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Research Article

Managing Motility Disorders of the Antro-Pyloro-Duodenal Segment: A Biomedical Engineering Perspective

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1. Abstract

The antrum, pylorus and duodenum form a dynamic segment of the upper gut that plays a central role in digestion. If the segment fails to function in a normal manner, it may lead to motility disorders causing diseases such as functional dyspepsia (FD), gastroparesis, dumping syndrome and intestinal pseudo-motility; which affects both the children and adolescents. These disorders markedly impair the quality of life of an individual. Rise in the epidemics of functional GI disorders have been an increasing concern, esp. due to the lack of an established etiology and cure. Since the pathophysiology is poorly understood, treatment modalities are mainly used to manage the symptoms. Treatment options have their own challenges such as difficulty in dietary control and life style changes, side-effects of prokinetic drugs, and surgical intervention. Electrical stimulation as a treatment modality is debatable. Developing an effective treatment option has been a challenge, possibly due to the lack of clear insights into the mechanisms involved. The purpose of this review is to critically assess the reasons as to why the treatments were ineffective, what are the underlying mechanisms involved in the etiology and how to facilitate the development of an effective treatment modality for the motility disorders of the APD segment.

3. Abbreviations: AP: Antro-Pylorus; APD:Antro-Pyloro-Duodenal; BER: Basic Electrical Rhythmicity; CNS: Central Nervous System; DBP: Duodeno-Biliary-Panceratic; EGG: Electrogastrography; ENS: Enteric Nervous System; Functional Gastrointestinal Disorders; FODMAP: Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols; GLP: Glucagon-Like Peptide; HRM: High Resolution Manometry; IBS: Irritable Bowel Syndrome; IPPW: Isolated Pyloric Pressure Waves; MRI: Magnetic Resonance Imaging; MMC: Multichannel Intraluminal Impedance; MII: Multichannel Intraluminal Impedance; PD: Pyloro-Duodenal; SBS: Short Bowel Syndrome; SIBO: Small Intestinal Bacterial Overgrowth; PD:Pyloro-Duodenal; SBS: Short Bowel Syndrome; SIBO: Small Intestinal Bacterial Overgrowth

4. Introduction

Antro-Pyloro-Duodenal (APD) segment is a part of the gastrointestinal tract that plays a key role in the digestion. They participate in the digestive process such as- 1) grinding of meal in antrum (the distal part of the stomach), valvular mechanism to control the flow of luminal contents through pylorus, and, mixing and transit of the contents in the duodenum. Studies indicate that the APD performs such complex task by interacting with a milieu of systems such as Central Nervous System (CNS), Enteric Nervous System (ENS), neurohormonal cues and other factors (such as stress). However during diseased condition they happen to demolish such integrity. It has been found that the motility disorders of the APD segment can lead to various diseases such as Functional Dyspepsia (FD), gastroparesis, dumping syndrome and intestinal pseudo-motility; which affects both the children (prevalence of 3-27% for FD) [1] and adolescents (10-30% for FC) [2]. These disorders markedly impair the quality of life of an individual. For example, in functional dyspepsia, the patient suffers from an early satiation, postprandial fullness, epigastric pain and epigastric burning without any organic, systemic or metabolic disease [3,4]. Due to limited treatment op-

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tions for functional dyspepsia, as no drugs were effective, the patients have to continue with the symptoms for the rest of life[5]. Managing such patients continues to be a challenge. According to the Boronat et al. *"during the last years, the burden of FGIDs is rising, but no biomarkers or gold standard tests are available to date for diagnosing gastrointestinal (GI) disorders without an established etiology"* [6]. It is believed that the FD is associated with the abnormalities in the GI motility patterns such as the impaired accommodation to a meal, antral hypomotility, gastric and duodenojejunaldysmotility [7-10]. This suggests that there exists an interaction between the motility and GI physiology. Yamawaki et al. emphasizes the role of gut-brain axis in his article as follows, *"Rome IV criteria defined that the diagnosis of functional dyspepsia required bothersome clinical symptoms, and the brain–gut axis was acknowledged as an important factor in the etiology of functional GI disorders"* [11].

Considering the complex regulating mechanisms involved in the APD physiology, we review the state of art in the area with specific focus on the exploring the underlying mechanisms to devise better treatment modalities. The review is structured as follows, 1) firstly we first discuss the digestive function of the APD segment from a biomedical perspective; emphasizing the necessity of engineering principles involved in digestion. Considered next is the role of gut-brain axis in the APD physiology, where, we discuss as to how the gut and brain communicates with each other through various channels such as neural, hormonal and others. Since the meal is known to be major determinant of the gut motility, we explore the state of art in the meal specific responses of the motor patterns that are elicited during various experiments performed by the authors. In conclusion, we describe the current perspectives on the patient management and treatment modalities of the APD motility disorder.

4.1.The Digestion: The Biomechanical Perspective

The Antro-Pyloro-Duodenal (APD) segment of human gastrointestinal tract performs a series of complex processes which help in breakdown of food (antrum), control of flow into the duodenum (pylorus), mixing with the Duodeno-Biliary-Pancreatic (DBP) secretion and chemical breakdown, absorption, and transport to the lower segments of the intestine (duodenum) [12]. The process is mechanical in nature and driven by the APD motility. In physiology, the APD segment is known to elicit different types of contraction pattern upon duodenal meal infusion that includes - gastric peristalsis/antral contraction wave, segmental contraction of the antrum, pyloric contraction, intestinal peristalsis, retroperistalsis of the intestine or antiperistalsis, standing contractions/ stationary waves, stationary segmental contraction of the small intestine/ cluster stationary contractions, migrating segmental contraction of the small intestine/ cluster migrating contractions, sleeve contraction/pendular movements, and Migrating Motor Complex (MMC). The characteristics and physiological function of these contractions are mentioned in the (Table 1).

In physiology, the transport of food occurs from the stomach to the duodenum (gastric emptying), however, due to reasons unknown, it can also lead to the backward flow of Duodenal Content (DGR). The process can be visualized from a biomechanics point of view as follows. The transport of fluid is a effect that is driven by the movement of the APD wall. As the wall moves, it bears an amount of momentum that is ready to be transferred to an adjacent fluid particle. With wall a motion, the momentum is dissipated continuously to the nearby fluid that later on transfers to its adjacent fluid particles. The process gradually leads to the generation of flows patterns that can cause transport (forward or backward) or mixing. Here we establish that the physiological behaviour of the APD segment, that is, APD motility is intertwined to the APD physiology. This suggests that the digestive capacity of the APD is driven by the flows developed in the lumen that are a reflection of the APD motility.

4.2. How Motility Disorder Affects the Digestion?

Contractions of the stomach, pylorus and upper intestine have direct influence on the physiological process of digestion that include -grinding and churning of the contents with gastric secretions in stomach and the Duodeno-Biliary-Pancreatic (DBP) secretions in duodenum. They also influence the absorption and transit to lower bowels. For the gut to perform its normal physiological function it needs to elicit appropriate contractions; otherwise, it can lead to abnormalities in digestion. For example, motility disorders of the stomach can lead to Gastroparesis (delayed gastric emptying), Dumping syndrome (rapid gastric emptying), and Functional dyspepsia (abdominal discomfort arising from functional loss of sensory and motility abnormalities) [13]. Similarly, the motility dysfunctions of the small intestine can lead to disorders such as the duodenal ulcer, intestinal pseudo-obstruction, Small Intestinal Bacterial Overgrowth (SIBO), Irritable Bowel Syndrome (IBS), and Short Bowel Syndrome (SBS). Pathologies of the small intestine do not arise directly but they occur in an indirect way that happens to change the normal motility patterns. If one assumes that contractions are the driving factors responsible for causing digestion in normal physiology, then, when they are abolished (due to some reasons) they will lead to stagnation of the contents over a gastrointestinal segment which increases the chance of bacterial colonization. For e.g., the low volumes of the bicarbonate secretion can influence the viscosity of the small intestinal luminal contents which in turn slows the transit and facilitate for bacterial overgrowth [14]. Using a wire-

less motility capsule it has become possible to study dynamics of pH profile in the proximal intestine and the nature of gastrointestinal transit profile [15]. Depending on the buffering capacity of the pancreas, pH in the duodenal lumen is directly influenced and part from the duodenal motility; stagnation increases the chances of duodenal ulceration. Further, if the contractions are abolished then it may also lead to the occurrence of duodenal ulcers which in turn can result in improper flushing of the duodenal lumen with alkaline secretions. Abnormalities can also result from motility disorders of the small intestine showing its influence right up to the stomach, the esophagus and the pharyngeal region. Failure of the motility patterns of the small intestine to clear the bile can result in backflow of the duodenal secretions of toxic chemical (bile salts) to enter the stomach. When this happens regularly they can have a damaging effect on the mucosal layers of the stomach, the esophagus and the pharyngeal regions. Bile salts have a dramatic impact upon its exposure to mucosa, causing the mucosa to transform from a normal epithelial like cells to those of an intestinal mucosal type (known as intestinal metaplasia) and can eventually lead to cancer [17].

The interaction between the food sensing and the motility provides further insights into the APD physiology. In patients suffering from Irritable Bowel Syndrome (IBS), it is advised to have a diet with low-FODMAP so as to reduce the chances of recurrence of the functional symptoms[17]. Fermentation of the FODMAPs leads to generation of gases in the lumen causing distension; which in turn may also affect the small intestinal motility[18]. According to Depoortere, the chemosensory pathways of the gut are amenable to change leading to the disturbances in the metabolic responses and the endocrine secretions [19]. Although these effects may not influence the motor patterns directly, however, channelize its effect through distension related [20], those mediated by CNS [21], or other unknown mechanisms [22,23].

4.3. Diagnosis

Measuring the motility of the APD segment has been a challenge for the given spatial and temporal resolution due to its anatomical location and the small opening of the pylorus [24,25]. Technical advances in ultrasound [26], scintigraphic method[27], High Resolution Manometry (HRM) [28], Impedance Measurement (MII) [29], Electro GastroGraphy (EGG) [30], Magnetic Resonance Imaging (MRI) [31] and bile measurement (using Bilitec spectrophotometer) have allow us to investigate the physiology and/or pathological conditions of the APD segment [32]. The Wireless Motility Capsule (WMC) is a relatively newer technique for measuring pH, pressure, transit time and contractile activity of the antroduodenal segment [33-35]. The WMC is a pill-sized device that travels through the length of the gastrointestinal tract and records the measurements taken for analysis purpose. The technology holds promising in therapeutics by capturing global gut motility profile of the patients to help diagnose effectively [36,37].

4.4. Why is it Difficult to Treat Motility Disorders of the Apd Segment?

Motility disorders pose numerous challenges in treatment modalities. Due to dynamic nature of the APD segment which responds differentially to various inputs/ stimuli, the etiological reasoning could not be established. Therapeutics options include regulation of meal intake, nutrition, and life style changes. The patients suffering from motility disorders of the stomach and duodenum have reduced digestive capacity. It is preferable to provide meals that are low in fat so as to prevent delays in the gastric emptying. Further, it is easier to digest liquids meal and regulate the symptoms in comparison to the solid food that necessitates for increased demand for peristaltic activity. Use of prokinetic agent (such as metoclopramide, erythromycin, domperidone and tegaserod) is an alternative strategy to help facilitate the peristalsis activity by participating in the neurohormonal control of the gut motility patterns. They are used in the treatment of gastroparesis with the objective of increasing the gastric emptying and help improve the symptoms. However, due to their side effects and limited understanding of the therapeutic action of these drugs, the use has been limited [38-40]. New therapeutic drugs design are in progress to address the side-effects of the use [41]. Surgical options include resection and electrical stimulation (gastric or intestinal). Electrical stimulation of the gut segment can be a pliable option in regulating the symptoms that does not affect the tissue and does not involve the resection procedures [42]. The studies on the electrical stimulation have been a topic of interest due to their minimally invasive procedure and their flexibility to help regulate the motility patterns. However, due to incomplete understanding on the effects of external stimulation on the physiology, the procedure continues to be debatable. Electrical stimulation aims at reconstructing the natural electrical stimulation of the neurons that are provided by the vagus nerve. The process of electrical impulse generation is a complex process that involves sensing of the gastric contents, interacting with various cues and communicating with the CNS/ENS. Unless we learn as to how these components are interacting, deducing as to what patterns of electrical stimulation would be required to generate the desired motility will be a challenge. The following sections discuss various control strategies of the gut motility that were investigated experimentally by various authors.

4.5. Complex Control of Motility: Gut-Brain Axis

Generation of motility patterns is in some way hardwired into sensors which are present and it is because of this reason that

the APD segment has acquired its ability to control and allow for a wide variation in its motility patterns[43]. The anatomical studies report that the Enteric Nervous System (ENS) comprises of hundreds of a million neurons that are spread across the walls of the alimentary canal [43]. The small intestine is innervated through the formation of a myenteric plexus that encroaches in the intramural regions of the intestinal wall [45]. From a set of few neurons controlling a specific function such as the acid secretion in stomach to ganglia in small intestine for functions such as the motility control, the neural innervations are an essential component of the control. They help communicate with the CNS via afferent and efferent nerve fibers of the vagus nerve to establish the function. About 90% of vagal fibres that interacts with CNS are afferent and an enteric nervous system spends significant effort in sending information to the CNS besides performing its own function [46,43]. It is through this channel that the gut-brain axis is established which can induce sensations of nausea, bloating, hunger, anxiety and depression [47], and other cognitive functions. Neural sensing of the intestinal contents for establishing the relationship between the gastrointestinal responses and cognitive functions is a challenge. The APD segment employs various strategies to help establish the physiological function that are discussed as follows.

4.5.1. Control through Neural Sensing

The information relating to the physiological condition of the APD segment is passed on to the CNS by the neurons. It is through this mode of communication that the APD segment is able to serve its physiological function by sensing pH [48], osmolarity [48-50], lipid (also ileum) [51,52], carbohydrates, proteins and other factors (mechanical factor like size of bolus) [49]. Based on the level of these parameters, the CNS/ENS communicates via the efferent neurons to help generate appropriate motor patterns to ensure proper digestion. The nature of communication that takes place has direct significance to physiological function. They help in mediating various functions such as vago-vagal reflexes (receptive relaxation), gastro-gastric (accommodation) and duodenal brake reflexes [53].

To support the relevance of sensory-motor integrity, Peter Holzer suggested that prevention of acid damage to the mucosal tissues are carried out by an *"elaborate network of acid-governed mechanisms"* that help protect the tissue from acidosis and maintain homeostatis [54]. The pH distribution of the gut lumen follows a particular trend, having lowest at the stomach (pH: 1-3) and then goes on increasing from proximal duodenum (pH: 1.7-5), distal duodenum (pH: 5-6) [55] to terminal ileum (pH : 7-9) [56,57]. On exposure of the duodenum to acidic contents they stimulate various defence mechanisms which include; increase in mucosal secretions, bicarbonate secretions and blood flow [58]. Together with this, hormones also play a major role in acid secretion at the stomach which in turn may contribute to the overall homeostasis. The pylorus, a tissue that connects stomach to the intestine, also plays a significant role in regulatory the digestive mechanisms. They primarily function as a valve to regulate the rate of flow of contents from the stomach to the duodenum (gastric emptying). Besides being a muscular tissue it also has sensors embedded within its mucosal layers which are involved in some control related activities; since they also share the neural tracts and the circular muscle layer with the terminal antrum and the proximal duodenum [59].

4.5.2. Control by the Endocrine System

Besides neuronal control, the gut also has its own hormonal control. Prior to the discovery of the gut hormones, Brown et al [60] speculated the involvement of some kind of molecule in eliciting motor activity upon alkaline infusion into dog's duodenum. Later, they isolated a new polypeptide that they speculated is responsible for the motor activity and hence named it as *"Motilin"*. Motilin is involved in eliciting strong gut contractions that are secreted by endocrine cells of duodeno-jejunal mucosa [61,62]. It has been reported in literature to be involved in the regulation of migrating motor complexes (MMC; also referred to as the interdigestive motor contractions). This finding was supported by the cyclic changes in plasma motilin concentrations which peak with strong contractions and disappear with meal ingestion and reappear during fasting [63]. The manner in which the motilin achieves such regulation is by directly binding to the motilin receptors present throughout the ENS (Enteric Nervous System) and gut smooth muscles; revealed through immunohistochemistry studies. The receptors are distributed differentially along the GI tract with higher density in the duodenum followed by ileum, jejunum, proximal colon, antrum, and colon(He et al.). It is reported that the contractions due to motilin are mediated by the cholinergic neural pathways of the myenteric system. Motilin are also found in the cortex which helps in the central regulation of gut motility [64]. Role of motilin and ghrelin (another GI hormone involved in hunger) [65] and their association with the hunger and feelings of satiety that are driven by the brain and GI function is a subject of interest to help devise drug therapies [66] for gut dysmotility and better management of patients [67-70]. For example, in patients with motility dysfunctions, the use of prokinetics can help regain their intestinal motility, reduce the symptoms of poor transit of the digesta and regulate the proliferation of bacteria in the intestine [71,68, and 39]. Post-surgical interventions as in gastrectomy(Buzga et al.) and non-surgical interventions of dieting and exercise [73], the physiological changes affecting regulation of GI hormones and their relation to hunger and satiety play an important role in the curing process

[74-76].

Gut hormones also mediate other activities such as appetite or hunger control and feeding behaviour by participating in the gut-brain axis [78]. The gut-brain axis is a framework through which the central nervous system (CNS) and enteric nervous system (ENS) communicate with each other via the afferent and efferent neurons for achieving regulation of various processes such as feeding, appetite control, and control of food intake. Besides motility and hunger control, the gut-brain axis also plays a significant role in digestion of fatty meals via bile secretion, a prerequisite for preparing the meal to be digested by the lipases.

Literature suggests that the APD motility is under neuronal control, which helps facilitate the digestion by stomach and intestine (Browning & Travagli). The APD motility in course of time gets modulated based on the type of food reaching the duodenum and through sensing via neuro-hormonal mechanisms. At any given point of time there are several hormones circulating in the blood, whose role and significance are not fully established. For example, ghrelin (hunger hormone - found in higher concentrations during fasting), motilin (for causing contraction), CCK (for causing gall bladder contraction and motility) [79], peptide YY (for satiation modulation), amylin (for glucose homeostasis), glucagon-like peptide-1 (GLP-1)[80] and glucagon-like peptide-2 (GLP-2 for motility) (Wu, Rayner, Young, & Horowitz, 2013) is not fully understood. These hormones are a result of secretion from endocrine cells which help in the regulation of acid release in the stomach, for example, the gastrin secreting G-cells help stimulate the acid secretion and pH-sensitive somatostatin secreting D-cells at the antrum inhibits the acid secretion. These hormones modulate the acid secretion mechanism by targeting the parietal cells of the gastric pit. The endocrine cells all together comprise of 1.2% of the total gastric epithelia which in turn contains 30% of histamine secreting ECL cells and 22% of D-cells [81]. In order to get a clear understanding as to how the digestive mechanisms are regulated, we need to recognize the neuro-hormonal regulation of the contractions together with the feedback mechanisms provided by the gastrointestinal system.

4.5.3. Pacemaker in the Stomach and the Duodenum

Is it necessary to correlate our understanding on motility patterns with the smooth electrical potentials of the muscles that are origins of various contractions? Yes, it is necessary because the nature of contraction, the amplitude and frequency of the waves are closely related to smooth muscle activity. In general, it is observed that the smooth muscles in both the stomach and duodenum exhibit electric potential; also known as the Basic Electrical Rhythmicity (BER). These potentials change in a periodic fashion, rising to their peak value and lowering to their minima in a cyclic fashion with a characteristic frequency. Contractions are evoked when the electric potential rises well above the threshold in BER of the APD segment, which are characterized by having different frequency of oscillations across the segments. The source of excitation for the BER comes from a pacemaker, which is responsible for such predefined oscillations that vary from one segment to the other (antrum/pylorus /duodenum). Like the cardiac pacemaker in heart and a pacemaker in the stomach, there is one such pacemaker available in the intestine. It is considered that the pacemaker is located somewhere between the duodenum and ileum or at the mid-duodenum [82]. Localization of a pacemaker near the ampulla of vater (approximately at the mid-duodenum region) is based on the following criteria: there is BER discontinuity between the antrum and the duodenum, presence of 1-1.5cm long hypomuscular isolation segment in canine duodenum aboral to pylorus, detection of highest intrinsic frequency by the conduction-ligation method, and change in BER due to cooling or warming of duodenal surface. It is reported that the contractions occurring in the upper intestine propagate from the duodenum to the upper jejunum without interruption [82]. BER and mechanical contractions travel from the pacemaker area of duodenum, i.e. near the ampulla of Water to a region as far as the first frequency decrease occurs. The pacemaker does not exist at the duodeno-jejunal flexure. The mechanism involved in the generation of intestinal motor patterns by ENS is thought to be resulting from sequence of inhibition and excitation of smooth muscle fiber [83,84].

Research in the gastric arrhythmia studies has provided insights into the slow wave conduction patterns [85-87]. Using high-resolution electrical mapping, the spatiotemporal dynamics of wave front propagation in the stomach is suggested to have a circumferential propagation near the pacemaker region and at a distal location it changes from circumferential conduction to a more longitudinal conduction which is followed by elliptical wave front patterns [88]. The slow wave propagation is more anisotropic near pacemaker region due to higher conduction along the circumferential direction (2.5 times) in comparison to the longitudinal direction. Arrhythmia is a non-synchronous conduction pattern that alters the physiological functions of the stomach and intestine; such as those resulting from ectopic event, blockade or those due to the tissue which does not couple [89-92]. Incisions in the APD wall can disturb the propagation of the slow waves which can have an impact on the gastric emptying and digestions [93]. Incisions of the gastric wall spanning about 2-3cm by Du et al. have demonstrated occurrence of a localized and inhomogeneous propagation of the slow waves [94]. Their study reports that the incision has an effect of altering the conduction patterns or conduction blockade. One of the abnormalities that can affect

the physiology is by changing the pacing activity or dysrhythmia of ICC; leading to gastric or intestinal dysfunctions resulting from a change in the coordination of the adjacent segments [95]. A pathological condition such as the gastroparesis (characterized by a delayed gastric emptying) has been recently associated with the gastric arrhythmia and the loss in the structural integrity of the ICC network [89,92]. Altered gastric arrhythmia leads to changes in the contraction pattern which can affect the normal mechanical function of the stomach, that is, the grinding, mixing and transport; indicated by the *in silico* studies of the stomach [96]. A similar damage (surgical procedure) to the intestinal ICC networks and the vagal innervations to the intestine may change the innate slow wave conduction pattern and the intestinal motility patterns that can affect the physiological functions of mixing and transport [97,98]. The concept that the physiological functions of the gut are associated to the pacing activity of the segments concerned has reinvigorated the arrhythmia studies of the gut(Lammers).

4.5.4. Coordination of the APD Motility

Contractions in the antrum, pylorus and duodenum are not independent of each other; however they share some degree of coordination. The antral contractions are known to have some relation to the onset of the pyloric and duodenalcontractions. Antral contractions which are initiated at one side of the pyloric segment generate antral pressures and the duodenal contractions on the other end generate duodenal pressure leading to the development of a pressure on both sides of the pylorus. Therefore the antrum and the duodenum behave like a dual pump where each tries to push the contents to the other side of the pylorus. Depending upon the degree of pressure difference there is a proportional flow rate occurring across the pylorus. Further, degree of pyloric opening can also modulate the flow rate and the volumes of flow. When APD contractions are well coordinated they lead to normal gastric emptying, however, when they lose coordination they can lead to abnormal flow. Little is known about the coordination between antral, pyloric and the duodenal contractions and their effect on transpyloric flow and the consequences resulting from a lack of coordination. More precisely, what remains to be understood is the following question, that is, how are the contractions in duodenum related to the antral and the pyloric contractions and how do they help in normal transport and under what circumstances they lead to pathology or reflux?

Control of gastric emptying is achieved by the coordinated contraction of the APD smooth muscles. The process is first initiated by neurons that signal the smooth muscles to undergo contraction and ultimately transfer the momentum from wall to the fluid underneath leading to the generation of flow patterns and transport. Thus, APD motility is under the influence of the enteric nervous system, the central nervous system, gut hormones, nutrient type and other factors. Given that there is built-in sensorymotor coordination it is not surprising to observe that the APD exhibits a complex behaviour in transport regulation.

The AP (antro-pylorus) and the PD (pyloro-duodenal) segments do not work in isolation rather they interact, however, the type and extent of this interaction has not been well studied. It seems logical to state that the overall coordination of the APD segment is necessary to perform normal physiological function at the prevailing state irrespective of whether it is the fasting or following a meal. The relationships among various segments of the gut are generally studied in terms of the relative incidence of motor activity across these segments. Motor responses of the APD to meal ingestion are complex and hence various definitions of APD motility have been used for their analysis. Brook et al observed that antral contractions during the fasted state had - 1) burst of contractions appearing at three numbers per min with each lasting for 5 min, 2) sporadic antral contractions and, 3) antral motor quiescence lasting at least 5 min [100]. Isolated duodenal contractions were defined as those that did not occur within 10sec of the preceding antral contraction. The presence or absence of the antral or the duodenal contractions within 2sec of the pyloric opening or closure activity or state was considered to understand the relationship between the pylorus, antrum and duodenum. The pyloric contractions occurring in absence of antral or duodenal contraction are referred to as the isolated pyloric pressure waves (IPPWs).

4.5.5. Role of Pylorus in the Coordination of the APD Segment

The pylorus can be thought as a conveyor that passes the food from stomach to the duodenum. It regulates the supply of nutrient meal to the duodenum through coordination of motor activities of adjacent segments. Let us consider that the antral contractions lead to a generation of higher antral pressure (Pa) relative to the duodenal pressure (Pd). Then according to the basic principle of mechanics, flow should occur from stomach to duodenum; however, if at that instant the pylorus were to be closed then it will completely block the transport of contents within the stomach. The same also holds true when Pd is greater than Pa. Therefore, in such a context the coordination of pylorus with the antral and duodenal activity becomes necessary for performing the physiological function of gastric emptying. It is necessary to note that the regulatory action of the pylorus in transport of food across the compartments relies on the APD motor coordination and also on the feedback mechanism - a switch relayed by neuronal and hormonal pathways exerting its influence by either contracting the pyloric muscles or by relaxing them. Such a control

is relayed via the sensors present on the duodenal mucosa, which, on activation by nutrients can cause the modulation of prevailing motility patterns of the stomach and the pylorus; thus influencing gastric emptying [54, 100 ,101].

4.5.6. Apd Motility is also Affected by the Nature of Meal

The contractions following a meal remain as long as the food is present inside the stomach, since these contractions grind the food, mix contents and finally empty it into the bowels. Depending on the type of meal or more specifically the nutrient content of the meal, the food can stay in the stomach from 1 to 4hrs [102-104]. Non-nutrient meals empty faster since they have zero calorific value and therefore the bowels do not need to be engaged in the digestion and absorption process. In the following section the motor activity of the APD segment during the fasting and following a meal are discussed with an emphasis on the motor responses elicited upon meal ingestion.

4.5.7. Migrating Motor Complexes

MMC or inter-digestive motility patterns are the contractions that prevail during fasted state. These inter-digestive motility patterns have been broadly classified into three types namely, phase 1, 2 and 3. The 1st phase is a quiescent phase, which after a long gap, make transition to phase-2 marked by irregular contraction and finally ending in phase-3, which lasts, for about 7min where the contractions are very regular. MMC is used as reference for performing experimental studies relating to the segment. For example, IV (intra-venous) injections for performing clinical studies are provided at the onset of meal ingestion and duodenal infusion of various substances (isotonic, saline solution, hydrochloric acid) is provided at the terminal MMC phase-3. Although sufficient manometry-based data for both controls and patients are available, attempts to distinguish the motility patterns of the patients and controls was a challenge [105]. The problem being the heterogeneity of the APD motor responses due to multiple factors including differences in meal type used for the study. The duodenal motor responses of meal are highly irregular and depending on the type of meal different kinds of motor patterns are elicited which together with pyloric segment show differential patterns that are reflected on manometry charts [106].

4.5.8. Switch from the Fed State Contractions to the MMC Pattern

Changes in MMC pattern following a meal are well reported in literature [107]. On infusion of a nutrient meal, the prevailing MMC pattern travelling through the duodenum to the terminal ileum changes to peristaltic contraction following a meal. Studies on nutrient infusion in duodenum show that changes in motor activity are dependent on the calorific content of the infused liquid meal and such motor patterns are modulated accordingly [108]. While MMC patterns continue to persist for low calorific meal (<0.5 kcal/min), amplitude and frequencies of the contraction wave do not show significant changes at low calorific meal infusion. However, the MMC is significantly suppressed at higher caloric load in comparison to controls with no-infusion [109]. The frequency and amplitude of contractions normally increase on duodenal infusion and a significant decrease in duodenal motility upon jejunal infusion, suggesting involvement of a feedback mechanism (the ileal brake) [110,111].

4.5.9. Motor Responses of theMeal

Nature of contractions elicited by a specific meal has not been well understood. Though there have been studies that shed some light on the conundrum responses, they have been unsuccessful in understanding the exact response of the duodenum upon infusion of nutrient directly into the duodenum [112-114]. Because the duodenum shares some kind of feedback control with the pylorus, the antrum and other segments of the intestine through complex pathways, deducing the nature of coordination and the luminal transport of contents has been a challenge [115,116]. In physiology, the contractions reported are a combination of various elementary contractions that consist of basic contractions such as antegrade or retrograde propagating wave and standing contractions that appear at low/high frequency which are also referred to as cluster contractions. It should be noted that the cluster contractions can also be propagatory in nature. Investigations into the variability of wave nature have been performed by Kwiatek et al [117] for the antral segment. They analyzed a sequence of MR scans obtained by dynamic imaging taken over the entire stomach for total gastric volume and meal volume calculation. By marking the contours of the gastric segment observable in the scans they were able to measure the shape and propagation details of each antral wave. For a 500mL glucose solution with a calorific value of 200kcal as a standard meal they reported regular antral motor patterns which were characterized by a periodicity of 23±2sec having amplitude of 0.7±0.08cm and a wavelength of 6±2cm travelling at 0.27±0.01cm/sec. Such quantification details have not been studied for the duodenal segment probably due to the irregular motor patterns that make it difficult to study. Although quantification details are not available, there are a few studies that report manometry data relevant for understating the normal physiological functions of the duodenum and its relationship with antrum and pylorus.

There are numerous literatures available on the motor responses of the meal when infused with various nutrients and its comparison with controls. Infusion of zero calorific meal or an isotonic solution had a minimal effect on the prevailing motility patterns, while 1pH HCl or 5%NaCl resulted in a significant increase in pressure events of large amplitudes along with propagatory con-

tractions. While acid infusion has been the primary choice in most studies, there have been studies which demonstrate that infusion of 5%NaCl solution also evokes contractions that have characteristics patterns of segmental, isolated and propagatory nature in duodenum[118,48]. Studies involving nutrient meal containing sodium oblate have shown contractions bearing low amplitude, isolated or short cluster of non-propagatory pressure waves and at times interspersed with propagating pressure waves. With acid infusion, the following changes in motility patterns occur - 1) there is a decrease in antral contractions, 2) lack of coordination of duodenal motility with development of random patterns, and 3) an increase in isolated pyloric pressure wave (IPPW) rates [115]. While it is not clear as to how these segments are related to each other in terms of coordination, evidence suggest that the contractions of antrum, pylorus and duodenum are in some way linked. When changing the saline infusion to 0.1M HCl acid it was found that antral contractions were suppressed, thereby, allowing phasic contractions of the pylorus and a reduction in the coordination among duodenal contractions [115]. Changes resulting in the inhibition of antral motility and an elevation in the IPPW have been found with meal infusion (10% lipid emulsion, 10% dextrose, hyperosmolar glucose, fat emulsion and amino acids infusions).

Rao et al conducted experiments with controlled injection of meal with variable calorific, osmotic contents and varying volumes in healthy individuals to study the meal response in the duodenum. Contractions were monitored by a 6-channel manometric catheter containing one channel each for terminal antrum and pylorus and the rest spanning the C-loop of duodenum [118]. While a 0.9%NaCl meal was used as the control or isotonic solution, a 5%NaCl meal was chosen to study the effects of osmolarity [119,50]. Bolus of sizes 10, 20 and 30ml at infusion rates of 20mL/min were administered at intervals of 5min while a 15min gap was introduced before switching to a different solution. The results showed that infusion of 0.9%NaCl caused generation of discrete and isolated contractions, whereas, the 100mmol/L HCl infusion generated high amplitude aboradpropagatory waves of the order of 40mmHg. 5%NaCl infusion showed a similar trend to that of HCl infusion with contractions being prevalent across all duodenal ports except for D3 (channel) where the incidence and amplitude were diminished for both infusions. Infusion of fats (Sodium oleate) resulted in generation of low frequency pressure waves of low amplitude, isolated and occasionally propagating type contraction. Further, IPPWs were also seen having a near phasic profile. Bile infusions were also performed with the notion that fatty contents stimulated bile secretions and in turn facilitated lipid metabolism. Motor responses to fats showed isolated contractions of small amplitude with occasional propagatory waves. Mean frequency and motility index obtained by multiplying pressure wave amplitude, duration and frequency of occurrence per minute were significantly higher for HCl and 5%NaCl infusion in comparison to sodium oleate and 0.9%NaCl infusion. This suggested that highly acidic and osmolar constituents of the chyme entering the duodenum elicits higher incidence of contractions. This was further supported by a study where HCl infusion evoked MMC-3 activity. In addition, APD has been shown to have a volume dependent motor response with significant motor activity for a 20ml bolus against 10ml bolus for HCl and 5% saline infusion.

Fats that are twice as calorific as proteins or carbohydrates show differential motor response. Previous studies have speculated that oleic acid infusion has an effect of increasing segmentation of the duodenum and decreasing the propulsive nature of the waves [120]. Therefore, such behaviour can only slow down gastric emptying which is a consequence of reduced duodenal clearance and increased resistance to flow. It is still unclear as to how coordination between segments is lost upon nutrient infusion and the mechanism involved in the development of irregularity of duodenal contractions upon infusion of various substances. Flushing out the duodenal lumen with HCl can have a damaging effect on the duodenal mucosa and increase the chances of ulceration. However, there are other events that cause the motion of the luminal content which mixes up and homogenize it so that the overall pH can be increased. Some relations can be drawn between poor duodenal clearances (which can be attributed to the disordered motility) with the amount of mixing (i.e. with bicarbonate secretions and thereby buffering the acid) that can result from the contractions [115]. Oleate resulted in isolated pyloric phasic contractions suggesting that such events are probably evoked by the presence of lipids in the duodenum along with small amplitude waves. In addition to this, motor responses are also found to be volume dependent. During the first 10min phase upon nutrient infusion no significant differences were observed in the motility patterns between non-nutrient cellulose meal and nutrient meal. However, in the later phase, local contraction with length of spread less than 4cm were found to be more predominant with 73.6% occurrence for nutrient meal, whereas, for the cellulose it lay at 55.7% occurrence with length of spread between 4 and >16cm suggesting that the local contraction of short length span help in processing nutrient meals [121].

The duodenum can also cause a brake to gastric outflow through chemical, osmotic, and nutrient sensing. Duodenal distension triggered by an increase in the volume also influences the motor activity. Infusion of hyperosmolar solution has been shown to increase duodenal contractions in a dose dependent manner by activating local osmo-receptors, located within 10cm of the proximal duodenum [122, 50]. Whereas, HCl and lipid infusion caused antral suppression and initiation of coordinated duodenal

motor activity with the motor response being faster for acid infusion[123]. On the other hand, iso-osmolar saline and relatively hyper-osmotic dextrose do not induce motor response. The reasons for instantaneous response for acid infusion can be attributed to the short lived motor response that rapidly spreads the acid across the duodenal mucosa and subsequently helps in buffering with the bicarbonates released from pancreas. The slower motor response for lipid infusion is likely to cause spread of nutrients across the surface of the duodenum to facilitate emulsification, digestion and absorption.

The duodenum makes use of the chemosensory systems, neural and endocrine mediators to perform the task of nutrient sensing [124-126] and homeostasis (such as in glycemic regulation [94] through feedback mechanisms involving the gut-brain communication). The intestine also contains stretch sensors which help in detecting events causing distension [127]. The sensory information is then relayed by the vagus nerve from the sensors present in the gastrointestinal tract or vagal sensory neurons in the mucosal or near lamina propria endings, intraganglionic laminar endings and intramuscular arrays [128-130]. Such sensing mechanism enables the APD segment to possess a chemospecific antroduodenal motor response [131,44]. To understand the mechanism we consider a well-studied example of CCK induced DBP secretion by fat. CCK has been known to drive the biliary secretion to cause the fat emulsification and metabolism in response to detection of fat in the duodenum [44]. In order to establish such task our digestive system contains I-cells (present in the duodenum) which upon sensing fat in the lumen secrets CCK. This hormone then binds to the CCK receptors present at the mucosal endings of vagal afferent neurons. The information relating to the presence of fat is conveyed to via the vagal afferents to the nucleus tractussolitarius (NTS) in the brain stem for further processing. As a response to the fat detection in the meal the brain send its response through vagal efferent pathways to stimulate DBP secretion by gallbladder and the pancreas. Likewise there are numerous transduction pathways which operate in sensing the nutrient contents and initiating a specific response [132].

4.5.10. Why Clinical Assessment of APD Motility is a Challenge?

There are no detailed studies on the quantification of contraction waves and understanding the nature of contractions elicited on meal ingestion. In one of the studies, a high resolution manometer was used to understand the spatiotemporal changes of pressure over the entire length of the human duodenum (approximately 1.5cm port spacing on manometer catheter) [133]. Their results indicated that, numerous propagating waves (PWs) observed during the fasting state were found to be suppressed with Intra Duodenal (ID) lipid infusion. Of these pressure waves, about 87-90% traversed a distance of 1.5-4.5cm, 5-10% traversed about 6-9cm and only 2-4% accounted for longer distances. Regardless of site of origin of the contraction and type of nutrient infused, most of the PWs travelled only a short distance of 3cm. Another important observation was that most of the contractions were predominantly antegrade than retrograde. In another study, Castedal et al have reported PWs containing bidirectional components rather than unidirectional travelling waves. Manometric and video-fluoroscopic studies in humans have shown that stationary, antegrade and retrograde type of contractions can occur in normal physiology. Antegrade and retrograde flow have also been reported both during the fasted and fed state.

Literature on the direction of propagation of duodenal contractions is contradictory. Some studies suggest that the direction of contractions can be only antegrade [134,135] during fasting and postprandial, whereas, other studies have reported the occurrence of retrograde peristalsis as well [135]. Retro-peristalsis (peristalsis contraction moving in reverse direction and towards the orad) is a prominent feature, whose occurrence coincides with phase-3 of MMC and more specifically during late phase-3 as per the high resolution manometry (HRM) study on duodenum [136]. Significant proportion of antegrade and retrograde contractions were also found in a study that made use of a manometric catheter which had four consecutive pressure ports placed over the duodenum [137]. Retro-peristalsis can also occur during postprandial state, originating at 2-4cm distal to the pylorus. The relative occurrence of antegrade contractions at four distinct duodenal segments is higher in comparison to the retroperistalsis during postprandial state. Percentage occurrences of retrograde movement of the contractions were found to constitute ~20% of all pressure waves event (pressure signature of the contraction captured through manometry) [135].

An ambulatory manometry recording shows that duodenal contractions occur with relatively higher amplitude and persist for longer duration against jejunal contractions during postpradial state [138]. There is a higher incidence of cluster contractions in the duodenum, whereas, the propagatory contractions are increased during the fed state in the duodenum and the jejunum suggesting that these contractions are involved in both mixing and propulsive activities. However, the differences in duration of individual contractions occurring at the duodenum and the jejunum are 0.3sec with 3mm Hg pressure difference and the incidence of propagating contractions differs by nearly 2.4%.

Inferring the enteric activity based on the activity of the muscles, that is spatio-temporal mapping of the intestinal contraction is currently being investigated and is considered to be the cutting edge of the field [84,139,140]. However, such studies are

performed only in animal. By combining the spatiotemporal details of diameter changes of the intestine, intraluminal pressure and impedance measurements for capturing bolus transit, authors were able to deduce the state of excitation or inhibition of smooth muscle fibres of the intestine [141]. Such analysis have allowed for capturing the dynamics of the small intestinal muscle such as isometric contraction/relaxation, auxotonic contraction/relaxation, isotonic contraction/relaxation, passive dilation/shortening, passive isometric pressure increase/decrease, occluded quiescence and distended quiescence.

4.5.11. Current Perspectives on Managing Motility Disorders

Managing the motility disorders of the APD and lower bowels can be done by regulating meals, use of prokinetic drugs and electrical stimulation [142-148,39]. Gastroparesis is one of the major motility dysfunctions of the APD segment where the gastric contents are emptying at a slower rate. As a result of meal retention in the stomach for a long duration, the patient becomes susceptible to malnutrituion, erratic glycemic control and decreases in the quality of life. In order to re-establish the healthy condition, dietary control can be adopted which includes frequent intake (4-5 times a day) of small meal that is low in fat and fiber content [149].

Gastric emptying, one of the physiological function of the APD segment, is a highly regulated process which involves coordination among the APD segments for generating pressure differences that is higher in the antral side compared to the pylorus[98]. It is through the coordinated activity that the gastric contents are emptied into the duodenum at a controlled rate. The pylorus, a tissue interconnecting the antrum and duodenum, acts as a primary regulator of the flow since it can directly suppress the flow by reducing the luminal diameter and completely occlude by closing the valve [150,98]. Increased resistance due to abnormal functioning of the pylorus has been indicated in the diabetes gastroparesis [151]. Botulinum toxin (an inhibitor of cholinergic transmission in neurons) has been used to improve both gastric emptying and symptoms [152]. Surgical procedures for pylorus such as pyloromyotomy for reducing the pyloric resistance have been reported to increase the risks for developing gastric dumping symptoms [153]. These procedures suppress the contractility of the segment which damages the integrity of the tissue.

Drugs such as prokinetics (e.g. metoclopramide, domperidone, and erythromycin) have been used for managing the motility dysfunctions of the gut [39]. They act by binding to the receptors and in the process can either enhance or strengthen the gut motility. By facilitating gut motility they also help to transit the luminal contents and improve the symptoms of various motility dysfunctions [154]. For example, in diabetes gastroparesis, erythromycin can be used as a potent agent to induce contraction by acting similar to the motilin [155]. Erythromycin induces phase III of the MMC by binding to the motilin receptors of smooth muscle cells of the antrum and duodenum [156]. Literature data indicating the side effects of the prokinetic agents are numerous. For example the erythromycin has been found to be involved with cardiovascular complications (torsade de pointes and cardiac arrest) [157], metoclopramide has been indicated in tardive dyskinesia [158], and domperidone in the QT prolongation and sudden cardiac arrest [159-161]. Due to these side effects and complications, the use of prokinetics has been restricted [162,163]. A potential drug therapy that targets various tissues (M1/M2, $5HT_4$, D2 and Ghrelin receptors) of the APD segment with minimal side effects is under trials [164-167,66].

Use of electrical stimulation has received increasing attention in the recent years for managing obesity [168-170], gastroparesis [171-173] and other gastrointestinal dysmotility disorders [174-176]. Electrical stimulation of the stomach has been reported to be beneficial in gastroparesis. In this method, the gastric electrical stimulation delivers an electric current (in the form of pulses) through the electrodes to the smooth muscle of the stomach. There are two method of providing the therapy, one which uses high-frequency stimulation (12 cycles/min) at low energy signal having pulse width of 330 micro seconds (also referred to as the Enterra therapy) and the other method involves delivering a high energy signals (or long duration pulse of ~300 milli seconds) at a lower frequency (matches to the slow wave of stomach ~3 cycles/min) [177]. Studies have been performed in both animal and humans to assess the treatment benefits for various motility disorders of the lower bowel motility disorders [178,179]. Duodenal electrical stimulation using intraluminal ring electrodes fitted to the feeding tube have been reported by Liu et al. to study the gastric emptying in humans [180]. The stimulation includes the application of pulses at 13 cycles/min of 4-10mA peak having pulse width of 100-500ms for 10min duration. Results indicate a delay in gastric emptying and decrease in water intake, suggesting a potential therapy for obese patients without surgical resection procedures. A *"First-in-Man Study"* of duodenal electrical stimulation as an alternative strategy for surgical intervention of various motility dysfunctions of the gastrointestinal system, has demonstrated feasibility of incorporating the duodenal stimulation system without adverse effects [181]. The method is found to be safe for improving the glycemic control in the patients. Electrical stimulation of the pylorus using long pulses at a 30 cycles/min reduces food intake capacity without development of noticeable symptoms; suitable for treating the patient suffering from obesity [182]. Animal studies of the electrical stimulation suggest the mechanisms of action of the therapy through impairment of the myoelectrical activity of the stomach [182]. Studies also indicate that the therapy can also be adapted to treat the symptoms of

intractable nausea and vomiting over a long run [183-185]. In regard to the success rate, the mortality rate was found to 12.7% in patients suffering from diabetic gastroparesis at 1 year of follow-up study [186,3] and 24% after 9 years of follow-up study [188].

To ensure effective therapy [168,42] through electrical stimulation of the gut segments one has to understand the underlying principles of generation of slow wave and its propagation. The interstitial cells of cajal (ICC) are also referred to as a pacemaker [189] which generate and sets the bioelectrical slow wave potential and its frequency which are responsible for initiating the smooth muscles contractions of the gut. Besides this, the ICC acts as a mediator by transmitting excitatory and inhibitory signals from ENS to smooth muscles of the gastrointestinal tract[190,191]. ICC is a highly organized network, arranged in different layers that are sandwiched between muscles layers of the gastrointestinal walls. There are network of ICC within the muscles layers of circular and longitudinal muscles, in the myenteric plexus region (between the circular muscle and longitudinal muscle layer), and in septa between muscle layer bundles [192,193]. The ICC helps generate the slow waves in the cells which acts as a trigger for initiating the contraction wave in the gastrointestinal segment. The frequency of the slow waves are specific to the gut segments such as 3Hz in stomach and 12Hz in duodenum and decreases aborally as one move to the ileum (8-9Hz) and colon (3-4Hz). ICC also helps to coordinate contractile activities of the gut segments, which are an essential part of the physiological activity of the GI tract, in order to perform its function. Loss of ICC or damage due to surgery can affect the slow wave setting in the gut segment and the coordination of the gut motility patterns [194, 195 and 65]. In order to re-establish the normal slow wave generation in the pathology, gastric pacing has been introduced as a therapy to help regain the physiological function of the stomach (i.e. normal gastric emptying). The methods of generation of slow wave entrainment is an active area of research to help address the question of what kind of gastric pacing can be effective in the therapeutic efficacy of the implants (esp. location of the gastric pacer, and the nature of stimulation such as continuous/pulsed signal, amplitude, frequency, and pulse width) [196-199]. Numerous authors have performed mathematical modelling of slow wave propagation. However, the model fails to predict the slow wave propagation behaviour to closeness due to anisotropic property [65,85] of the tissue and non-consideration of the physiology, the modelling remained a challenge [200,85]. A recent multiscale 3D stomach model by Sathar et al. that incorporates the anisotropic conduction of the tissue shows better prediction of the slow wave conduction and therefore can be potential tools for devising and analyzing the gastric pacers.

In view of the fact that the contraction drives the flow in the gastrointestinal segments, it is necessary to understand as to how the flow is developed due to the prevailing motility patterns. The dynamics of trans-pyloric flow has direct significance to the pathophysiology - if the flow is forward and slow it leads to gastroparesis, and if the flow happens more often in the reverse direction it leads to DGR [201]. Measurement of gastric emptying and duodenogastric reflux rates has technical limitations, as it is difficult to capture the flow dynamics with good spatial and temporal resolution. Hausken et al.[202,203] while studying duodenogastric reflux using ultrasound report the occurrence of duodenogastric reflux both in the middle of antral peristalsis as well as at the end of antral peristalsis before the closure of pylorus. However, in another study duodenogastric reflux was found to be caused by retrograde peristalsis and segmental contraction of the duodenum in the presence of open or opening pylorus. These observations suggest that the control of flow is complex in nature and require coordination among the APD segment. Conundral responses of APD motility to meal and complex neuro-hormonal controls make the system more complex. Simulation studies performed using a 2D geometry approximated as a channel flow provide clues but not sufficient enough to elucidate the mechanism that underlie the DGR[204]). A 3D *in silico* study of the APD segment modelled as close to the physiology using the MR images indicate that the nature of duodenal contractions play a major role in the digestive process[98]. Some of the contractions were found to be inducing duodenogastric reflux whereas some appear to facilitate emptying [98]. The frequency of contraction, wavelength, luminal occlusion, and speed of propagation affects the flow patterns and the trans-pyloric flow rates[98]. Computational methods can be valuable tool in this context where, using the Newton's laws of motion, one can do predictions of the nature of flow patterns emerging due to the prevailing contractions in APD segment; similar to those analyzed by Pal and Brasseur [205-214,96] and others[215-219]. Recent studies on the duodenal contraction provide details as to how the contractility can impact the formation of luminal flows that are crucial to the intestinal physiological function[220]. Studies on advancing local longitudinal shortening indicate that they work in coordination with circular contraction to help improve the propulsion of bolus at higher occlusion optimally; suggesting economical means of intestinal pumping [220,221].

5. Conclusion

The state of art review suggests that the APD segment is a complex tissue that interacts with various cues such as ICC, ENS/CNS, and hormones to perform the digestion. If the tissue fails to undergo contractions in a normal manner then it may lead to pathology. Opting for surgical resection does not recover the motility patterns of the APD segment since the underlying neural connections are broken and the structural integrity is lost. Dietary control is a natural way to evade the symptoms and help

improve the quality of life, however, does not serves to cure the disease. Although pharmaceutical method suffers from side effects, new developments offer better treatment options by selectively targeting the receptors. However, they provide temporary solution to the problem and necessitates for administering drugs on a regular basis. Electrical stimulation is a relatively newer method and relies on the neuromodulation of the gut motility by delivering pulses of current. Despite the recent trials of successful implantation of electric pacers in alleviating symptoms and the pathophysiology, and lack of large-scale studies, the procedure necessitates for further studies and standardization. They need reconsideration on the specificity of the target tissue. Since the APD motility is highly meal dependent, treatment procedures may have to be modulated in accordance with the APD responses to the stimuli. They should be able to develop appropriate motility patterns to perform the digestion of a meal (that is, differentially for liquid and solids) and help in the transit. In addition to this, they should be able to regulate the sensations of nausea, bloating, hunger, anxiety and depression. Finally we conclude that by understanding the complex regulatory mechanisms regulating the APD digestion, we may be able to manage the patient suffering from motility disorders and provide better treatment modalities.

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