with diabetes mellitus (DM). DM induced intestinal and colonic structural and biomechanical remodeling are closely related to motor-sensory abnormalities of gut in DM. These changes due to DM are associated with diarrhea, constipation, gut microbiota modification and colon cancer. Understanding the DM-induced changes in the gut and the clinical consequences provides clinicians with a better understanding of the gastrointestinal disorders in diabetic patients and facilitates the improvement of treatments for these patients.

INTRODUCTION

Diabetes mellitus (DM) is a popular metabolic disease which affects many populations worldwide[1]. Complications in different organ systems including the gastrointestinal (GI) tract will occur if the DM is treated inappropriately. NCD Risk Factor Collaboration has demonstrated that the number of adults with DM in the world increased from 108 million in 1980 to 422 million in 2014[1]. Furthermore, huge healthcare expenditures are needed in order to prevent and treat DM and its complications[2].

DM patients often suffer from GI disorders which are recently recognized as one of the most common complications in DM[3]. The whole GI tract can be affected in the DM and common complaints include diarrhea, constipation and fecal incontinence[4]. The symptoms are usually non-specific, but occasionally they may be severe enough to decrease the quality of life. The pathophysiological mechanisms of the symptoms are very complex; they may involve multiple factors and are inadequately explored. However, it is well known that the motor-sensory dysfunctions often seen in the DM patients are closely associated with diabetic autonomic neuropathy (DAN)[5-7]. Furthermore, it has been recently recognized that DAN also includes the disorders of the enteric nervous system (ENS)[7]. It is well known that DM induces histomorphological and biomechanical remodeling of small intestine and colon in type-1 DM patients[5] and in DM animals[8-10]. Such remodeling is closely related to motor-sensory dysfunctions in DM patients[9]. Understanding the mechanisms of DM-induced changes of the intestine and colon is of key importance for the optimization of treatment and for finding new therapeutic approaches.

In this review, we discuss: (1) DM-induced intestinal and colonic histomorphological changes and biomechanical remodeling; (2) intestinal and colonic sensory-motor dysfunction in relation to DM and its relation to the remodeling of intestine and colon; and (3) the clinical consequences of DM-induced changes in intestine and colon including diarrhea, constipation, GM change and colon cancer. It is well known that esophageal and gastric motility disorders are also very common in DM patients; however, these have been reviewed in detail recently (see references[11,12]). Furthermore, as we focus on the topic of DM-induced mechanophysiological changes in the small intestine and colon, the topic of esophageal and gastric disorders in the DM are not included in this review.

NORMAL ANATOMY, STRUCTURE AND BIOMECHANICAL PROPERTIES IN THE INTESTINE AND COLON

Anatomy and structure of normal intestine and colon

Understanding the anatomy and structure of normal intestine and colon is essential in order to gain an insight into the biomechanical properties and the DM-induced remodeling. Intestine and colon are tubular organs. From proximal to distal, the intestine consists of duodenum, jejunum and ileum. The ligament of Treitz marks the anatomical demarcation between duodenum and jejunum, whereas there is no distinct demarcation between jejunum and ileum. A mesentery anchors the jejunum (proximal 40%) and ileum (distal 60%) to the posterior wall of abdomen and allows the intestine to be freely moveable within the peritoneal cavity. The distal end of the intestine is in continuity with colon and the transition is marked by the ileocecal valve which prevents the retrograde flow of colonic contents into the small intestine[13]. The colon is composed of five parts namely cecum, ascending colon, transverse colon, descending colon and sigmoid colon. The external appearance of colon is distinctly different from that of the intestine. The longitudinal layer of muscle fibers forms three discrete bands named tenia, and the formation of sacs filled with adipose tissue on the inner surface gives the colon a segmented appearance characterized by small pouches named haustra.

The histologic characteristics of the intestine and colon shares many similarities. The wall is composed of four layers: Mucosa, submucosa, muscularis, and serosa with the mucosa being the innermost layer. The mucosa consists of sublayers of glandular epithelium, lamina propria, and muscularis mucosae. The glandular epithelium forms cylindrical structures called crypts. The lamina propria serves to support the epithelium and consists of reticular connective tissue with elastin, reticulin, and collagen fibers and cellular components such as lymphocytes, plasma cells, and eosinophilic granulocytes, as well as lymphatics and capillaries. The muscularis mucosae is a thin layer of smooth muscle intertwining the mucosa and submucosa. The submucosa is a fibrous connective tissue layer that contains fibroblasts, mast cells, blood and lymphatic vessels, and extraordinarily an autonomous nerve plexus called the Meissner's plexus which consists of non-myelinated, postganglionic sympathetic fibers and parasympathetic ganglion cells[14,15]. The muscularis propria beneath the submucosal layer consists of smooth muscle fibers and is responsible for the contractility of the intestines. The muscle fibers are arranged in a helicoidal pattern in two layers, an inner circular layer and an outer longitudinal layer. Between these two muscle layers there is a second autonomous nerve plexus named the myenteric plexus or Auerbach's plexus[15,16]. Parasympathetic and postganglionic sympathetic fibers in the plexus

terminate in parasympathetic ganglion cells; from here, the postganglionic parasympathetic fibers terminate in smooth muscle and influence the intestinal contractility by the release of neurotransmitters. The serosa is the outermost layer of the intestines and consists of connective tissue. Interstitial cells of Cajal (ICC) are present in both the small intestine and the colon and influence the contractility of the smooth muscle fibers. These cells act as pacemaker cells and are located in the myenteric plexus, the muscularis propria and the submucosa[17]. The ICCs express the receptor for tyrosine kinase (c-kit). Thus, immunohistochemical stains that utilize antibodies against c-kit allow the ICCs to be labeled[18].

Biomechanical properties of normal intestine and colon

One important function of both small intestine and colon is the transportation of food by peristaltic contraction. Furthermore, the mixing function by segmental contraction is also important for small intestine in order to establish close contact between the food and mucosa and fully absorb the nutritional contents. Both types of contraction are involved in the force (stress) changes and deformation (strain) in the wall of intestine and colon. Therefore, understanding the normal biomechanical properties is essential for the understanding of the physiological functions of small intestine and colon. Descriptions of biomechanical properties include elasticity such as tension-strain or stress-strain relations, and viscoelasticity such as creep and stress relaxation. Generally the biomechanical properties of small intestine and colon display an exponential behavior and are anisotropic with large axial and location variations[19-40]. The biomechanical characteristics of the normal small intestine and colon can be summarized in Table 1.

The variation of biomechanical properties along and across the wall of intestine and colon have important physiological significance. The residual strain makes the stress distribution through the wall more uniform in the pressurized state[27]. The compression residual stress reduces the stress concentration at the inner wall, thereby offering a better protection of intestine and colon against injury due to contractile activity and against the flow of luminal contents. Furthermore, the different stiffness has been demonstrated in different segments of intestine and colon. For example, the duodenal segment is stiffest whereas the ileum is softest in the small intestine. These may relate to the specialized functions in the proximal and distal locations. Duodenum acts as a capacitative resistor during gastric emptying whereas the transit of distal ileum is slow and acts as a reservoir[32]. The flow patterns of intestine may also relate to biomechanical properties. The stiff duodenal wall will be in favor of a lesser degree of bolus passing whereas the soft ileal wall will be in favor of pooling of luminal content and decreased flow.

DIABETES-INDUCED HISTOMORPHOLOGICAL AND BIOMECHANICAL CHANGES IN THE SMALL INTESTINE AND COLON

Histomorphological remodeling

DM-induced histomorphological changes involve different tissue components of the intestinal and colonic wall including epithelia, smooth muscle cell (Figure 1A, Figure 2), neurons, ICC and extracellular matrix (Table 2). Many animal and human studies have demonstrated that DM generally induces changes in the proliferation of different layers[5,8,10,41-51]. Increased expression of advanced glycation end of product (AGE) and AGE receptor (RAGE) has been demonstrated in the DM intestinal and colonic wall[49,51,52]. Furthermore, the number and density of neurons and ICC are changed, and the expressions of some neuropeptides alter as well (Table 2).

Biomechanical remodeling

In comparison with DM-induced histomorphological remodeling, there are not so many data in relation to the biomechanical remodeling in the small intestine and colon. Data on tension-strain relations has demonstrated that the stiffness of wall in the rat jejunum and ilem increases in DM rats[53]. Lately, the research group of Zhao *et al*[8,25] and Sha *et al*[48] did a series of studies investigating the histomorphological and biomechanical remodeling of small intestine in STZ-induced DM rats. They found in diabetic rats that (1) the opening angle and residual strain became smaller in the duodenum and larger in the jejunum and ileum; (2) the stiffness of the intestinal wall increased as function of time of DM development (Figure 1B and C); and (3) the stress of intestinal wall relaxed less(Figure 1D). More recently, remodeling of the jejunal wall in type 2 DM rats (GK rat) has been reported[47]. It was shown that the opening angle and residual strain were reduced and the wall stiffness increased in the circumferential direction. Furthermore, we demonstrated that increasing blood glucose level and the increased AGE/RAGE expression were associated with the remodeling. However, data on biomechanical changes in the diabetic colon is sparse. We have also investigated DM-induced biomechanical and morphometric remodeling in rat colon[10]. It was found in diabetic colon that the opening angle and residual strain became bigger and the stiffness of the colon wall increased with the duration of DM both in the circumferential and longitudinal directions (Figure 2). More recently, the remodeling of the distal colon in DM was studied by Siegman *et al*[51] in rats. A major finding from the study was the marked decrease in resting compliance and increase in stiffness of the smooth muscle cells of the distal colon in DM rats. Such changes are associated with increased production of type 1

Table 1	Biomechanical properties of normal small intestine and colon

	Biomechanical properties
Intestine	Tension-strain or stress-strain curves show an exponential behavior[19-23]
	The stiffness differs between the duodenal, jejunal and ileal segments[20,21,24]
	All segments are stiffest in longitudinal direction[20,21,24]
	The opening angle and residual strain shows a large axial variation[25]. The axial variation correlates to the morphometric variation[26]
	The serosal residual strains are tensile and the mucosal residual strains are compressive[24,25,27]
	The residual strains in longitudinal direction are smaller than those in circumferential direction[24], especially on the mucosal side
	The opening angle changes over time for all the small intestine segments. The viscoelastic constant of the rat small intestine is fairly homogenous along its length[28]
	The collagen in submucosa layer is important for the passive biomechanical properties[29,30]
	The villi are important for the biomechanical properties of the small intestine in circumferential direction[31]
Colon	The rat colon has a tensile strength of around 50 g/mm² and increases in strength from proximal to distal[33]
	Quasi-static P-V curves in colon are approximated to a power exponential function and revealed hysteresis, indicative of viscoelasticity[34]
	The opening angle vary along the rat colon with the highest values in the beginning of the proximal colon[35]. The residual strain is negative at the inner surface and positive at the outer surface[35]
	The stress-strain curves are exponential. All segments were stiffer in longitudinal direction than in the circumferential direction[35]
	In human sigmoid colon, the spatial distributions of the biomechanical parameters are non-homogeneous. The circumferential length, strain, pressure and wall stress increase as a function of bag volume[36]
	The wall stiffness of human sigmoid colon is reduced in response to butylscopolamine[36]
	The phasic and tonic responses to the meal in two colonic regions of human are quantitatively different but qualitatively similar[37]
	Smooth muscle cells in the gastrointestinal tract are constantly being deformed due to forces generated by the muscle cells themselves or by the surroundings[38,39]
	A mechanical creep behavior in the isolated rat colon smooth muscle cells could be described by a viscoelastic solid model[40]

Table 2	Diabetes mellitus-induced histomorphological changes of intestine and colon

	Intestine	Colon
Mucosa	Increased thickness[5,8,47,49]; Damaged tight junctions[260]; Proliferation of villi and crypt[41]; Decreased membrane fluidity[110]; Enhanced transport of glucose, amino acid, bile salts, phosphate, fatty acids, fatty alcohols, and cholesterol[110]; Decreased protein synthesis[261]; Increased expression of the monosaccharide transporters[262,263]; Increased expression of AGE and RAGE[47,49]	Increased thickness[10,49]; Increased thickness of the subepithelial collagen layer[276,277]; Abnormalities of endocrine cells[278]; Increased expression of RAGE[49]; Increased expression of AGE, RAGE, TGF-β1 and TGF-β1 receptor[52]
Submucosa	Increased thickness[5,8,47]	Increased thickness[10]; Increased expression of AGE, RAGE, TGF-β1 and TGF-β1 receptor[52]
Muscle	Increased thickness[8,47]; Increased expression of AGE and RAGE[49]	Increased thickness[10]; Hypertrophy of smooth muscle cells[51]; Increase type I collagen and expression of AGE[51]; Increased expression of AGE, RAGE, TGF-β1 and TGF-β1 receptor[52]
Wall as a whole	Increased thickness[8,47-50]; Increase expression of substance P[264] and neuronal nitric oxide synthase[265]; Dcreased expression of substance P[266], vasoactive intestinal polypeptide[262] and neuronal nitric oxide synthase[267]; Increased RAGE mRNA level[50]	Increased thickness[10,49]; Increase in substance P levels[264]
Nerve and ICC	Nuroaxonal dystrophy[48,268]; Decreased myenteric ganglia[269]; Decreased nitrergic neuronal cell number[270]; Decreased density of myenteric neurons[120]; Decreased number of myenteric neurons[271,272]; Increased expression of RAGE[49]; Decreased myosin-V-immunoreactive neurons[273]; Decreased ghrelin cell density[274]; Reduced number of ICC[99,275]	Impairment of nitrergic enteric neurons[111]; Decrease density and size of the myenteric neurons[15]; Decreased nitrergic neuronal cell number[280]; Decreased the numbers of nNOS, CHAT neurons and total neurons[279]; Increased expression of RAGE[49]; Apoptosis of neurons[244]; Decreased ghrelin cell density[274]; Reduced number of ICC[99,110,124,280] and impairment in the ultrastructures of ICC[99]

AGE: Advanced glycation end of product; RAGE: Advanced glycation end of product receptor; ICC: Interstitial cells of Cajal.

collagen and AGEs.

Mechanisms of histological and biomechanical remodeling

Hyperphagia: There is study which suggests that hyperphagia is related to DM-induced GI growth[54]. However, other researchers have found that when DM rats and normal rats are fed with same caloric diets, the intestinal mass and DNA synthesis in crypt still increases considerably in diabetic rats[55,56]. This indicates that DM-induced GI growth depends not only on increased nutrient consumption but also on other adaptation factors. It has been demonstrated that there is a close relation between glucagon-like peptide-2 (GLP-2) and DM-induced GI growth[57]. Increasing blood GLP-2 could precede the changes of intestinal mass[57]. Therefore, the increased nutrient in DM-induced GI growth may relate to its role in the stimulation of hormonal release
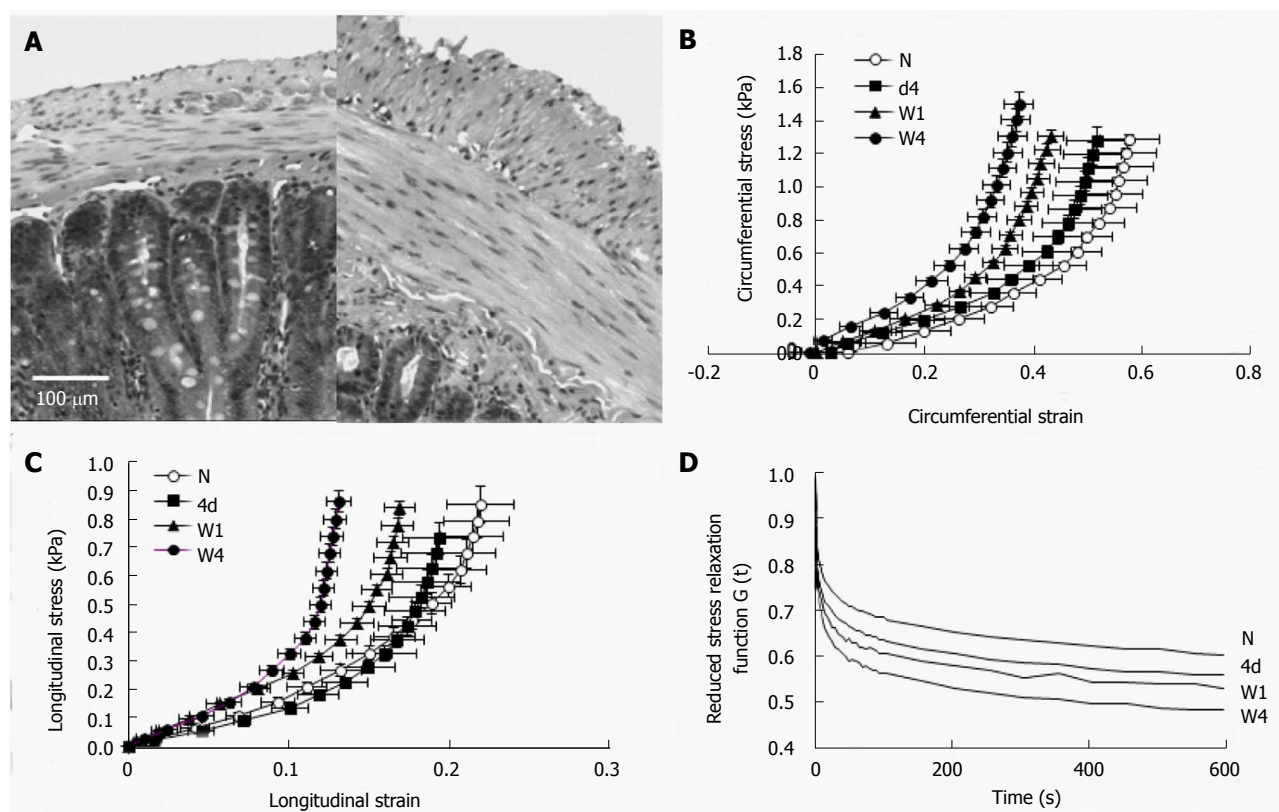
Figure 1 Duodenal remodeling in STZ-induced diabetic rats. A: The micro-photographs showed the normal (left) and 4 wk diabetic (right) duodenal histological sections. It clearly demonstrated that the muscle and submucosa layers in the diabetic duodenum became much thicker than in the normal duodenum. The bar is 100 μm; B: The circumferential stress-strain relations; C: The longitudinal stress-strain relations. The stress-strain curves in both directions (B and C) shifted to the left during experimental diabetes indicating the duodenal wall became stiffer during the development of diabetes; D: The mean reduced relaxation function curves in the time period of 600 s. The curves appear in the order of largest-to-smallest G (t) as W4, W1, 4d and N. The stress relaxation of duodenum decreased with the development of experimental diabetes. N: Normal control; 4d: 4 d of diabetes; W1: 1 wk of diabetes; W4: 4 wk of diabetes; W8: 8 wk of diabetes.

in the GI tract. The nutrient content in the small intestine is greatly increased due to hyperphagia and fast gastric emptying[56] in DM rats. It is well known that the luminal nutrients such as fat and carbohydrate could stimulate physiological L cells[58], therefore the increased luminal nutrients could stimulate GLP-2 secretion and its action on the intestinal epithelium. Furthermore, the balance of the epithelial homeostasis is regulated by cell proliferation and death. It has been shown that apoptosis is inhibited in DM rats which in turn results in the increase of mucosal mass in the small intestine[44].

Non-enzymatic glycation of protein: Hyperglycemia is the most important feature of DM. The increased glucose can induce AGEs formation through non-enzymatic glycation of protein amino groups and by oxidation reaction[59]. The overproduction and accumulation of AGEs in the tissues could alter the structure and function of proteins[60] in the intestinal wall such as collagen. Such changes cause cross-linking of collagen, basement membrane thickening and the loss of matrix elasticity[61-63]. AGEs and corresponding receptors (RAGE) have been demonstrated to be up-regulated in the GI tract both in the experimental type 1[49] and type 2[64] DM rats. Furthermore, there is an association between AGEs and RAGE with DM-induced intestinal

and colonic remodeling[47,51]. Two major mechanisms are mainly involved in the link between AGEs and DM-induced GI morphological and biomechanical remodeling. One is a receptor-independent pathway where the AGEs induce changes in the extracellular matrix architecture through the formation of protein cross-links. The other is a receptor-dependent pathway where the AGEs modify cellular functions through the RAGE[65-67].

AGEs and RAGE also play an important role for DAN[68-70]. The expression of AGEs has been demonstrated in the peripheral nerves in DM animals[71] and in the axons and Schwann cells of patients with DM[72]. Increased expression of RAGE in peripheral nerves in DM rats has also been demonstrated[73]. The AGEs-induced changes of proteins could cause structural and functional changes in the peripheral nerves[74]. Modification of major axonal cytoskeletal proteins such as tubulin, neurofilament, and actin by AGEs impairs axonal transport and contributes to the development of atrophy and degeneration of nerve fibers[75,76]. Micro-vessels in peripheral nerves affected by AGEs may also contribute to the damage of peripheral nerves[77]. Therefore, long-term hyperglycemia induced GI tissue nonenzymatic glycation appears to play an important role in the remodeling of GI wall in DM.
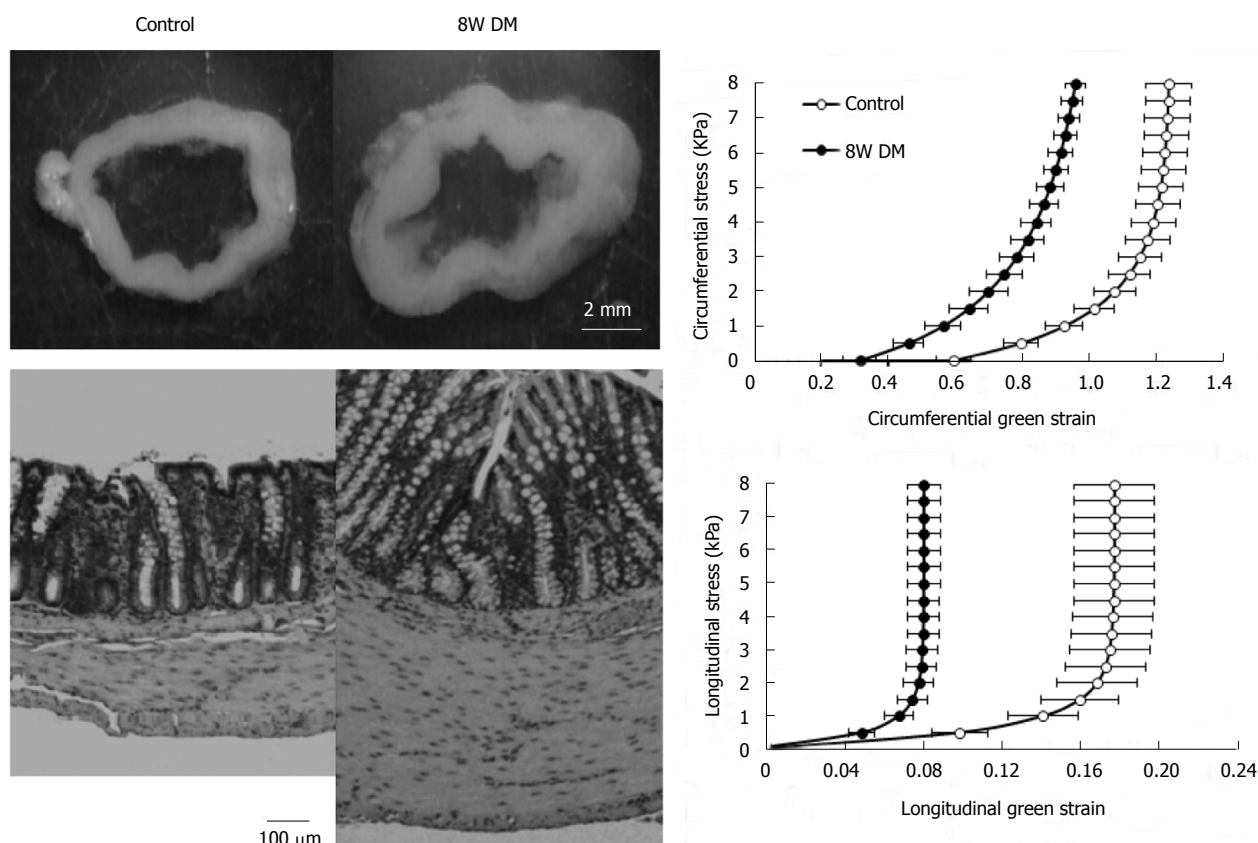
Figure 2 Colonic remodeling in STZ-induced diabetic rats. The top-left figure showed the no-load tissue rings of colon from control (left) and 8W streptozotocin-induced diabetic rats (right). It clearly demonstrated that the wall thickness increased in the diabetic colon. The low-left figure showed micro-photographs of the control (left) and 8 wk diabetic (right) colonic histological sections. It clearly demonstrated that the mucosa and muscle layers in the diabetic colon became much thicker than in the normal colon. The bar is 100 μm. The right figures showed the relation between circumferential (top) and longitudinal (bottom) stress and strain. Both in the circumferential and the longitudinal directions, the stress-strain curves shifted to the left in the 8W diabetic groups compared to those in the control group. Thus, the colon wall stiffness increased in both directions during the development of diabetes. Control: Normal control; 8W DM: 8 wk of diabetes.

DIABETES-INDUCED SENSORY-MOTOR CHANGES IN THE INTESTINE AND COLON

DM-induced GI remodeling likely affects the sensory-motor function through the modification of the mechanical environment and structural basis around the motor and sensory nerves in the wall of intestine and colon. DM-induced increase in wall stiffness can change the tension and stress distribution around the mechanosensitive afferents. DM-induced structural and deformational changes can alter the relative position and response rate of the motor-sensory afferents. Furthermore, DAN involves both the sensory nerve supply to the intestine and colon, the ENS and processing in the central nerve system (CNS). Therefore, it is important to explore DM-induced sensory-motor changes in the intestine and colon and its mechanisms.

Diabetes-induced motor changes in the intestine and colon

Small intestine (Table 3): Both delayed and rapid transit has been demonstrated in DM animal models[78,79]. It has been found in DM rats that the

increase in transit time and decrease in intestinal tone are associated with up-regulated cholinergic activity and low-regulated beta-adrenergic receptor activity[80]. Stress-strain analysis of jejunal contractility in response to flow and ramp distension demonstrated that the jejunal contractility was hypersensitive to stimulations after carbachol application[81,82] in type 2 DM rats (Figure 3). However, the force generated per unit of smooth muscle was decreased in the DM rats, and could be partly compensated by hyperplasia and hypertrophy of the smooth muscle[82]. Furthermore, it was demonstrated that the ileal segment from type-1 DM rats was hypersensitive to distension for contraction induction[83]. However, the contraction force produced by smooth muscle was lowest in DM rats. Increased AGE and RAGE expressions were found to be associated with contractility changes in DM rats.

In DM patients, the delay in intestinal transit time has also been demonstrated by using different tests such as breath hydrogen appearance time[84], radiopaque markers[85] and metal-detector[43]. On the contrary, increased intestinal transit time has been found in insulin-dependent DM (IDDM) patients[86]. In patients with long standing IDDM, it has been demonstrated that the duodenal transit is disturbed and the chyme
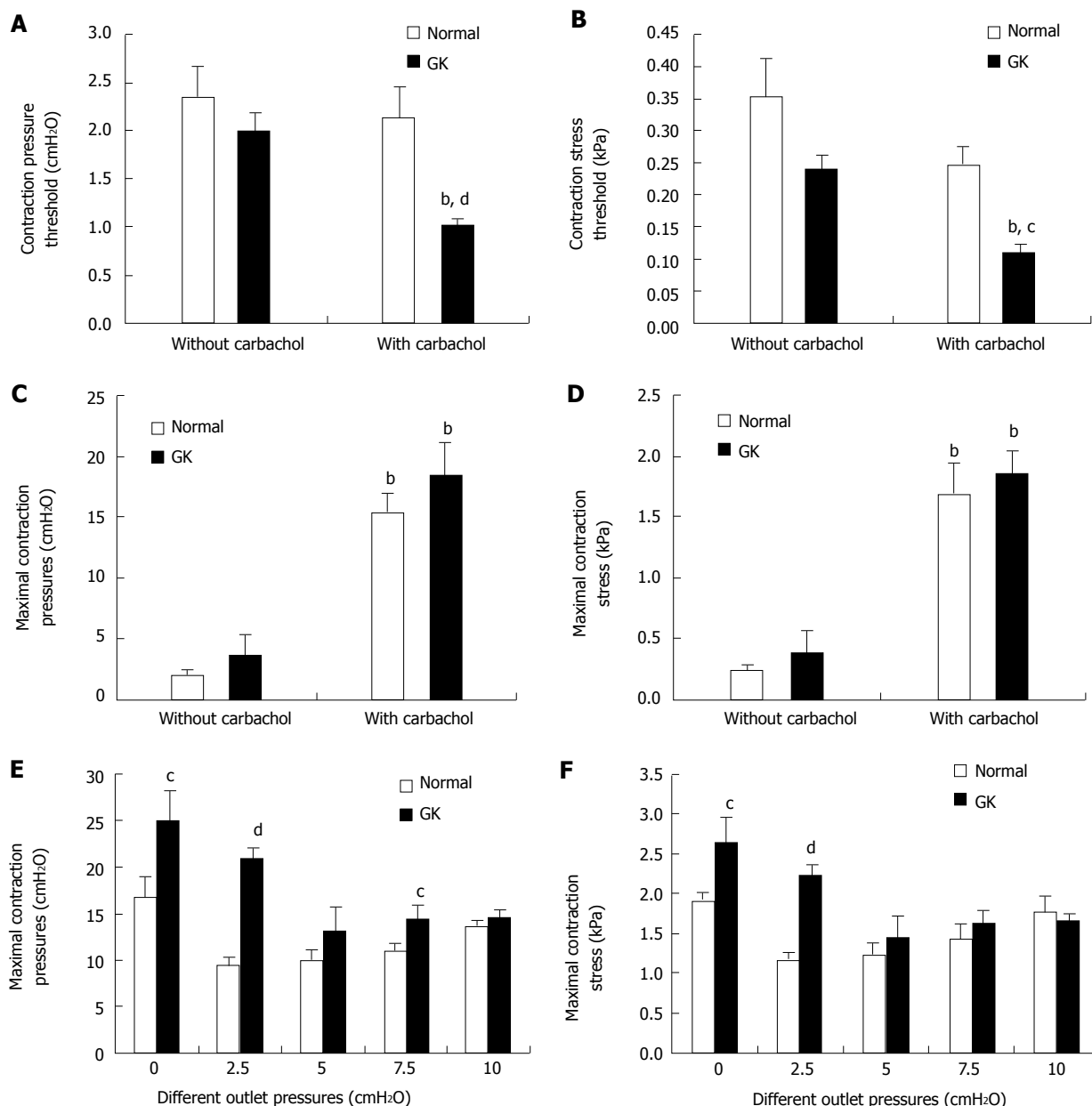
Figure 3 Jejunal contractility in response to flow and ramp distension in type 2 diabetic GK rats after carbachol stimulation. Top figures showed the pressure (A) and circumferential stress (B) at the contraction threshold during ramp distensions. The pressure and stress thresholds were significantly decreased in GK group but not in Normal group after carbachol application (compared with without carbachol application, [b]$P < 0.01$). Furthermore, the pressure and stress thresholds were significantly smaller in the GK group than in Normal group after carbachol stimulation (compared with Normal group, [c]$P < 0.05$; [d]$P < 0.01$). Middle figures showed the maximum contraction pressure (C) and stress (D) during basic contraction. After carbachol application, the maximum contraction pressure and stress significantly increased both for Normal and GK groups (compared with without carbachol application [b]$P < 0.01$). Bottom figures showed the maximum contraction pressure (E) and stress (F) in the flow-induced contraction after carbachol application. Compared to the Normal group, the maximum contraction pressure and stress were significantly bigger at outlet pressure levels of 0 and 2.5 cmH$_2$O in the GK group ([c]$P < 0.05$, [d]$P < 0.01$).

clearance activity is decreased[87]. In one study, it has been reported that about 80% of patients with long-standing DM had abnormal motility of the small intestine[88]. The DM-induced dysmotility can occur either in the postprandial or fasting state[89,90]. In noninsulin-dependent DM (NIDDM) patients with diarrhea and DAN, grossly disordered motility such as migrating motor complex disorders has been reported[89]. Although disorders of postprandial motility in small intestine have been reported in DM patients, the findings are inconsistent[90].

Colon (Table 3): Colonic dysmotility is often seen in DM patients[85,91-97] and animal models[97-103]. DM patients with DAN are expected to have delayed transit in the entire gut, this finding is apparent to some extent in the distal colon but not in the proximal colon[92]. Delayed transit is most frequent in male patients with long-term IDDM where the total colonic transit time is prolonged[93]. Even in type II diabetic patients without clinical presentation of neuropathic symptoms, significant elongation of the transit time has been observed in the lower digestive tracts compared

Table 3	Diabetes mellitus-induced motor and sensory changes of intestine and colon	
Changes	**Intestine**	**Colon**
Motor	Transit time ↑↓[43,78-80,84,87]	Transit time ↑[85,92-99,101,102,106]
	Muscle tone ↓[80]	Contractility ↑↓[104,108,109,111-113]
	Jejunal contractility in response to flow and ramp distension after carbachol application ↑[81]	Carbachol induced contractions in muscle ↑↓[100,107,112]
	Ileal contractility in response to distension ↑[83]	Spontaneous contractility ↑↓[100,102]
	The force generated by the smooth muscle per unit ↓[82,83]	Contraction and relaxation of circular muscle strips from DM were impaired[105]
	Dysmotility DM patients[88,90]	
	Migrating motor complex disorders[89]	
Sensory	Sensitivity of human duodenum to the combination of mechanical, thermal and electrical stimulations ↓[114]	Sensitivity of rat colon to the mechanical stimulation ↑[103,115,116]
	Sensitivity of rat jejunum to the mechanical stimulation ↑	

DM: Diabetes mellitus.

to control subjects[85]. Jorge *et al*[95] found that at 24 h after ingestion, there was no difference in the number of radiopaque particles in the colon between DM patients and controls. However, at 72 h past ingestion, the mean number of radiopaque particles in the colon was significantly higher in DM patients than in healthy controls. Furthermore, The DM patients with constipation had longer colonic transit times than those without constipation[94,96]. Hyperglycemia could inhibit long and short neural reflexes to modulate colonic motility which may contribute to constipation in DM[104]. The postprandial colonic motility is increased in DM patients with mild constipation but not in DM patients with severe constipation, the later may be due to DAN-induced absence of the postprandial gastrocolonic response[91]. Chandrasekharan *et al*[105] demonstrated that colonic circular muscle strips from DM subjects showed impaired contraction and relaxation responses compared to that of healthy controls. Such changes may be caused by the loss of enteric neurons in the colon due to increased oxidative stress and apoptosis.

Results from animal studies are ambiguous and have shown both delay and enhancement in the colon transit time in DM. Similarly, both reduced and increased colon contractility for whole segment or muscle strips in DM animals are reported. Delayed colonic transit has been found in alloxan-induced DM mice[98], db/db mice[99] and DM rats[101,102]. The prolonged transit time in db/db mice is associated with reduced areas of ICC and the expression of SCF in colon[99]. Insulin-like growth factor 1 (IGF-1) treatment can inhibit the DM-induced colonic smooth muscle cell apoptosis and may be involved in the alleviation of colonic dysmotility in DM rats[102]. However, Domènech *et al*[106] reported that DM RIP-I/hIFNβ transgenic mice showed an enhanced gut transit associated with gut remodeling including neuroplastic changes and overt myenteric neuropathy. In relation to the contractility, however, carbachol-induced and Ems-induced contractions in the colon muscle were significantly reduced in DM mice[107]. Wang *et al*[101] showed that endogenous IGF-1 and SCF protein and their mRNA expressions were significantly

reduced in the DM colonic muscle tissues. Kim *et al*[100] demonstrated that spontaneous contractility decreased, carbachol-induced contractility decreased and the number of interstitial cells of Cajal networks was greatly reduced in the proximal colon of DM rats. In addition, the degree of relaxation in response to nitric oxide in the proximal colon of DM rats also appeared to be attenuated. Their results suggest that the decrease of interstitial cells of Cajal network, cholinergic receptors, and neuronal nitric oxide synthase in the proximal colon plays important roles in DM-related dysfunction of colon. Touw *et al*[108] showed that Type 1 DM is associated with decreased depolarization-induced Ca(2+) influx in colonic smooth muscle, leading to attenuated myosin light chain phosphorylation and impaired colonic contractility. Sung *et al*[103] showed that the frequency, not the amplitude, of colonic spontaneous contraction in vitro was significantly decreased in DM rats compared to control rats. However, enhanced contractility of the colon in the DM animals has also been reported[109,110]. The increased contractility is associated with loss and injury to ICC in the submucosa and muscle layers[110]. Yoneda *et al*[111] showed that the colonic peristaltic reflex is enhanced by impairment of enteric nitrergic inhibitory neurons in spontaneous DM rats. Xie *et al*[112] demonstrated that carbachol-induced contractions of distal colonic strips were greater in DM rats in which β-arrestin2 is involved in the increase of distal colonic contraction in DM rats. Chang *et al*[113] indicate that the increased contractions of distal colon in DM rats are partly mediated by the IL-6 receptor pathway.

Diabetes-induced sensory changes in the intestine and colon

Compared with published studies on motor disorders in DM, only few studies have addressed the sensory function of intestine and colon in the DM (Table 3). In relation to the small intestine, it has been demonstrated in a human study that there was an overall hyposensitivity to the combination of all stimulations including mechanical, thermal and electrical stimulations in the duodenum in the DM patients[114]. Furthermore, it

was found that these patients demonstrated a 46% increase in the somatic referred pain areas. This may indicate that central neuronal changes are involved in the sensory changes of gut. Thus, the mechanisms of GI symptoms in long-standing DM patients are likely to involve the interactions between peripheral and central systems[114]. In relation to the colon, Grabauskas *et al*[115] showed that visceromotor responses to colorectal distension were significantly higher in STZ-induced DM rats 8 wk after the induction of DM. Such visceral hypersensitivity is mediated by abnormal IA current resulting from an increased phosphorylation of MAPK and Kv4.2 in dorsal root ganglion neurons. Similarly Hu *et al*[116] has also demonstrated that STZ-induced DM rats had colonic hypersensitivity to mechanical stimulation. The hypersensitivity was associated with an enhanced neuronal excitability of primary sensory neurons that showed an up-regulated expression of voltage-gated sodium channels (VGSCs, *i.e.*, NaV1.7 and NaV1.8 subunits). Visceral hypersensitivity is also demonstrated in a rat model of type 2 DM accompanied by weight loss[103].

Mechanism of sensory-motor function changes

It is important to understand the mechanism behind the DM-induced sensory-motor changes of gut in order to enhance treatment approaches for the DM patient with gut disorders. As mentioned previously, the histomorphological and biomechanical remodeling could alter the baseline of the mechanosensitive afferents activity and the biomechanical environment around the mechanosensitive afferents. Therefore, DM-induced changes of gut structure and biomechanical properties can induce the changes observed in sensory-motor functions. On the other hand, the sensory-motor changes of the gut may reflect the structural and functional changes of peripheral nerve, ENS and the CNS in patients with DM. It seems that the more severe the neuropathy, the greater the likelihood of the involvement in gut sensory-motor disorders is[9].

More than 30% long-standing DM patients have DAN, therefore DAN is the most prevalent DM complication which is also related to other diabetic complications including GI complications[117]. The sensory nerves and ENS can be affected by peripheral DAN[7,118,119]. There is proof that the nerves in different layers of the GI wall undergo DAN changes and that the parasympathetic fibers in the gut are disrupted in DM patients[114]. Furthermore, ICCs are pacemaker cells in the GI tract distributed along the GI wall[120]. In GI tract, ICCs play an important role for the link between the autonomic nervous system, enteric neurons and smooth muscle cells[121]. Animal studies have demonstrated that the number of ICCs is reduced in different parts of GI tract such as the stomach[99,122], small intestine[99,123] and[99,124] colon. Therefore, the mechanisms of DM-induced sensory-motor function changes extensively involve the autonomic nervous system, ENS and ICCs.

Many factors are related to DAN. As mentioned above, the formation and accumulation of AGEs in peripheral nerves are associated with DAN directly by affecting structural and functional proteins and indirectly by activating receptors for AGEs. In addition to the formation of AGEs, the microvascular complications to DM causing neuropathy include other biochemical pathways. For example, DM can induce oxidative stress which is enhanced by AGE formation and polyol pathway activation[125]. Many data have shown that oxidative stress-induced tissue injury is associated to DAN[77]. Experimental and clinical data provide evidence that C-peptide is related to nerve dysfunction in DM since the C-peptide administration by subcutaneous injections seems to ameliorate nerve dysfunction in DM[126]. Human and animal studies have demonstrated that Na$^+$, K$^+$-ATPase activity is impaired in the cell membrane of many tissues (see details in review)[127]. Thus, the impairment of Na$^+$, K$^+$-ATPase activity also plays an important role in the development of DAN by different pathways[128]. Furthermore, increased polyol pathway in DM has long been regarded as important in DAN[129]. Animal data suggests that glucose shunting through the polyol pathway alters nerve excitability due to the formation of sorbitol[130]. Furthermore, structural alterations of the nerves including thickening of the capillary basal membrane, loss of capillary pericyte coverage and endothelial hyperplasia, all lead to disturbances in capillary flow compromising the exchange of oxygen and glucose[131].

CLINICAL CONSEQUENCES OF DIABETES-INDUCED CHANGES IN INTESTINE AND COLON

DM-induced sensory and motor dysfunction can affect part of or the entire GI tract, therefore, the perceived symptoms may be associated with one or several parts of the GI tract. In the patients of both IDDM and NIDDM, the GI symptoms are very common and can reach 75%[132-138]. Due to the non-specific nature of GI symptoms in DM patients, differential diagnoses should be considered when clinicians deal with GI symptoms. As DM-induced DAN can affect the enteric nerves supplying the small intestine and colon, abnormal motility, secretion, absorption and transportation can occur as possible outcomes. The clinical manifestation of these can be symptoms such as central abdominal pain, bloating, diarrhea, incontinence and constipation. An overrepresentation of celiac disease has been observed in insulin dependent DM patients, as this is a known etiologic factor of severe diarrhea, celiac disease should be excluded when clearing up the matter of general DM diarrhea[139]. Recent evidence indicates that GM is strongly associated with the development of type 1 and type 2 diabetes[97,140,141]. Furthermore, a close relationship between DM and increased risk of colon cancer has been demonstrated in both women and men[142,143]. DM is considered an independent risk factor

for colon and rectal cancer[144].

Diarrhea and diabetes

Chronic diarrhea is a frequent presenting symptom, seen by both general practitioners and gastroenterologists. The differential diagnosis is broad, and diagnostic evaluation may be complicated[145,146]. Diarrhea is an important and often debilitating feature of DM enteropathy occurring in up to 20% of the patients[147]. It has also been reported that chronic diarrhea is more frequent in type I DM patients[148]. The diarrhea is typically painless, may be associated with fecal incontinence and occurs more often at night[149]. Therefore when gastroenterologists are confronted with patients suffering from chronic diarrhea, DM should be considered as a differential diagnosis, especially poorly controlled DM with co-existing DAN.

Many factors may relate to diarrhea in DM patients. These include food composition, intestinal motility disorders, GM changes, excessive loss of bile acids, pancreatic insufficiency and *etc*.[148,150-152]. Both increasing and decreasing GI transit time in DM patients may cause diarrhea. If the transit time become fast, intraluminal contents reaching the caecum will increase[153]. If the transit time is slow, there is a risk of bacterial overgrowth. Therefore, both conditions can potentially induce DM diarrhea[154]. The etiology of DM diarrhea is not fully understood and is most likely multifactorial[4,155], involving reversible and irreversible processes. The diarrhea does not always correlate with the duration of DM or glycemic control, therefore DAN is thought to be a main underlying mechanism[156].

The colon likely plays a secondary or permissive role in patients with steatorrhea which could be caused by pancreatic insufficiency, celiac disease, or bacterial overgrowth[157]. However, the colonic dysfunction may be a primary contributor in DM diarrhea where the steatorrhea is absent. Other causes of diarrhea also need to be excluded, such as infectious diarrhea, celiac disease, bile salt diarrhea, and the concomitant use of drugs that may cause diarrhea such as metformin, GLP-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, proton pump inhibitors, and statins[158] as well as functional diarrhea[159].

Constipation and diabetes

Constipation may be the most common GI complaint in DM patients[4,96,147,157,160-165]. Constipation also represents the most severe symptomatic problem[132]. The severe constipation may clinically present as obvious abdominal distention, severe nausea and vomiting as well as electrolyte disturbances[157]. Long-term and severe constipation may also cause stercoral ulcerations and perforation.

The etiology of DM constipation is not well understood; however, all factors in the DM patients affecting motor-sensory function of the colon are likely associated with constipation[164]. Among these factors, hyperglycemia is suggested to be the most important one. Inadequate glycemic control and consequent DAN have great influence on the sensory and motor functions of the GI tract[105]. DM angiopathy and vascular complications secondary to chronic hyperglycemia can also cause intestinal ischemia and impair nerve and muscle function resulting in DM gastroenteropathy[166]. Hyperglycemia causes apoptosis of enteric neurons and changes in their chemical code, resulting in motility changes[105]. It is well known that long-term hyperglycemia can induce the formation and accumulation of AGEs which play an important role for DAN[68-70]. ICC, together ENS and smooth muscles, play an important role in the regulation of motility[120]. One study demonstrated that a high dietary saturated fat intake is associated with significant increase in the prevalence of constipation in patients with uncontrolled DM[167]. The long term high dietary saturated fat consumption leading to slower GI motility and constipation may be related to gastrocolic reflux by several mechanisms. In addition, other factors such as stress, inflammation and functional changes in relation to DM may also be associated with constipation in DM patients[164].

Gut microbiota modification

The greatest concentration of microorganisms is found in the GI tract, and they consist mostly of bacteria[168]. The GM plays an important role in normal intestinal function and maintenance of the host health[168]. Composition of GM is affected by many factors such as diet, disease state, medications as well as host genetics. Therefore, GM has been associated with immune functions, immune mediated diseases, energy homeostasis and obesity[169,170]. To date, it has become increasingly evident that GM contributes to both type 1 and type 2 DM[140,141,171]. In recent years, many reviews have discussed the impact of GM on the development of obesity and DM[140,171-174]. However, to the best of our knowledge, there are few reviews which discuss how the DM-induced GI changes in turn affect the GM. It is well known that the GM inhabits the gut, therefore the DM-induced intestinal and colonic changes are likely to modify GM composition, in turn, the GM changes may also affect intestinal structure and motility.

As we discussed above in this review, motility disorders are common in diabetic patients[78-97]. There is evidence to suggest that modification of GI transit time can affect the composition of the GM community[175-177]. A close relationship exists between transit time and GM mass[175] and the motility shapes the composition and function of GM[176]. Therefore, the abnormal motility of gut in DM such as decreased or increased transit time can be an independent factor affecting the amount, the composition and the function of GM[178]. The changes of GM may further affect gut function through the brain-gut-axis[179]. The GM can interact with the gut-brain-axis by means of the modulation of afferent sensory nerves to modulate the motility of the intestine[180,181]. The GM can also directly affect the ENS by different molecular pathways[182,183]. Furthermore, the GM can modulate

gut motility by nitric oxide generating pathway[184] and by interacting with the vanilloid receptor on capsaicin-sensitive nerve fibers[185].

The DM-induced intestinal histomorphological changes such as mucosa damage may also be related to GM modification and function. The leaky epithelium presumably alleviates the penetration of bacteria through the intestinal epithelium, initiating a pathologic cascade and disturbing the intestinal immunology, which is a critical element in the development of type 1DM[169]. On the other hand, the GM changes may also affect the integrity of intestinal mucosa[186] and smooth muscle functions[187]. The bidirectional interplay between GM and DM-induced intestinal changes contributes to the pathogenesis of GI disorders in DM.

GLP-1 regulates glucose homeostasis by stimulating the secretion of insulin from pancreatic β-cells[188] and plays important roles in metabolism as well as GI motility[188-190]. In relation to DM, GLP-1 acts as a pharmacological agent with definite therapeutic potential in DM treatment, regulating blood glucose by stimulating insulin secretion from insulin-producing β-cells in a blood-glucose dependent manner and inhibiting glucagon secretion from the glucagon-producing α-cells[191,192]. On other hand, it has been demonstrated that GLP-1 is progressively up-regulated in pancreatic islets during type 2 DM development[193]. More recently, the link between GLP-1/GLP-1 receptor (GLP-1R) expression and GI motility mediated by GM has been investigated[194]. They found that the expression of GLP-1R in myenteric neural cells in the GI tract was suppressed and the GI transit time became shorter in Germ-free (GF) mice after transplantation of GM. Therefore, they suggest that the GM accelerates the GI motility while suppressing the expression of GLP-1R in myenteric neural cells throughout the GI tract. There are also other anti-diabetic agents which act in the GI tract such as alpha-glucosidase inhibitors[195] and GLP-1 receptor agonists[196,197]. It is interesting to notice that alpha-glucosidase inhibitors and GLP-1 receptor agonists also affect the GM[198-200]. Alpha-glucosidase inhibitors such as acarbose treatment has been demonstrated to increase the content of gut Bifidobacterium longum and partially restore the imbalance of GM in patients with type 2 DM[198], and the changes in GM are strongly associated with the levels of various metabolic indicators[200]. In contrast, GLP-1 receptor agonists such as liraglutide seem to modulate the composition of the GM[199]. Other therapeutic agents targeting DM such as metformin[201] and antibiotics[202] also affect the GM. Thus, there is an interplay between drugs used for DM and the GM, however, the exact mechanism of the interaction is complex and needs to be investigated more thoroughly.

Colon cancer and diabetes

Type 2 DM mellitus has been reported to increase the risks of a wide spectrum of cancers including colorectal cancer[142-144,203-206]. Colorectal cancer is a significant health problem; it is one of the most common malignancy of the GI tract[207]. Therefore, understanding the association between DM and the risk of colon cancer is crucial.

Although some studies have reported no overall associations between DM and colon cancer risk[208-211], most studies support the finding of an association between DM and colon cancer. Large prospective studies have demonstrated that DM is associated with an increased risk of colon cancer in people investigated[211-217]. Many meta-analysis studies also support a correlation between DM and increased risk of colon cancer[142-144,218-222]. A population-based cohort study investigating the overall sex- and age-specific risks of colorectal cancer in association with DM was done by Chen *et al*[223]. They showed that DM significantly increased the risk of colorectal cancer, especially in patients aged 45-64 years. A multiethnic Cohort study also found that DM is a risk factor for colorectal cancer[224]. In addition, DM was found to negatively impact the survival outcomes of patients with colon cancer[225].

The mechanisms to explain the association between DM and increased colon cancer risk remain unclear. It has been demonstrated that AGEs and RAGE are up-regulated in the DM GI tract[49,64], and AGEs and RAGE are associated with DM-induced intestinal and colonic histomorphological remodeling[47,51] and DAN[125] which is closely related to motor-sensory disorders[9]. High glucose levels and AGEs increase the proliferation and migration of cultured colon cancer cells[226]. Hyperglycemia and AGEs could also induce oxidative stress and inflammation, which can cause further damage to the cellular components and contribute to malignant cell transformation[227]. Inflammation is a critical component of DM-induced target organ injury and colon cancer initiation and progression[228,229]. The inflammasome regulates the microbiota and the inflammatory response of epithelial cells to the GM[230], and the GM has been shown to be associated with GI malignancy including colonic cancer[231,232]. Recent studies suggest that RAGE signaling plays an important role in colorectal tumor progression[233]. Furthermore, AGEs may promote cancer cell proliferation through the activation of the RAGE signaling[234,235]. Therefore, hyperlipidemia, AGEs, inflammation, extracellular matrix alterations, and altered microbiota may induce GI tissue injury that may favor the development of colonic cancer. It has also been demonstrated that the slower bowel transit time in DM patients could enhance the exposure of the colorectal epithelium to carcinogens such as bile acids, nitrosamines and polycyclic hydrocarbons[236]. The above-mentioned findings show a possible link between DM-induced intestinal mechanophysiological changes and colonic cancer. The potential molecular mechanisms mediating the link between DM and colon-rectal cancer have been reviewed in detail recently[237], however the exact mechanisms need to be explored further.
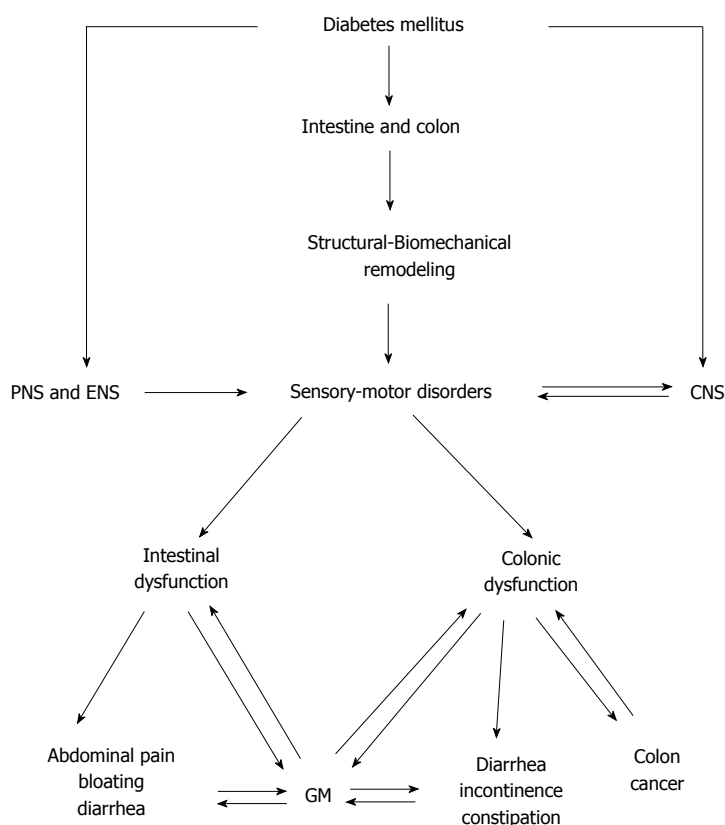
Figure 4 The diagram shows the diabetes mellitus-induced intestinal and colonic changes and clinical consequences. CNS: Central nerve system; PNS: Peripheral nerve system; ENS: Enteric nervous system; GM: Gut microbiota.

Furthermore, other factors as mentioned below are also likely associated with colon cancer. Metabolic syndrome, characterized by abdominal obesity, hyperglycemia, raised blood pressure, elevated triglyceride levels, and low high-density lipoprotein-cholesterol levels, is often seen in diabetic patients and has been reported to be associated with colon cancer[238-241]. As dietary fibers reduce the risk of metabolic syndrome, dietary fibers may have a role in the prevention of colon cancer in patients with type 2 DM[242]. Chronic hyperinsulinemic state and the elevation of insulin-like growth factor-1 levels may play a crucial role in the proliferation of cells and the occurrence of colon cancer[243] by different molecular mechanisms[244]. Elevated insulin receptor protein expression in colonic tumors has also been proposed as a possible biological mechanism for colonic tumorigenesis as *in vivo* studies have shown that insulin receptors contribute to cell transformation[245]. Different treatments of DM may also be related to colon cancer in DM patients. Chronic insulin therapy has been reported to be associated with an increased risk of colorectal adenoma[246] and cancer risk[247] among type 2 DM patients. Sulfonylureas stimulate endogenous insulin secretion and have therefore been suggested to be associated with an increased risk of colon cancer[248], however other reports showed that sulfonylurea use was associated with a lower colon cancer risk in DM patients[249]. Data on potential carcinogenic effects of thiazolidinediones are inconsistent, but most studies have found no increased risk of colon cancer[244,250,251] or even reduced risk of colon cancer. Metformin lowers the amount of circulating insulin and there is evidence on Metformin acting as a protective agent against colon cancer[234,252-254], this may be due to a reduction of the formation of precancerous lesions[255,256]. GLP-1-based therapeutic approaches have also been suggested as potential carcinogenic factors[102]. However, animal studies have shown that GLP-1 receptor activation reduced growth and survival in mouse CT26 colon cancer cells[257] and GLP-1 receptor agonists did not accelerate neoplasia in carcinogen treated mice[258]. A recent study also demonstrated that DM medication in general did not impact cancer recurrence or survival[259].

CONCLUSION

DM-induced intestinal and colon changes are summarized in Figure 4. DM is a chronic disease and is one of the major public health problems worldwide. Disorders of intestine and colon are common in DM. DM is associated with structural changes in the connective tissue matrix and in the muscles in the wall of intestine and colon and further causes biomechanical remodeling. As demonstrated in the text above, many mechanophysiological changes occur in the diabetic intestine and colon such as changed dimensions and changed passive and active tissue properties. Remodeling also occurs in the nerve structure and function. The interplay between these changes is extremely complex and need a scientific base to be explored fully. The changes may to various degrees be part of the mechanisms responsible for the intestinal and colonic

sensory-motor disorders causing a variety of symptoms. The complexity is even more difficult to deal with since the symptoms are associated with changes in the central processing of visceral afferent signals from the gut wall. As DM-induced DAN can affect the enteric nerves supplying the intestine and colon, abnormal motility, secretion, absorption and transportation can occur. This presents clinically as symptoms including central abdominal pain, bloating, diarrhea, incontinence and constipation. The DM-induced structural changes and motility disorders of the intestines are associated with GM changes in DM, on the contrary the GM changes may in turn affect intestinal structure and motility. Furthermore, studies suggest an association between DM and increased risk of colon cancer in both women and men, and the link between DM-induced intestinal mechanophysiological changes and colon cancer need to be explored further. Therefore, an insight into DM-induced intestinal and colonic changes and the clinical consequences is important in order to explore better treatment approaches for the gut disorders in diabetic patients.

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