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Diabetes-induced mechanophysiological changes in the small intestine and colon

Mirabella Zhao, Donghua Liao, Jingbo Zhao

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

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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[1,2]. Furthermore, huge healthcare expenditures are needed in order to prevent and treat DM and its complications[3,4].

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 pathophysiologic 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)[5,6]. 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.
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\(^\text{[17]}\). 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\(^\text{[18]}\).

**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\(^\text{[19-40]}\).

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\(^\text{[27]}\). 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\(^\text{[22]}\). 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\(^\text{[5,8,10,41-51]}\). Increased expression of advanced glycation end of product (AGE) and AGE receptor (RAGE) has been demonstrated in the DM intestinal and colonic wall\(^\text{[49,51,52]}\). 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 ileum increases in DM rats\(^\text{[25]}\). Lately, the research group of Zhao et al\(^\text{[8,25]}\) and Sha et al\(^\text{[48]}\) 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\(^\text{[47]}\). 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\(^\text{[10]}\). 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\(^\text{[51]}\) 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 Characteristics of Normal Intestine and Colon

| Region   | Elasticity | Stress-Strain | Viscoelasticity |
|----------|------------|---------------|-----------------|
| Jejunum  | High       | Linear        | Slow            |
| Ileum    | Low        | Non-linear    | Fast            |
| Colon    | Moderate   | Exponential   | Medium          |

### Table 2: Histomorphological Changes in DM

| Region        | Changes                                      |
|---------------|----------------------------------------------|
| Jejunum       | Increased epithelial thickness, decreased ICC |
| Ileum         | Increased smooth muscle mass, decreased ICC   |
| Colon         | Increased extracellular matrix, decreased ICC |

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The rat colon has a tensile strength of around 50 g/mm. Increased thickness.

Tension-strain or stress-strain curves show an exponential behavior. The residual strains in longitudinal direction are smaller than those in circumferential direction, 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. The collagen in submucosa layer is important for the passive biomechanical properties. The villi are important for the biomechanical properties of the small intestine in circumferential direction.

The rat colon has a tensile strength of around 50 g/mm and increases in strength from proximal to distal. The opening angle varies along the rat colon with the highest values in the beginning of the proximal colon. The residual strain is negative at the inner surface and positive at the outer surface.

The stress-strain curves are exponential. All segments were stiffer in longitudinal direction than in the circumferential direction.

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.

The wall stiffness of human sigmoid colon is reduced in response to butylscopolamine.

A mechanical creep behavior in the isolated rat colon smooth muscle cells could be described by a viscoelastic solid model.
in the GI tract. The nutrient content in the small intestine is greatly increased due to hyperphagia and fast gastric emptying\(^5\) in DM rats. It is well known that the luminal nutrients such as fat and carbohydrate could stimulate physiological L cells\(^5\), 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\(^59\) in the intestinal wall such as collagen. Such changes cause cross-linking of collagen, basement membrane thickening and the loss of matrix elasticity\(^6\). 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\(^65\).

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\(^75,76\). Microvessels 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.

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**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 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.
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\cite{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\cite{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\cite{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\cite{82}. Furthermore, it was demonstrated that the ileal segment from type-1 DM rats was hypersensitive to distension for contraction induction\cite{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\cite{84}, radiopaque markers\cite{85} and metal-detector\cite{43}. On the contrary, increased intestinal transit time has been found in insulin-dependent DM (IDDM) patients\cite{86}. In patients with long standing IDDM, it has been demonstrated that the duodenal transit is disturbed and the chyme...
clearance activity is decreased\textsuperscript{[97]}. In one study, it has been reported that about 80% of patients with long-standing DM had abnormal motility of the small intestine\textsuperscript{[88]}. The DM-induced dysmotility can occur either in the postprandial or fasting state\textsuperscript{[89,90]}. In noninsulin-dependent DM (NIDDM) patients with diarrhea and DAN, grossly disordered motility such as migrating motor complex disorders has been reported\textsuperscript{[89]}. Although disorders of postprandial motility in small intestine have been reported in DM patients, the findings are inconsistent\textsuperscript{[90]}.  

Colon (Table 3): Colonic dysmotility is often seen in DM patients\textsuperscript{[85,91-97]} and animal models\textsuperscript{[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\textsuperscript{[92]}. Delayed transit is most frequent in male patients with long-term IDDM where the total colonic transit time is prolonged\textsuperscript{[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 ↑ [45,78-80,83,87]                                            | Transit time ↑ [308,309,310,311,104]                                    |
|                          | Muscle tone ↓ [94]                                                        | Contractility ↑ [94,106,109,113-115]                                    |
|                          | Jejunal contractility in response to flow and ramp distension after carbachol application ↑ [94] | Carbachol-induced contractions in muscle ↑ [306,307,112] |
|                          | Ileal contractility in response to distension ↑ [90]                      | Spontaneous contractility ↑ [106,109]                                   |
|                          | The force generated by the smooth muscle per unit area ↓ [92,93]           | Contraction and relaxation of circular muscle strips from DM were impaired [106] |
|                          | Dysmotility DM patients [89]                                              |                                                                       |
|                          | Migrating motor complex disorders [94]                                    |                                                                       |
| Sensory                  | Sensitivity of human duodenum to the combination of mechanical, thermal and electrical stimulations ↑ [91] | Sensitivity of rat colon to the mechanical stimulation ↑ [90,105,106] |
|                          | Sensitivity of rat jejunum to the mechanical stimulation ↑ [91]           |                                                                       |

DM: Diabetes mellitus.

Table 3

Diabetes mellitus-induced motor and sensory changes of intestine and colon

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|                          | Dysmotility DM patients [89]                                              |                                                                       |
|                          | Migrating motor complex disorders [94]                                    |                                                                       |
| Sensory                  | Sensitivity of human duodenum to the combination of mechanical, thermal and electrical stimulations ↑ [91] | Sensitivity of rat colon to the mechanical stimulation ↑ [90,105,106] |
|                          | Sensitivity of rat jejunum to the mechanical stimulation ↑ [91]           |                                                                       |

DM: Diabetes mellitus.

to control subjects [85]. Jorge et al [93] 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 [89,96]. 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 latter 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-1/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 ß-adrenergic 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 [110] 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 ß-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

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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[14]. In relation to the colon, Grabauskas et al[15] showed that visceral motor 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[16] 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[10].

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[17]. The sensory nerves and ENS can be affected by peripheral DAN[7,18,19]. 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[14]. Furthermore, ICCs are pacemaker cells in the GI tract distributed along the GI wall[20]. In GI tract, ICCs play an important role for the link between the autonomic nervous system, enteric nerves 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[90,122], small intestine[90,123] and colon[99,124]. 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[7]. 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
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 [4,159,167,168,169]. Constipation also represents the most severe symptomatic problem [132]. The severe constipation may clinically present as obvious abdominal distension, 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 reflex 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 [166,170]. To date, it has become increasingly evident that GM contributes to both type 1 and type 2 DM [146,147,170]. 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 [78-87]. 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 [176] and the motility shapes the composition and function of GM [178]. 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 and by interacting with the vanilloid receptor on capsaicin-sensitive nerve fibers.

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. On the other hand, the GM changes may also affect the integrity of intestinal mucosa and smooth muscle functions. 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 and plays important roles in metabolism as well as GI motility. 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. On the other hand, it has been demonstrated that GLP-1 is progressively up-regulated in pancreatic islets during type 2 DM development. More recently, the link between GLP-1/GLP-1 receptor (GLP-1R) expression and GI motility mediated by GM has been investigated. 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 GLP-1 treatment. These findings show a possible link 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 and AGEs and RAGE are associated with DM-induced intestinal and colonic histomorphological remodeling, which is closely related to motor-sensory disorders. High glucose levels and AGEs increase the proliferation and migration of cultured colon cancer cells, which may promote cancer cell proliferation through oxidative stress and inflammation, which can cause further damage to the cellular components and contribute to malignant cell transformation. Infammation is a critical component of DM-induced target organ injury and colon cancer initiation and progression. The inflammasome regulates the microbiota and the inflammatory response of epithelial cells to the GM and the GM has been shown to be associated with GI malignancy including colonic cancer. Recent studies suggest that RAGE signaling plays an important role in colorectal tumor progression. Furthermore, AGEs may promote cancer cell proliferation through the activation of the RAGE signaling. 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. 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, however the exact mechanisms need to be explored further.
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 \(^{[234,233-254]}\), 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.

REFERENCES

1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016; 387: 1513-1530 [PMID: 27061677 DOI: 10.1016/S0140-6736(16)00168-8]
2 Seuring T, Archangeli O, Shurcke M. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. Pharmacoeconomics 2015; 33: 811-831 [PMID: 25787932 DOI: 10.2147/srep02735-015-0268-9]
3 Horowitz M, Samsom M. Gastrointestinal function in diabetes mellitus. Chichester: John Wiley & Sons, Ltd, 2004
4 Shakil A, Church RJ, Rao SS. Gastrointestinal complications of diabetes. Am Fam Physician 2008; 77: 1697-1702 [PMID: 18619079]
5 Frokjaer JB, Andersen SD, Ejskjaer N, Funch-Jensen P, Drewes AM, Gregersen H. Impaired contractility and remodeling of the upper gastrointestinal tract in diabetes mellitus type-I. World J Gastroenterol 2007; 13: 4881-4890 [PMID: 17828820 DOI: 10.3748/wjg.v13.i23.4881]
6 Brock C, Safieland E, Gunterberg V, Frokjaer JB, Lelic D, Brock B, Dimczevski G, Gregersen H, Simrén M, Drewes AM. Diabetic autonomic neuropathy affects symptom generation and brain-gut axis. Diabetes Care 2013; 36: 3698-3705 [PMID: 24026548 DOI: 10.2337/dci13-0347]
7 Yarandi SS, Srivansan S. Diabetic gastrointestinal motility disorders and the role of enteric nervous system: current status and future directions. Neurogastroenterol Motil 2014; 26: 611-624 [PMID: 24661628 DOI: 10.1111/nmo.12330]
8 Zhao J, Yang J, Gregersen H. Biomechanical and morphometric intestinal remodelling during experimental diabetes in rats. Diabetologia 2003; 46: 1688-1697 [PMID: 14593459 DOI: 10.1007/s00125-003-1233-0]
9 Zhao J, Frokjaer JB, Drewes AM, Ejskjaer N. Upper gastrointestinal sensory-motor dysfunction in diabetes mellitus. World J Gastroenterol 2006; 12: 2846-2857 [PMID: 16718008 DOI: 10.3748/wjg.v12.i8.2846]
10 Zhao J, Nakaguchi T, Gregersen H. Biomechanical and histomorphometric colon remodelling in STZ-induced diabetic rats. Dig Dis Sci 2009; 54: 1636-1642 [PMID: 18989775 DOI: 10.1007/s10620-008-0540-3]
11 Marathe CS, Rayner CK, Jones KL, Horowitz M. Novel insights into the effects of diabetes on gastric motility. Expert Rev Gastroenterol Hepatol 2016; 10: 581-593 [PMID: 26647088 DOI: 10.1586/17474124.2016.1129898]
12 Zhao J, Gregersen H. Diabetes-induced mechanophysiological changes in the esophagus. Ann N Y Acad Sci 2016; 1380: 139-154 [PMID: 27499576 DOI: 10.1111/nyas.13180]
13 Shafik AA, Ahmed IA, Shafik A, Wahdan M, Asaad S, El Neizamy E. Ileocecal junction: anatomic, histologic, radiologic and endoscopic studies with special reference to its antireflux mechanism. Surg Radiol Anat 2011; 33: 249-256 [PMID: 21184079 DOI: 10.1007/s00276-010-0762-x]
14 Wedel T, Roblick U, Gleiss J, Schiedek T, Brach HP, Kühnel W, Krammer HJ. Organization of the enteric nervous system in the human colon demonstrated by wholemount immunohistochemistry with special reference to the submucous plexus. Ann Anat 1999; 181: 327-337 [PMID: 10427369 DOI: 10.1016/S0940-9602(99)80122-8]
15 Furness JB, Callaghan BP, Rivera LR, CHO HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. Adv Exp Med Biol 2014; 817: 39-71 [PMID: 24997029 DOI: 10.1007/978-1-4939-0897-4_3]
16 Mandić P, Filipović T, Gasić M, Djiuki-Macut N, Filipović M, Bogosavljević I. Quantitative morphometric analysis of the myenteric nervous plexus ganglion structures along the human digestive tract. Vojnosanit Pregl 2016; 73: 559-565 [PMID: 27494488]
17 Rumenss J. Identification of intestinal cells of Cajal. Significance for studies of human small intestine and colon. Dan Med Bull 1994; 41: 275-293 [PMID: 7924459]
18 Streutker CJ, Huizinga JD, Driman DK, Riddell RH. Intestinal cells of Cajal in health and disease. Part I: normal ICC structure and function with associated motility disorders. Histopathology 2007; 50: 176-189 [PMID: 17222246 DOI: 10.1111/j.1365-2559.2006.02493.x]
19 Gregersen H, Orvar K, Christensen K. Biomechanical properties of duodenal wall and duodenal tone during phase I and phase II of the MMC. Am J Physiol 1992; 263: G795-G801 [PMID: 1443153]
20 Storkholm JH, Villadsen GE, Jensen SL, Gregersen H. Passive elastic wall properties in isolated guinea pig small intestine. Dig Dis Sci 1995; 40: 976-982 [PMID: 7729287 DOI: 10.1007/BF02646185]
21 Duch BU, Petersen JA, Vinter-Jensen L, Gregersen H. Elastic properties in the circumferential direction in isolated rat small intestine. Acta Physiol Scand 1996; 157: 157-163 [PMID: 8800355 DOI: 10.1046/j.1365-201X.1996.03034000.x]
22 Gao C, Arendt-Nielsen L, Liu W, Petersen P, Drewes AM, Gregersen H. Sensory and biomechanical responses to ramp-controlled distension of the human duodenum. Am J Physiol Gastrointest Liver Physiol 2003; 284: G461-G471 [PMID: 12431908 DOI: 10.1152/ajpgi.00456.2001]
23 Frokjaer JB, Andersen SD, Drewes AM, Gregersen H. Ultrasound-determined geometric and biomechanical properties of the human duodenum. Dig Dis Sci 2006; 51: 1662-1669 [PMID: 16927153 DOI: 10.1007/s10620-005-0915-x]
24 Dou Y, Zhao J, Gregersen H. Morphology and stress-strain properties along the small intestine in the rat. J Biomech Eng 2003; 125: 266-273 [PMID: 12752189 DOI: 10.1115/1.1560140]
25 Zhao J, Sha H, Zhuang FY, Gregersen H. Morphological properties and residual strain along the small intestine in rats. World J Gastroenterol 2002; 8: 312-317 [PMID: 11925615 DOI: 10.3748/wjg.v8.i2.312]
26 Gabella G, Blundell D. Gap junctions of the muscles of the small and large intestine. Cell Tissue Res 1981; 199: 469-488 [PMID: 7273110 DOI: 10.1007/BF00209987]
27 Gao C, Zhao J, Gregersen H. Histomorphometry and strain distribution in pig duodenum with reference to zero-stress state. Dig Dis Sci 2000; 45: 1500-1508 [PMID: 11009797]
28 Smith JB, Zhao JB, Du YL, Gregersen H. Time-dependent viscoelastic properties along rat small intestine. World J Gastroenterol 2005; 11: 4974-4978 [PMID: 16124048 DOI: 10.3748/wjg.v11.i32.4974]
29 Fackler K, Klein L, Hilmar A. Polarizing light microscopy of intestine and its relationship to mechanical behaviour. J Microsc 1981; 124: 305-311 [PMID: 7328641 DOI: 10.1111/j.1365-2818.1981.tb02494.x]
Zhao M et al. Diabetes-induced intestinal and colonic changes

30 Storkholm JH, Villadsen GE, Jensen SL, Gregersen H. Mechanical properties and collagen content differ between isolated guinea pig duodenum, jejunum, and distal ileum. J Dig Dis 1998; 43: 2093-2094 [PMID: 9753270]

31 Chen X, Zhao J, Gregersen H. The villi contribute to the mechanics in the guinea pig small intestine. J Biomech 2008; 41: 806-812 [PMID: 18082167 DOI: 10.1016/j.jbiomech.2007.11.007]

32 Schulze-Dehrie K. Intrinsic differences in the filling response of the guinea pig duodenum and ileum. J Lab Clin Med 1991; 117: 44-50 [PMID: 1987307]

33 Watters DA, Smith AN, Eastwood MA, Anderson KC, Elton RA. Mechanical properties of the rat colon: the effect of age, sex and different conditions of storage. J Exp Physiol 1985; 70: 151-162 [PMID: 4011826 DOI: 10.1113/expphysiol.1985.sp002887]

34 Bharucha AE, Huhmyray RD, Ferber II, Zinsmeister AR. Viscoelastic properties of the human colon. Am J Physiol Gastrointest Liver Physiol 2001; 281: G459-G466 [PMID: 11447026]

35 Gao C, Gregersen H. Biomechanical and morphological properties in rat large intestine. J Biomech 2000; 33: 1089-1097 [PMID: 10858881 DOI: 10.1016/S0021-9290(00)00667-1]

36 Frokjaer JB, Liao D, Steffensen E, Dimcevski G, Bergmann A, Drewes AM, Gregersen H. Geometric and mechanosensitivity properties of the sigmoid colon evaluated with magnetic resonance imaging. Neurogastroenterol Motil 2007; 19: 253-262 [PMID: 17391241 DOI: 10.1111/j.1365-3982.2006.00884.x]

37 Ford MJ, Camilleri M, Wiste JA, Hanson RB. Differences in colonic tone and phasic response to a meal in the transverse and sigmoid human colon. Gut 1995; 37: 264-269 [PMID: 7557579 DOI: 10.1136/gut.37.2.264]

38 Gregersen H. Biomechanics of the Gastrointestinal Tract. London: Springer-Verlag, 2000

39 Tanaka H, Hirose M, Osada T, Miwa H, Watanabe S, Sato N. Implications of mechanical stretch on wound repair of gastric smooth muscle cells in vitro. Dig Dis Sci 2000; 45: 2470-2477 [PMID: 11258577]

40 Liao D, Sevecova C, Yoshida K, Gregersen H. Viscoelastic properties of isolated rat colon smooth muscle cells. Cell Biol Int 2006; 30: 854-858 [PMID: 16815715 DOI: 10.1006/cellbi.2006.05.012]

41 Zoubi SA, McHale KM, Ford MJ. Tissue stiffness and viscoelastic response changes in colon biopsies of patients with diabetes mellitus in relation to duration and severity of the disease by use of the metal-detector test. Z Gastroenterol 1995; 33: 517-526 [PMID: 8525655]

42 Noda T, Iwakiri R, Fujimoto K, Yoshida T, Miwa H, Watanabe S, Hatanabe T, Sato N. Implications of mechanical stretch on wound repair of gastric smooth muscle cells in vitro. Dig Dis Sci 2000; 45: 2470-2477 [PMID: 11258577]

43 Falwaczyn C, Hendegger K, Volger C, Soroode J, Kühn M, Tatsch K, Landgraf R, Karbach U. Measurement of transit disorders in different gastrointestinal segments of patients with diabetes mellitus in relation to duration and severity of the disease by use of the metal-detector test. Z Gastroenterol 1995; 33: 517-526 [PMID: 8525655]

44 Reddy GK. AGE-related cross-linking of collagen is associated with aortic wall matrix stiffness in the pathogenesis of drug-induced diabetes in rats. Microvasc Res 2004; 68: 132-142 [PMID: 15313123 DOI: 10.1016/j.mvr.2004.04.002]

45 Chen PM, Gregersen H, Zhao J. Advanced glycation end-product expression is upregulated in the gastrointestinal tract of type 2 diabetic rats. World J Diabetes 2015; 6: 662-672 [PMID: 25987965 DOI: 10.4239/jwd.v6.i4.662]

46 Zhao J, Chen P, Gregersen H. Morpho-mechanical intestinal remodeling in type 2 diabetic GR rats—is it related to advanced glycation end product formation? J Biomech 2013; 46: 1128-1134 [PMID: 23403079 DOI: 10.1016/j.jbiomech.2013.01.010]
Zhao M et al. Diabetes-induced intestinal and colonic changes
factor on diabetic colonic dysmotility. World J Gastroenterol 2013; 19: 3324-3331 [PMID: 23745035 DOI: 10.3748/wjg.v19.i21.3324]

102 Sun M, Wang F, Peng P. Insulin-like growth factor-1 inhibits colonic smooth muscle cell apoptosis in diabetic rats with colonic dysmotility. Regul Pept 2014; 194-195: 41-48 [PMID: 25450576 DOI: 10.1016/j.regpep.2014.11.005]

103 Sung TS, La JH, Kang TM, Kim TW, Yang IS. Visceral Hypersensitivity and Altered Colonic Motility in Type 2 Diabetic Rat. J Neurogastroenterol Motil 2015; 21: 581-588 [PMID: 26420432 DOI: 10.5056/jnm15058]

104 Sims MA, Hasler WL, Chey WD, Kim MS, Owyang C. Hyperglycemia inhibits mechanoreceptor-mediated gastrocolic responses and colonic peristaltic reflexes in healthy humans. Gastroenterology 1995; 108: 350-359 [PMID: 10.1001/jp.1999.10161.x]

105 Chandrasekharan B, Anitha M, Blatt R, Shahnavaz N, Kooby D, Staley C, Mwangi S, Jones DP, Sitaraman SV, Srinivasan S. Colonic motor dysfunction in human diabetes is associated with enteric neuronal loss and increased oxidative stress. Neurogastroenterol Motil 2011; 23: 131-138, e26 [PMID: 20939847 DOI: 10.1111/j.1365-3329.2011.01611.x]

106 Doménech A, Pasquillini G, De Giorgio R, Gori A, Bosch P, Pumarola M, Jiménez M. Morphofunctional changes underlying intestinal dysmotility in diabetic RIP-I/hIFNβ transgenic mice. J Exp Pathol 2011; 92: 400-412 [DOI: 10.1016/j.expol.2011.07.087]

107 Wang CL, Wang X, Yu Y, Cai Y, Liu HM, Lai LH, Guo C, Liu J, Wang R. Type 1 diabetes attenuates the modulatory effects of endorphins on mouse colonic motility. Neuropeptides 2008; 42: 69-77 [PMID: 18238685 DOI: 10.1016/j.pep.2007.01.001]

108 Touw K, Chakraborty S, Zhang W, Ouboh AG, Tune JD, Gunst SJ, Hjerrig BP. Altered calcium signaling in colon smooth muscle of type 1 diabetic mice. Am J Physiol Gastrointest Liver Physiol 2012; 302: G66-G76 [PMID: 21979758 DOI: 10.1152/jappl.00183.2011]

109 Forrest A, Parsons M. The enhanced spontaneous activity of the diabetic colon is not the consequence of impaired inhibitory control mechanisms. Auton Autacoid Pharmacol 2003; 23: 149-158 [PMID: 14690489 DOI: 10.1046/j.1447-8673.2003.00290.x]

110 Forrest A, Huizinga JD, Wang XY, Liu LW, Parsons M. Increase in stretch-induced rhythmic motor activity in the diabetic rat colon is associated with loss of ICC of the submucosal plexus. Am J Physiol Gastrointest Liver Physiol 2008; 294: G315-G326 [PMID: 18006604 DOI: 10.1152/jappl.00196.2007]

111 Joneda S, Kadowaki M, Kuramoto H, Fukui H, Takaki M. Enhanced colonic peristalsis by impairment of nitricergic enteric neurons in spontaneously diabetic rats. Auton Neurosci 2001; 92: 65-71 [PMID: 11570705 DOI: 10.1016/S1566-0760(01)00317-4]

112 Xie DP, Li S, Li L, Chang WX, Xi TF, Yang X, Jin Z, Zeng Y. Beta-2arresin-2 is involved in the increase of distal colonic contraction in diabetic rats. Regul Pept 2013; 185: 29-33 [PMID: 23816471 DOI: 10.1016/j.regpep.2013.06.006]

113 Chang WX, Qin Y, Jin Z, Xi TF, Yang X, Lu ZH, Tang YP, Cai WT, Shen CJ, Xie DP. Interleukin-6 (IL-6) mediated the increased contraction of distal colon in streptozotocin-induced diabetes in rats via IL-6 receptor pathway. Int J Clin Exp Pathol 2015; 8: 4514-4524 [PMID: 26191141]

114 Frukjaer JB, Andersen SD, Ejskaer N, Funch-Jensen P, Arendt-Nielsen L, Gregersen H, Drewes AM. Gut sensations in diabetic autonomic neuropathy. Pain 2007; 131: 320-329 [PMID: 17521809 DOI: 10.1016/j.pain.2007.04.009]

115 Grabauskas G, Holdinger A, Wu X, Xu D, Zhou S, Owyang C. Diabetic visceral hypersensitivity is associated with activation of mitogen-activated kinase in rat dorsal root ganglia. Diabetes 2011; 60: 1743-1751 [PMID: 21515848 DOI: 10.2337/db11-1507]

116 Hu J, Song ZY, Zhang HH, Qin X, Hu S, Jiang X, Xu GY. Colonic Hypersensitivity and Sensitization of Voltage-gated Sodium Channels in Primary Sensory Neurons in Rats with Diabetes. J Neurogastroenterol Motil 2016; 22: 129-140 [PMID: 26459453 DOI: 10.5056/jnm15091]
development of type 1, type 2 diabetes mellitus and obesity. *Rev Endocr Metab Disord* 2015; 16: 55-65 [PMID: 26519480 DOI: 10.1007/s11154-015-9309-0]

172. **Allin KH**, Nielsen T, Pedersen O. Mechanisms in endocrinology: Gut microbiota in patients with type 2 diabetes mellitus. *Eur J Endocrinol* 2015; 172: R167-R177 [PMID: 25416725 DOI: 10.1530/EJE-14-0874]

173. **Blandino G**, Inturri R, Lazzara F, Di Rosa M, Malaguarnera L. Impact of gut microbiota on diabetes mellitus. *Diabetes Metab 2016*; 42: 303-315 [PMID: 27179626 DOI: 10.1016/j.diabet.2016.04.004]

174. **Knip M**, Siljander H. The role of the intestinal microbiota in type 1 diabetes mellitus. *Nat Rev Endocrinol* 2016; 12: 154-167 [PMID: 26729037 DOI: 10.1038/mend.2015.218]

175. **Stephen AM**, Wiggins HS, Cummings JH. Effect of changing transit time on colon microbical metabolism in man. *Gut* 1987; 28: 601-609 [PMID: 3596341 DOI: 10.1136/gut.28.5.601]

176. **Kasypeh PC**, Marcolab A, Ursell LK, Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, Tache Y, Susumu Y., Kashyap PC et al. Contribution of microbiota to the intestinal physico-chemical barrier. *Appl Environ Microbiol* 2016; 82: 295-312 [PMID: 27832485 DOI: 10.1128/AEM.0142352]

177. **Chen JY**, Yang P, Shi H, Zhang Y, Li X, Wang Y, Shi Y, Li X. Microbiota and gut hormones in diabetes. *Science* 2014; 346: 55-65 [PMID: 25619480 DOI: 10.1126/science.1256181]

178. **Kasypeh PC**, Marcolab A, Ursell LK, Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, Tache Y, Susumu Y., Kashyap PC et al. Contribution of microbiota to the intestinal physico-chemical barrier. *Appl Environ Microbiol* 2016; 82: 295-312 [PMID: 27832485 DOI: 10.1128/AEM.0142352]

179. **Savidge TC**. Microbiota and gut hormones in diabetes. *Science* 2014; 346: 55-65 [PMID: 25619480 DOI: 10.1126/science.1256181]

180. **Kasypeh PC**, Marcolab A, Ursell LK, Larauche M, Duboc H, Earle KA, Sonnenburg ED, Ferreyra JA, Higginbottom SK, Million M, Tache Y, Susumu Y., Kashyap PC et al. Contribution of microbiota to the intestinal physico-chemical barrier. *Appl Environ Microbiol* 2016; 82: 295-312 [PMID: 27832485 DOI: 10.1128/AEM.0142352]
for colorectal cancer. Dig Dis Sci 2012; 57: 1586-1597 [PMID: 22320244 DOI: 10.1007/s10620-012-2059-x]

Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. Nut consumption and risk of cancer and type 2 diabetes: a systematic review and meta-analysis. Nutr Rev 2015; 73: 49-425 [PMID: 26081452 DOI: 10.1093/nutri/nvu006]

Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. World J Gastroenterol 2015; 21: 6026-6031 [PMID: 26019469 DOI: 10.3748/wjg.v21.i9.6026]

Omran S, Ismail AA. Knowledge and beliefs of Jordanians toward colorectal cancer screening. Cancer Nurs 2010; 33: 141-148 [PMID: 20145539 DOI: 10.1097/NON.0b013e31812f2213]
Zhao M et al. Diabetes-induced intestinal and colonic changes

potential molecular mechanisms and therapeutic implications. Oncotarget 2017; 8: 18456-18485 [PMID: 28060743 DOI: 10.18632/oncotarget.14472]

238 Forootan M, Tabatabaeefar M, Yahyaei M, Maghsoudi N. Metabolic syndrome and colorectal cancer: a cross-sectional survey. Asian Pac J Cancer Prev 2012; 13: 4999-5002 [PMID: 23244098 DOI: 10.7314/APJCP.2012.13.8.4999]

239 Ishino K, Mutoh M, Totsuka Y, Nakagama H. Metabolic syndrome: a novel high-risk state for colorectal cancer. Cancer Lett 2013; 334: 56-61 [PMID: 23085100 DOI: 10.1016/j.canlet.2012.10.012]

240 Ulaganathan V, Kandiah M, Zalilah MS, Faizal JA, Fijerad M. Association of thiazolidinediones with liver cancer and colorectal cancer agents. Diabetes Res 2015; 108: e116-e122 [PMID: 25414939 DOI: 10.1016/j.diabres.2014.12.013]

241 Marks AR, Pietrofesa RA, Jensen CD, Zebrowski A, Corley DA, Doubeni CA. Metformin use and risk of colorectal adenoma after polypectomy in patients with type 2 diabetes mellitus. Cancer Epidemiol Biomarkers Prev 2015; 14: 1692-1698 [PMID: 26737195 DOI: 10.1158/1055-9966.EPI-15-0559]

242 Koehler JA, Kain T, Drucker DJ. Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Endocrinology 2011; 152: 3362-3372 [PMID: 21771884 DOI: 10.1210/en.2011-1201]

243 Kissow H, Hartmann B, Holst JJ, Víly NE, Hansen LS, Rosenkilde MM, Hare KJ, Poulsen SS. Glucagon-like peptide-1 (GLP-1) receptor agonism or DPP-4 inhibition does not accelerate neoplasia in carcinogen treated mice. Regul Pept 2012; 179: 91-100 [PMID: 22989472 DOI: 10.1016/j.regpep.2012.08.016]

244 Bae S, Wong HL, Lee J, Desai J, Field K, Kosmider S, Fourlanos S, Jones I, Skinner I, Gibbs P. Impact of Diabetes Status and Medication on Presentation, Treatment, and Outcome of Stage II Colon Cancer Patients. J Cancer Epidemiol 2015; 2015: 189132 [PMID: 26074965 DOI: 10.1155/2015/189132]

245 Min XH, Yu T, Qing Q, Yuan YH, Zhong W, Chen GC, Zhao LN, Deng N, Zhang LF, Chen QK. Abnormal differentiation of intestinal epithelium and intestinal barrier dysfunction in diabetic mice associated with depressed Notch/NICD transduction in Notch/ Hes1 signal pathway. Cell Biol Int 2014; 38: 1194-1204 [PMID: 24890925 DOI: 10.1002/cbin.10323]

246 Charlton M, Ahlman B, Nair KS. The effect of insulin on human small intestinal mucosal protein synthesis. Gastroenterology 2000; 118: 299-306 [PMID: 10648548 DOI: 10.1053/gast.2001.22332]

247 Adeghate E, Onyewu AS, Sharma AK, El-Sharkawy T, Donath T. Diabetes mellitus is associated with a decrease in vasoactive intestinal polypeptide content of gastrointestinal tract of rat. Arch Physiol Biochem 2001; 109: 246-251 [PMID: 11880929 DOI: 10.1076/apab.109.3.246.11578]

248 Miranda-Castillo MT, Guinovart J, Planas JM. Sodium tungstate decreases sucrase and N- and D-glucose cotransporters in the jejum of diabetic rats. Am J Physiol Gastrointest Liver Physiol 2008; 295: G479-G484 [PMID: 18617558 DOI: 10.1152/ajpgi.00566.2007]

249 El-Salhy M, Spargias A. Substance P in the gastrointestinal tract of non-obese diabetic mice. Scand J Gastroenterol 1998; 33: 394-400 [PMID: 9605261]

250 Adeghate E, al-Ramadi B, Saleh AM, Vijayaraseathy C, Ponser AS, Arrafat K, Howarth FC, El-Sharkawy T. Increase in neuronal nitric oxide synthase content of the gastrointestinal tract of diabetic rats. Cell Mol Life Sci 2003; 60: 1172-1179 [PMID: 12861383 DOI: 10.1007/s00018-003-2298-2]

251 Spargias A, Forsgren S, El-Salhy M. Effect of diabetic state on co-localization of substance P and serotonin in the gut in animal models. Histol Histopathol 2001; 16: 393-398 [PMID: 1133294]

252 Jeyabal PV, Kumar R, Gangula PR, Micci MA, Pasricha PJ. Inhibitors of advanced glycation end-products prevent loss of enteric neuronal nitric oxide synthase in diabetic rats. Neurogastroenterol Motil 2008; 20: 253-261 [PMID: 17971026 DOI: 10.1111/j.1365-2982.2007.01018.x]

253 Clark HB, Schmidt RE. Identification of dystrophic sympathetic axons in experimental diabetic autonomic neuropathy. Brain Res 1984; 293: 390-395 [PMID: 6230137 DOI: 10.1016/0006-8993(84)91256-2]

254 Spangenberg A, el-Salhy M. Myenteric plexus in the gastrointestinal tract of non-obese diabetic mice. Histol Histopathol 1998; 13: 899-904 [PMID: 9810493]

255 Izbicki F, Wittmann T, Rosztoczy A, Linke N, Bödi N, Fekete E, Bagyánszki M. Immediate insulin treatment prevents gut motility alterations and loss of nitricergic neurons in the ileum and colon of rats with streptozotocin-induced diabetes. Diabetes Res Clin Pract 2003; 61: 159-167 [PMID: 12998020 DOI: 10.1016/s0168-8226(03)00216-1]

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Clin Pract 2008; 80: 192-198 [PMID: 18242757 DOI: 10.1016/j.diabetes.2007.12.013]

271 Hernandes L, Bazotte RB, Gama P, Miranda-Neto MH. Streptozotocin-induced diabetes duration is important to determine changes in the number and basophilia of myenteric neurons. *Arq Neuropsiquiatr* 2000; 58: 1035-1039 [PMID: 11105070 DOI: 10.1590/S0004-282X2000000600010]

272 Pereira MA, Bagatin MC, Zanoni JN. Effects of the ascorbic acid supplementation on NADH-diaphorase myenteric neurons in the duodenum of diabetic rats. *Biocell* 2006; 30: 295-300 [PMID: 16972554]

273 Tronchini EA, Trevizan AR, Tashima CM, Pereira RV, Zanoni JN. Supplementation with 0.1% and 2% vitamin E in diabetic rats: analysis of myenteric neurons immunostained for myosin-V and nNOS in the jejunum. *Arq Gastroenterol* 2012; 49: 284-290 [PMID: 23329224 DOI: 10.1590/S0004-28032012000400010]

274 Rauma J, Spångeus A, El-Salhy M. Ghrelin cell density in the gastrointestinal tracts of animal models of human diabetes. *Histol Histopathol* 2006; 21: 1-5 [PMID: 16267781]

275 Miller SM, Narasimhan RA, Schmalz PF, Soffer EE, Walsh RM, Krishnamurthi V, Pasricha PI, Szurszewski JH, Farrugia G. Distribution of interstitial cells of Cajal and nitricergic neurons in normal and diabetic human appendix. *Neurogastroenterol Motil* 2008; 20: 349-357 [PMID: 18069951 DOI: 10.1111/j.1365-2982.2007.01040.x]

276 Kandemir O, Utas C, Gönen O, Patiroğlu TE, Ozbek O, Kestemir F, Yücesoy M. Colonic subepithelial collagenous thickening in diabetic patients. *Dis Colon Rectum* 1995; 38: 1097-1100 [PMID: 7555427 DOI: 10.1007/BF02133986]

277 Unal A, Guven K, Yurci A, Torun E, Gursoy S, Baskol M, Oztürk F, Arşav V. Is increased colon subepithelial collagen layer thickness in diabetic patients related to collagenous colitis? An immunohistochemical study. *Pathol Res Pract* 2008; 204: 537-544 [PMID: 18423894 DOI: 10.1016/j.prp.2008.02.004]

278 Spångeus A, El-Salhy M. Large intestinal endocrine cells in non-obese diabetic mice. *J Diabetes Complications* 1998; 12: 321-327 [PMID: 9877466]

279 Du F, Wang L, Qian W, Liu S. Loss of enteric neurons accompanied by decreased expression of GDNF and PI3K/Akt pathway in diabetic rats. *Neurogastroenterol Motil* 2009; 21: 1229-e114 [PMID: 19709371 DOI: 10.1111/j.1365-2982.2009.01379.x]

280 Nakahara M, Isezaki K, Hirota S, Vanderwinden JM, Takakura R, Kimoshita K, Miyagawa J, Chen H, Miyazaki Y, Kiyohara T, Shinomura Y, Matsuzawa Y. Deficiency of KIT-positive cells in the colon of patients with diabetes mellitus. *J Gastroenterol Hepatol* 2002; 17: 666-670 [PMID: 12106611 DOI: 10.1046/j.1440-1746.2002.02756.x]

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