Effects of dietary changes on intestinal biomechanical properties

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The gastrointestinal (GI) tract is an important part of the human digestive system, which plays a role in transporting, digesting, and absorbing food. Food can be mixed, grinded, absorbed, and excreted by GI peristalsis. Many factors can affect the GI histomorphology and mechanical properties. For example, the changes in diet can affect the GI tract microbiota and intestinal homeostasis. Then the GI histomorphology and biomechanical characteristics can be remodeled. Furthermore, by studying the mechanical properties of the intestinal wall under dietary changes, we can better study the remodeling of the GI structure and biomechanical characteristics. The purpose of this review was to provide a panorama on diet-induced biomechanical properties remodeling of intestine, with particular focus to the recent advances in this field. The normal, aging, diet-induced intestinal structure and biomechanical properties, and some common research methods of intestinal biomechanics were discussed with their roles on GI other functions.

Keywords: Gastrointestinal tract; biomechanics; intestine; diet change; remodeling.

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Introduction

The gastrointestinal (GI) tract is an important system of human being. It is a muscular duct including esophagus, stomach, small intestine, large intestine, *etc*. Food can be mixed, grinded, absorbed, and excreted by GI tract. The intestinal structure and function are always affected by many factors, such as disease, growth, and aging [1]. Common diseases include irritable bowel syndrome (IBS) [2, 3], diabetes [4-7], Parkinson's disease [8], diverticulosis [9]. With the age increase, the aging phenomenon on the body will show. This age-mediated influence not only affects the physiology and function of the intestine, but also further reconstructs the pharmacokinetics of the drug. Age-mediated factor is also the main cause of GI diseases in the elderly [10]. Studies have shown that aging intestinal cells demonstrate different cellular and molecular changes and aging intestinal smooth muscle cells demonstrate many changes in signal transduction pathways that regulate contraction. Aging enteric neurons have been shown to exhibit phenotypes associated with aging [11-14]. The pattern of daily diet also has a profound effect on the GI tract. Abnormal or irregular eating patterns can make the cells' spontaneous circadian rhythm and the periodic expression of key metabolic regulators uncordially, leading to obesity and metabolic disorders [15]. Eating patterns can also affect the gut microbiome. When diet changes, the gut microbiota can respond quickly [16, 17]. These changes can also cause an impact on the immune system [18]. Some researchers have found that increasing the dietary fiber intake of children can alleviate the symptoms of recurrent abdominal pain in children [19]. After increasing the high protein content of the diet, the selected α-taste and αtransducer cell subsets in different regions of the pig's GI tract were up-regulated [20, 21]. Dietary intake is related to many factors, such as folk culture, regional customs, behavioral diseases. When the diet changes, it will inevitably affect the digestive system.

At present, research on the influence of diet on intestinal immune function, microbiota or cells is very popular. However, there are few studies on the influence of dietary structure changes on intestinal biomechanics. This review is to describe the influence of dietary structure on the morphological and biomechanical properties of the intestine.

Intestinal structure and biomechanical properties

The main functions of the intestine include secretion, digestion, absorption, and movement. The intestinal wall has a layered structure, which, from the inside to the outside, is the mucosal layer, submucosal layer, muscle layer, and serosal layer (Figure 1). The mucosal layer is mainly composed of epithelium, connective and muscle tissue, with the main function of transporting dissolved substances from the lumen of the digestive tract to the blood circulatory system. The submucosa is almost made by connective tissue. It contains a variety of small cells with general maintenance and immune functions. The submucosa also contains neural networks and small blood vessels that feed the mucosal layer. The muscular layer includes several layers of muscle fibers, and the arrangement direction of the muscle fibers in each layer is different. Most digestive organs have two layers of muscles with inner circular muscles and outer longitudinal muscles. Between the circular muscle and the longitudinal muscles, there is a neural network (myenteric plexus). The serosa is a layer of connective tissue that forms the outer layer of the digestive organs. Inside the wall of the digestive tract, the enteric nervous system is a unique and complex nervous system, which is independent of the central nervous system to some extent [22].

The intestinal lumen can spontaneously respond to external stimulation through rhythmic deformation, which is an important functional mechanical response of the intestine. The intestine can drive the transport of its contents and the mixing with liquid through the deformation of the intestinal wall (Figure 2). Another important functional mechanical response is controlled sphincter contraction, including the lower esophageal sphincter, Ileocecal sphincter, pyloric sphincter, and external anal sphincter. By changing the force of opening the lumen of the sphincter, the fluid delivery process through the sphincter is controlled. The reason for the fluid movement that occurs during transportation and mixing is that the mechanical force balance between the food bolus (or chyme) and the intestinal wall muscles has changed, similar to the solid-fluid interaction. With the aid of physical means, the balance relationship between viscous force/stress, pressure/stress, and acceleration of fluid and material elements is quantitatively described through mathematical forms, thereby describing the mechanical properties of the intestine [23-25].

Common research methods of intestinal biomechanics

When stimulated by an external force, the intestinal lumen responds to it through rhythmic deformation, which will cause changes in the local pressure inside the cavity. Complete and accurate recording of these pressure changes can better understand the motor function of the intestine [26-28]. The common research methods for studying the intestinal biomechanical properties are the manometry [29-32], the tensile experiment (uniaxial, biaxial, and triaxial mechanics experimental methods) [33, 34], the balloon expansion technology and impedance measurement area technology [35-37]. Figure 3

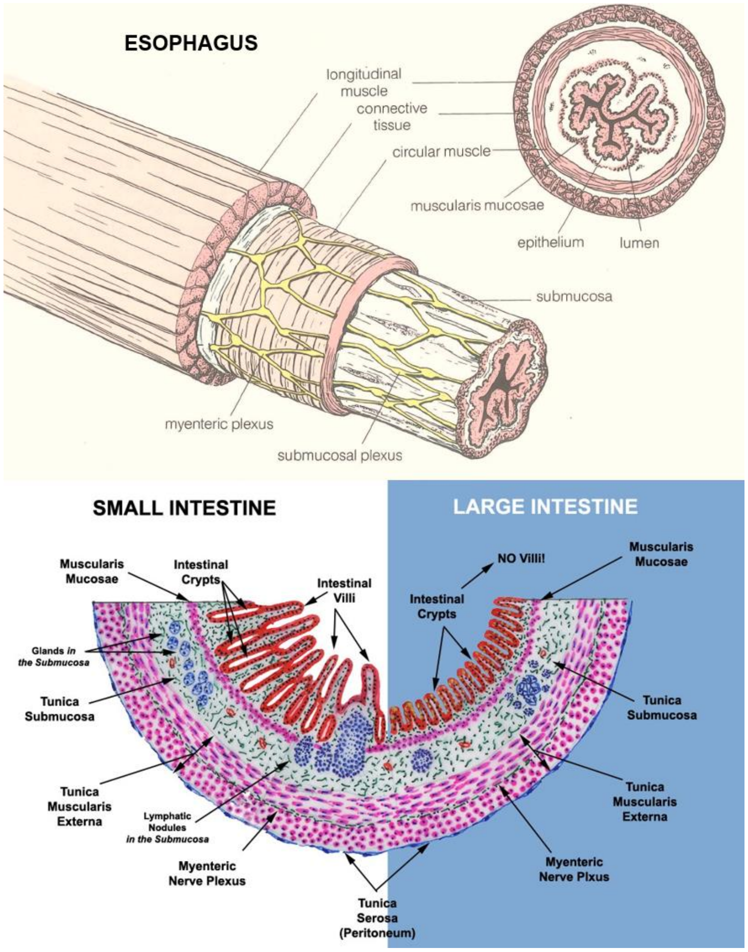

Figure 1. The basic structure of ecsophagus, small, and large intestines. The GI tract's wall is a laminar structure with four layers including mucosa, submucosa, muscle, and serosal layer typically. These layers constitute different kinds of tissues including muscle, connective tissue, nerves, and epithelium [28].

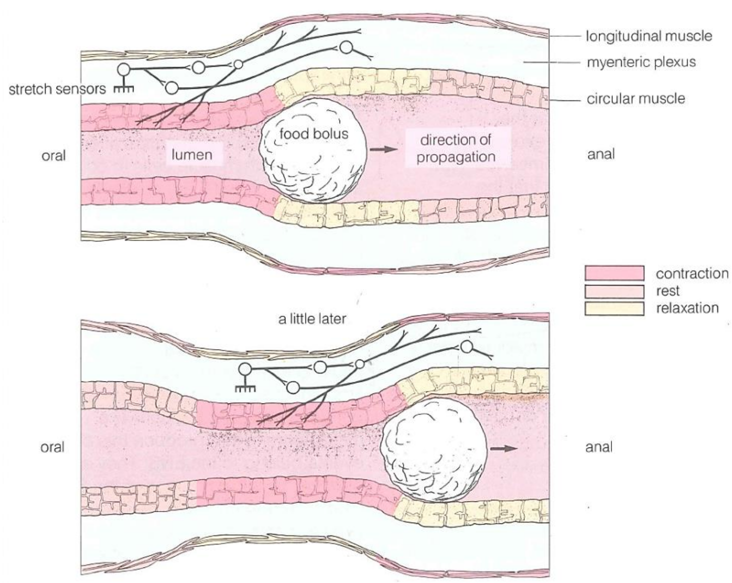

Figure 2. A peristaltic contraction wave is propagated through a segment of the interstine [22].

A

B

C

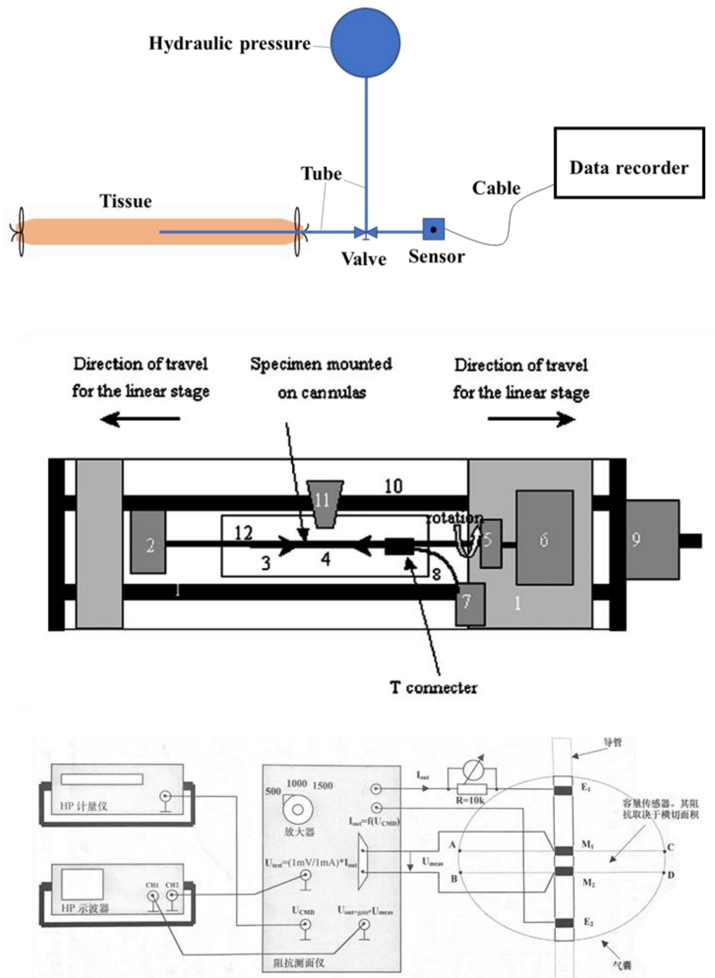

Figure 3. **A**: Typical schematic diagram of manometry device. **B**: Typical schematic diagram of tensile testing device [47]. **C**: The diagram of the balloon and the impedance measurement [47].

shows the general description of these three common research methods.

Uniaxial experiments are often used for the pharmacological study of the properties of GI smooth muscle, and also for the mechanical properties of various layers of smooth muscle tissues, such as circular muscles and longitudinal muscles [33, 34]. Comparing to uniaxial experiments, biaxial or triaxial experiments can obtain more specific stress-strain relationships, which can provide complete information for establishing tissue constitutive equations. Biaxial experiments are often used in intestinal tissue expansion-tension experiments to detect the circumferential and longitudinal deformation characteristics of the intestinal wall structure, and then, using the stress-strain analysis method analysing the biomechanical properties of the tissue. The triaxial experiment is similar to the biaxial experiment. It can not only apply force and displacement stimulation to the tissue in the two orthogonal directions of the circumferential and longitudinal directions, but also can test the torsion of the cavity tissue, such as intestine, blood vessel, and so on. This can provide complete expansibility, extensibility, and shear comprehensive information for establishing the constitutive equation of GI tissue.

Balloon expansion technology is mainly used in the study of the biomechanical properties of cavity-like tissues to measure the pressure, volume, and cross-sectional area of the cavity. With reference to these data, the corresponding stress-strain relationship curve can be drawn to obtain the biomechanical properties of the tissue [35]. Impedance area measurement technology, also known as space tilt principle, four-electrode technology. Its basic principle is Ohm's law, which calculates the cross-sectional area (CSA) by measuring electrical impedance [36, 37]. In clinical practice, the balloon expansion method is often used in combination with impedance measurement technology and intracavitary ultrasound technology for the diagnosis and treatment of diseases, such as non-cardiogenic chest pain, atherosclerosis, esophageal varices bleeding, achalasia, *etc*. [38-40]. Figure 3C shows an example of the combined use of the balloon expansion method and impedance measurement technology. Now scholars have established some new biomechanics research methods, which have been well applied in clinical practice [41-46].

Growth and remodeling of GI tract

The intestinal mechanical function is mainly to drive the transportation of its contents and the mixing of contents and liquid through deformation. Mechanical force is the main determinant of organizational behavior and may be the most important factor affecting tissue growth and reconstruction. The dynamic characteristics of the intact organ can reflect the state of the tissue structure, which can determine whether the function of the organ is in a normal or abnormal state. For example, in obstructive diseases, the structure of the tube wall has changed, and this change makes the stress adaptive [48, 49]. Because biological tissue contains a lot of water, the tissue has the mechanical properties of solid and viscous liquid including large deformation, nonlinearity, heterogeneity, anisotropy, *etc*., and it is time dependent. Therefore, when studying the adaptability of the intestine to mechanical forces, it should be carried out from two aspects, the tissue’s biomechanical and morphological properties.

Esophagus is a multi-layered, anisotropic, tube-like tissue with mobility, which causes large deformation through its viscoelasticity and softening behavior, thereby pushing the food in its inner cavity to the stomach and intestines for digestion and absorption [50-52]. With the increase of age, the esophagus will experience senescence, which is manifested as the weakening of chemosensitivity and mechanical sensitivity [53]. Studies showed that the morphological parameters of the aging rat esophagus changed with larger lumen and decreased expansion angle while its circumferential and longitudinal stiffness increased significantly. The diabetic rats’ esophagus biomechanical properties were also remodeled in each structural layer [54]. The esophagus of patients with systemic sclerosis manifested as an increase in the cross-sectional area of the terminal lumen and impaired normal peristaltic function [55]. The above evidence showed that the growth and reconstruction of the esophagus could lead to changes in esophageal mechanosensation and function.

The small intestine and large intestine, like the esophagus, also have an impact on its own mechanical sensation and function during the process of growth and reconstruction. The small intestine is the main place to digest and absorb food. As the rat grows, the unit wet weight and cross-sectional area of the small intestine increase, while the expansion angle decreases. Stress-strain analysis showed that the hardness of the small intestine in the early stage was greater than that in the later stage [56, 57]. In some disease models, the morphology and biomechanics of the small and large intestines were also reconstructed. Morphologically, the intestinal weight, mucosal wall area, and thickness of each layer in the diabetic rats’ small intestine increased. The circumferential and longitudinal stiffness of the intestinal wall increased in biomechanics, and its viscoelasticity also changed significantly [58-60]. This phenomenon also exists in small bowel obstruction. The high-stress area at the proximal end of the obstruction appears to thicken the tube wall and increase the amount of collagen, which directly leads to the change of the elastic modulus of the intestinal tissue [61]. In the diabetic rat model, the large intestine was also rebuilt like the small intestine. The circumferential stiffness of large intestine wall increased with the unit wet weight and the thickness of each layer of the intestinal wall increased too [62]. Although the cause of diverticulosis that occurs in the large intestine is still unclear, the diverticulum is a morphological manifestation of smooth muscle hypertrophy. Comparing to the normal large intestine, the abnormal large intestine shows higher intraluminal pressure when it contracts, which indicates that the motor function of the abnormal large intestine is significantly stronger than that of the normal large intestine. It can be inferred that the diverticulum on the intestinal wall is likely to be formed due to excessive intraluminal pressure squeezing the intestinal wall. When the intestine grows and rebuilds, the structure of the intestinal sensitive nerve fiber ends and the biomechanical environment are also changed [63]. By measuring the contraction response of the intestine to external stimuli, the sensitivity and strength of the intestine and the frequency of slow waves in the digestive tract can also be understood.

In summary, the intestinal tract will undergo morphological and biomechanical reconstruction due to its own growth, disease, and aging. With the aid of physics, mathematics, biology, and other means, these changes can be quantified and analyzed to obtain biomechanical parameters. These parameters can help us to further study the pathological and physiological mechanisms of intestinal diseases [64, 65].

Effect of diet on intestinal biomechanics

Diet will affect not only the microbiota and immune function in the intestine, but also the mechanical properties of the intestine. The intestinal tract digests and absorbs its contents through peristalsis, and the peristaltic process depends on the mechanical properties of the intestinal wall.

Hunger is a common natural phenomenon and part of animal survival. Hunger occurs when food is scarce. In clinical practice, patients who fast after surgery, suffer from anorexia, or restrict eating due to self-enforcement can also experience hunger. During fasting, the body will be in a negative-nitrogen balance, metabolic changes, and/or weight loss [66]. Similar to the adaptation conditions for partial intestinal ulcer resection, the structure and function of the intestine will also be adjusted during fasting [67]. Researchers have studied the changes in biomechanical properties induced by fasting. The results showed that the body weight of the rats was significantly reduced after starvation. Morphometric indicators such as tube wall thickness, circumference, area, *etc*. in the fasting state were significantly reduced. Opening angle in the zero-stress state was also significantly reduced in the fasting state. The surface residual strain of the jejunum and ileum increased under starvation, while no change ws observed in the duodenum. The stress-strain curve of the three sections of small intestine shifted to the right under fasting, which indicated that the stiffness of the circumferential and longitudinal intestinal walls decreased under fasting [68]. Under fasting, the intestinal tract will be rebuilt significantly. This is similar to the results of intestinal remodeling produced by the low-protein intake model [69]. The histological results and the stress-strain curves are shown in Figure 4.

Lately we found that the biomechanical and histomorphological properties in rabbits' small intestine would change after low fiber diet feeding. It was shown as the thickness of intestinal wall, collagen content, and the softness of intestinal wall were decreased [70]. Histological data showed that the main reason for intestinal remodeling was caused by the mucosal layer thinning. Furthermore, comparing

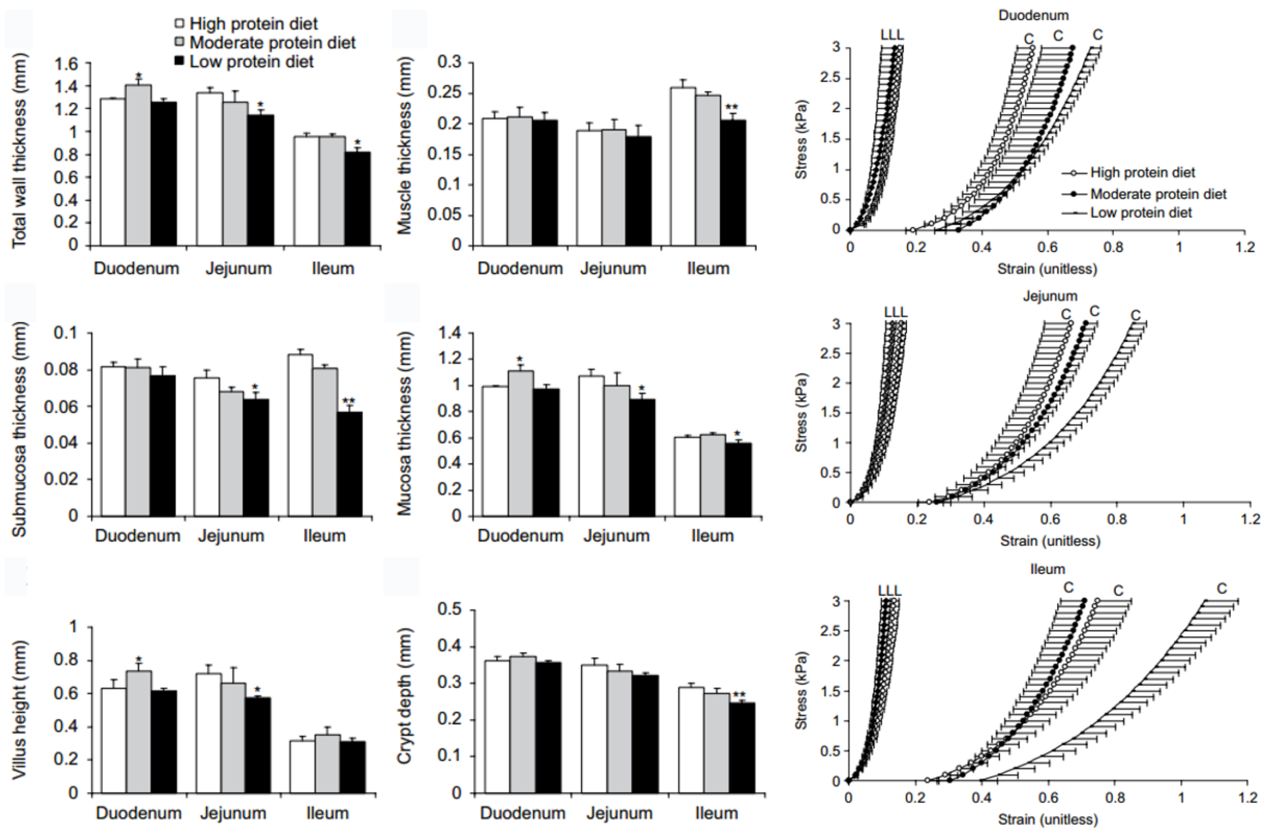

Figure 4. The histology data (left side) and the small intestinal stress-strain curves (right side) after feeding the minks with high, moderate, and low protein diets. The total wall thickness of the low protein group was smaller than that of other two groups. The reason was the decrease in the thickness of the submucosa and mucous layer. The circumferential stress-strain curves of all the small intestine from the low protein group moved to the left, indicating that the wall of the intestine became soft circumferentially. There is no difference in longitudinal direction (L: longitudinal; C: circumferential) [69].

to the control group, the stress-strain curve of the small intestine fed with low-fiber diet moved to the right, which indicated that the wall of the small intestine was softened. Correlation analysis showed that the intestinal wall softening was related to the decrease of intestinal wall thickness and intestinal wall area. Similar results also observed during the three-month long-term breeding [71].

The histomorphological and biomechanical remodeling will affect the environment of structure and biomechanics, where the sensitivity nerve fiber endings in GI tract are exposed and the sensitivity of those nerve endings may be changed [72, 73]. In addition, the low fiber diet for a long time resulted in the decrease of muscle layer thickness, which may possibly affect the muscular contraction force [74]. Our team found that the low fiber diet could change not only the intestinal contraction thresholds and amplitude but also the frequencies, particularly the mechanical stress and strain parameters were outstanding [75, 76].

Conclusions and perspectives

Food composition changes are very common among the health, psychological disorders, and diseases. The diet structure is very important to the intestine, which not only affects the intestinal homeostasis, but also affects the structure and function [77]. As discussed above, lots of biomechanical changes occur in the intestine. Just like dimensions, passive and active tissue properties change. The relationship among these changes is very complicated. It needs the scientific foundation in order to be fully explored. Dietary changes are common in healthy people and diseased patients. The reconstruction of tissue morphology and biomechanical properties caused by diet may affect intestinal function in different ways. The process of intestinal reconstruction can cause significant changes in the thickness of each layer of the intestinal wall, thereby weakening muscle function, and affecting the mechanical sensitivity of the intestine by changing the position of the mechanosensory afferent nerve in the intestinal wall. Therefore, it can be inferred that changes in digestive tract function are related to changes in diet. Dietary changes may cause many other changes, such as intestinal epithelial cells, intestinal microbial structure, and physiological structure. This review covers the relationship between dietary changes and changes in intestinal physiology.

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