

X-Ray Imaging of the Esophagus and Lower Esophageal Sphincter and Its Role in the Diagnosis of Gastroesophageal Reflux Disease

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ABSTRACT

Currently, the use of pH monitoring and pH-impedance monitoring is recommended to document the diagnosis of gastroesophageal reflux disease (GERD). However, these methods give about 30% false negative conclusions. X-ray examination is not recommended, as it is considered to have low reliability. The purpose of the work is to evaluate the reliability, x-ray examination when using the highest possible pressure in the stomach. Material and methods. 60 patients were examined, including 3 adolescents. The rest were aged from 53 to 76 years (62 ± 4). They had at least one GERD symptom that they could not control, including 53 patients receiving proton pump inhibitors. Of the 39 patients undergoing endoscopy (from 1 to 4 times), only 1 (3%) was diagnosed with GERD and 18 (46%) with gastritis. In 2 cases where pH monitoring was performed, the DeMeester value was $<4\%$. Method. The patient drink barium in a horizontal position without interruption. When the barium ends, the patient raises his straight legs, which serve as a sign to take an x-ray. After 5 minutes, a repeat radiograph is taken at rest. Increased pressure in the stomach causes increased tone of the upper and lower esophageal sphincters (LES). In healthy people, barium enters the stomach without delay. In patients with GERD, barium tightly fills the esophagus between the contracted sphincters. The length of the LES is defined as the space without contrast agent between the barium in the esophagus, and in the stomach. This method allows you to diagnose GERD based on functional and anatomical changes relative to the norm, including shortening of the LES, dilation of the esophagus, formation of the phrenic ampulla, the presence of longitudinal folds, changes in contours, identification of functional and peptic narrowing of the esophagus. Results. X-ray examination with provocation of maximum pressure in the stomach, the diagnosis of GERD was established in 59(98%) of 60 patients with symptoms that occur with GERD, including in 2 (3%) of 59 patients in whom the DeMeester score was $<4\%$, and in 38 (64%) patients in whom it was not detected by endoscopy. All patients had an organic nature of the disease. This made it possible to prescribe complex pathogenetic treatment for GERD. Conclusion. X-ray examination of the esophagus with provocation of maximum pressure in the stomach, provides high accuracy

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of the diagnosis of GERD (98%). The most reliable sign of GERD was shortening of the LES less than the lower limit of the age norm. At the same time, high diagnostic accuracy of clinical symptoms was proven, which allows starting not "ladder", but complex treatment of the disease, regardless of the clinical symptoms. The proposed diagnostics showed the absence of functional diseases, including 2 (3%) cases, in whom the DeMeester score was <4%. In doubtful cases, endoscopy and/or x-ray examination with maximal gastric pressure are recommended to clarify the diagnosis.

Keywords: Gastroesophageal Reflux Disease, Lower Esophageal Sphincter, X-Ray Diagnostics, Physiology of the Gastroesophageal Junction, High Stomach Pressure, Esophageal pH Monitoring, Pathophysiology, Gastroscopy.

INTRODUCTION

Etiology of GERD

The overproduction of acid and the associated illnesses linked to hypersecretion have a lifetime prevalence of 25-35% in the United States [1]. In the historical aspect, ideas about the hypersecretion of hydrochloric acid can be divided into two periods. Prior to the introduction of pH monitoring of the esophagus, i.e., almost until the end of the 20th century, all studies argued that gastritis and gastric ulcers, as well as duodenal ulcers, occur mainly because of gastric hypersecretion [2-4]. For example, Christie and Ament concluded "that, on average, hypersecretion of gastric acid does occur in children with duodenal ulcer disease [3]. Uspenskiĭ showed, that an increase in the number of main cells, and parietal cells of the stomach, that are observed in duodenal ulcer and pre-ulcer condition, "they are observed in normal subjects with constitutional hypersecretion of hydrochloric acid and pepsin" [4]. Collen et al concluded "that a subgroup of patients with long-standing symptomatic gastroesophageal reflux disease who do not respond to standard ulcer-healing doses of histamine2-receptor antagonists are hypersecretors of basal gastric acid" [5]. Numerous studies have confirmed the validity of this hypothesis, which stated that acid-dependent diseases occur in individuals with hypersecretion of hydrochloric acid. This hypothesis has become a generally accepted theory, since up to the present day not a single study has been published that contradicts it. It served as the basis for the development of acid-suppressing drugs. Studies have shown that all people are divided into normally acid-secreting, gastric hypersecretors and hyposecretors [6]. The experiment proved that the damaging power of gastric juice depended not only on the amount of hydrochloric acid, but also on the presence of endogenous pepsin [7]. During this period, it was believed that healthy people could not have a reflux. Therefore, the very fact of reflux testified to the failure of the

antireflux function of the esophagealgastric junction (EGJ). The detection of reflux in an X-ray study was considered evidence of a disease that was called gastroesophageal reflux (GER) [8]. Inflammatory and ulcerative processes in the esophagus, as well as the so-called hiatal hernias (HH), revealed during endoscopic examination, did not raise doubts about the presence of GER [9,10]. The first studies of esophageal pH found that "reflux into the oesophagus of gastric contents of low pH occurs almost as commonly in people without symptoms as in those with symptoms..." [11]. Since it was not possible to differentiate normal from abnormal based on pH monitoring, Pattrick concluded that "The oesophageal measurements of pH have a limited use as a diagnostic measure". At the same time, he stated, - "normal people without symptoms of reflux do in fact reflux small quantities of acid into the oesophagus., and ...This 'physiological' incompetence in the upright position is not of great importance" [11]". There were three errors in this study that led the author to an unjustified conclusion. Firstly, this study cannot be considered physiological since the presence of a pH probe in the esophagus disrupted its function. Second, these studies are not standardized on the amount and quality of food consumed. And most importantly, that 24-hour esophageal pH measurement has a false negative rate of 15% to 30% [12]. The overall prevalence of esophageal disorders among supposedly health individuals by GI endoscopy was 17.3% [13]. Stål et al. stated that "Symptom evaluation is not sufficient to exclude significant gastroesophageal reflux in healthy volunteers" [14]. In addition, some patients have only extraesophageal symptoms [15]. Thus, it is highly likely that in the control group, which included individuals without complaints, there were also patients with GERD. A new (second) stage in the development of gastroenterology began with the articles by DeMeester et al [16,17]. In 1974, they published an article proposing a normal range for esophageal pH monitoring. It was defined as pH < 4 for 4% of the 24 hours of monitoring 5 cm proximal to the LES. To do this, the authors examined 15 individuals who believed that they had no problems with the digestive system. Since then, this boundary has been called the "DeMeester score", and the proposed method of pH monitoring has long been considered the gold standard for diagnosing gastroesophageal reflux disease.

To compare different methods of diagnosing GERD, it is necessary to briefly dwell on reliable knowledge about the anatomy and physiology of the esophagus and esophagogastric junction (EGJ).

The normal anatomy and physiology

The normal anatomy and physiology of the esophagus and lower esophageal sphincter (LES) is the basis

for understanding the pathological physiology of gastroesophageal reflux disease (GERD).

Anatomy

The length and width of the esophagus depend on the age. Bott et al showed that in healthy children the mean diameter at the cranial point of measurement was 6.75 mm at the lower weight (2.6 kg) and 14 mm at 74 kg [18]. The average width of the esophagus in healthy adults is 15 mm with small individual fluctuations [19]. According to pull-through manometry with catheter in control adults the length of the LES was 34 ± 9 mm [20], 35 ± 4 mm [21]; 36 ± 12 mm [22]; 37 ± 1 mm [23]; 4.1 cm [24]. Part of the LES is in the abdominal cavity. Its length was 23 ± 7 mm [21,24]; 2.1 cm [25]. The LES pressure was well developed by 2 weeks of age. In children less than 1 year of age, mean LES pressure (43.3 ± 2.4 mmHg) was significantly greater than mean LES pressure (30.6 ± 2.3 mmHg) children older than 1 year of age and LES sphincter length increased with age [26]. The LES in adults is the same as in adolescents. However, we did not find any measurements of the LES length in children of different ages.

Physiology

In response to esophageal distension the pressure (tonus) of the LES decreases [27,28] to pass the bolus to the stomach. During the fundus or body of the stomach is stretched the pressure (tonus) of the LES increases to prevent reflux of aggressive gastric contents into the esophagus [29,30]. Shafik et al found that gastric balloon filling volume greater than 100-110 ml causes a reflex contraction of the upper and lower esophageal sphincters [31]. This physiological feature formed the basis of the method I developed for diagnosing esophageal pathology during high pressure in the stomach.

Conventional radiological diagnosis of gastroesophageal reflux disease

Standard GI x-rays study

Until the middle of the 20th century, gastric and duodenal ulcers were the main gastroenterological problems. When gastroscopy began to be used, there were reports of frequent detection of inflammatory changes in the esophagus, which were due to the reflux of acidic stomach contents into the esophagus. This pathology was called "gastroesophageal reflux" (GER) [32,33]. A standard X-ray examination for the diagnosis of GER was widely used. The GER was diagnosed if an episode of reflux or radiologic signs of peptic esophagitis was detected [34]. Thus, the presence of reflux during the X-ray examination was considered evidence of GER, and there was no question of the possibility of physiological reflux. First, because it would mean a priori to recognize the EGJ function as not perfect, which is not normally observed

in other sphincter areas of the intestine, biliary and urinary systems. Secondly, with hypersecretion of hydrochloric acid, which causes ulceration in the stomach and bulb of the duodenum, which have specific protection from damage, there is no logical explanation why the esophagus, which does not have such protection, is not damaged by refluxant. By the last decade of the 20th century, it became clear that radiological examination based on the detection of episodes of reflux had low reliability. For example, in a significant number of patients with typical symptoms of GER, including those with a diagnosis confirmed by gastroscopy, reflux was not detected during x-ray examination (false negative diagnosis). In rare cases, episodes of reflux were observed in the absence of clinical symptoms and normal gastroscopy (false positive diagnosis) [33,34]. Subsequently, another feature of GER was discovered: at least 20–30% of patients with GER had no obvious symptoms of the disease [23,24] or had only non-typical symptoms, for example, from the nasopharynx [22]. Comparison of the above data allows us to draw the following conclusions. (1) Standard GI x-rays studies give a high false negative rate. (2) However, the detection of barium reflux in patients without significant clinical symptoms, without signs of inflammation on gastroscopy, and at pH < 4% on pH monitoring does not mean that we are dealing with a false positive conclusion and does not mean that reflux can be physiological. First, because GER can be asymptomatic. Second, gastroscopy does not reveal the so-called non-erosive GER.

X-ray study with provocative tests

To increase the reliability of radiographic diagnosis of GER, researchers have begun to use provocative tests, simulating conditions that contribute to reflux. They recorded fluoroscopic observations of spontaneous reflux and of reflux elicited by coughing, the Valsalva maneuver, rolling from supine to the right lateral position, and the during water-siphon test [37,38]. Barium studies showed unprovoked, spontaneous reflux in 26% of subjects proved by pH measurements to have gastroesophageal reflux. When the water-siphon test was used, the sensitivity of fluoroscopic detection rose to 70%, with a specificity of 74% and positive predictive value of 80%. Meanwhile, clinically significant reflux was detected radiographically in five patients in whom it was not detected by pH monitoring [39]. In all articles the reliability of radiological diagnosis of GERD compares with the results of pH monitoring, which has long been considered the gold standard. This has led to the national gastroenterology guidelines do not recommend barium esophagography for the evaluation of GERD, where clearly state that "barium radiographs should not be performed to diagnose GERD; listed as a strong recommendation with a high level of evidence" [40]. Currently, pH monitoring is

not recognized as the gold standard, because about 30% of patients with GERD are not diagnosed with this method [41,42]. Moreover, it is not uncommon for proven GERD to be diagnosed with X-ray but denied by pH monitoring [39,43].

X-ray visualization of the lower esophageal sphincter

Determination of the normal length of the LES

Considering that an increase in pressure in the stomach causes an increase in the tone of the LES, we applied abdominal compression while taking barium in a horizontal position. In patients without GERD symptoms, peristalsis of the esophagus despite abdominal compression pushed the contrast agent into the stomach without delay (Figure 1, a, b & c). In some patients during abdominal compression between the esophagus and stomach, filled with barium, a gap appeared without contrast material (Figure 1d). These observations showed that in healthy individuals it is impossible to measure the length of the LES because the LES does not close under abdominal compression. At the same time, based on manometric and histological studies, it is known that in some patients with GERD the length of the LES is shorter than normal. It is shortened due to weakening and opening of the abdominal part of the LES [20,25,44-46]. To measure the length of the LES, to eliminate the possibility of error because of the simultaneous contraction of the crural diaphragm (CD), I performed an X-ray of the EGJ after 30

seconds of abdominal compression. As Shafik et al showed that "The CD response disappeared when straining was sustained for more than 15-18 seconds (mean 16.8 ± 1.2) and was not evoked after frequent successive straining... due to the fact that the CD consists of striated muscle fibers which are easily fatigable and cannot remain contracted for long period" [47]. Thus, abdominal compression for 30 seconds allowed only the length of the LES to be measured, because by this time the CD was already in a relaxed state. It should be noted that the strength of abdominal compression is not of significant importance, since contraction of the anterior abdominal wall is a standard response of the child to abdominal compression. In a previous study to determine the standards, we selected 42 studies in which abdominal compression resulted in LES contraction. These were patients with mild GERD, in whom GERD symptoms were either absent or appeared less than a month ago. Therefore, we considered that the length LES did not have time to change significantly compared to the norm. On radiographs, we measured the width of the esophagus and the length of the gap between the barium in the esophagus and stomach (see Figure 1). To get the true dimensions, we multiplied the readings measured on the X-ray by the projection distortion factor. The latter is equal to the ratio of the true L-1 height for a given age (Table 1) to the height of its image on the roentgenogram [26].

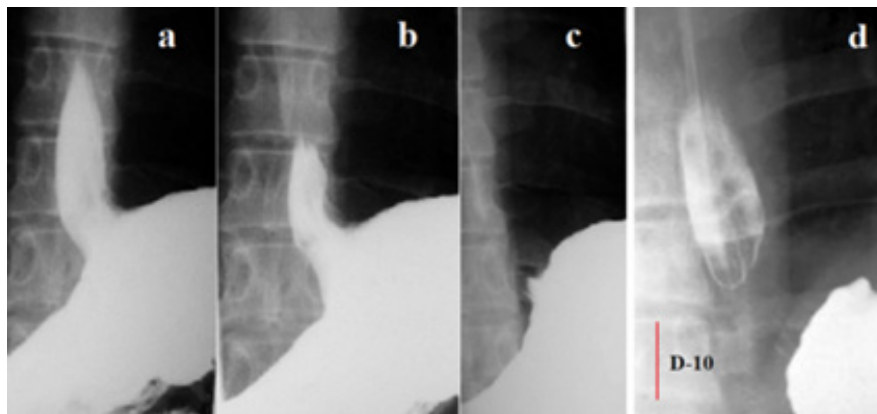


Figure 1. The passage of the bolus through the EGJ during abdominal compression in the horizontal position of patients. **(a, b, c)** In a patient without GERD symptoms, the peristaltic wave overcame the increased tone of the LES, because of which barium passed into the stomach without delay and the LES could not be detected. **(d).** In a patient with GERD, as evidenced by longitudinal folds in the esophagus and at the level of the LES, abdominal compression resulted in LES contraction. Its length can be measured as the distance without contrast medium between the esophagus and the stomach. Since the height of D-10 is approximately 2 cm, the true length of the LES can be calculated. It is 2.4 cm.

Table 1. Height L-1 (cm) in children of different ages (1-15 years)

Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
L-1	1.3	1.4	1.4	1.5	1.5	1.6	1.7	1.8	1.8	1.8	1.9	2.0	2.1	2.2	2.2

The true sizes of LES in different age groups are shown in Table 2.

Table 2. Normal length LES in different age groups

Age	Length of lower esophageal sphincter (cm)					
	Up to 1 year	1–3 years	4–7 years	8–10 years	11–15 years	21–65 years
Limits	0.7 – 1.0	1.2 – 1.5	1.5– 1.8	1.9 – 2.3	2.3 – 2.9	3.2 – 4.2
M± M	0.86±0.03	1.40±0.02	1.72±0.07	2.10±0.05	2.45±0.11	3.60±0.08

I believe that the results obtained are close to the true ones, since they coincide with the normal length LES measured by the manometric method in adults: 34 ± 9 mm [20], 35 ± 4 mm [21]; 36 ± 12 mm [22]; 37 ± 1 mm [23]; 4.1 cm [24].

Mapping of the esophago-gastric junction (EGJ)

On some radiographs in adult patients with GERD during the contraction of the LES, it is noticeably shorter than normal both due to the opening of its proximal and distal (abdominal)

parts. In such cases contracted only the segment of the LES that is in the diaphragmatic (hiatal) channel. On numerous radiographs, the minimum length of this segment was 1 cm. By comparing different radiographs and determining the true dimensions, I was able to determine the different parts of the LES and their relationship with the CD, i.e., create a map of the EGJ. A typical example is shown in **Figure 2 a. b. c.**

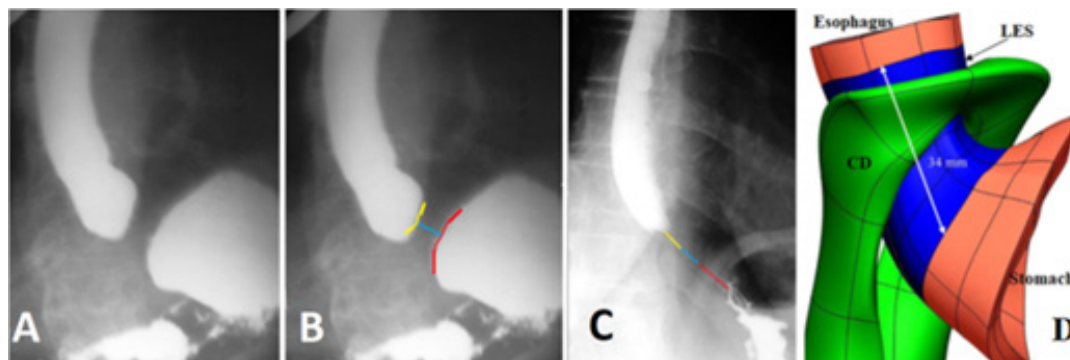


Figure 2. Radiograph (A) and scheme to it (B) of patient with GERD was done in a horizontal position with the abdominal compression. The sharp shortening of the LES because of the opening of the supra-diaphragmatic part of the LES (yellow) and inside the abdominal part of the LES (red) is determined. Only the diaphragm part (blue) of the sphincter is closed. (C). Radiograph of this patient in an upright position taken during abdominal compression. The LES contracted in response to the increased pressure in the stomach. It is visible as two longitudinal folds between the esophagus and stomach. Since the actual height of D-10 is ≈ 2 cm, the actual length of the LES is ≈ 3.4 cm. The LES parts: red - the abdominal segment, blue - inside the diaphragm, yellow - above the diaphragm. (D). Three-dimensional model of the EGJ from the article by Yassi et al [48]. The length of the LES is 3.4 cm (blue). Its abdominal part is ≈ 2 cm. About 1 cm is located at the level of the CD and 0.4 cm above the diaphragm.

The aim of this study is to increase the accuracy of GERD diagnostics using the highest possible gastric pressure that causes simultaneous contraction of both the upper and lower esophageal sphincters [31]. From the point of view of GERD pathophysiology, the maximum load on the LES will allow measuring only the functioning part of the LES, while the supradiaphragmatic and intra-abdominal parts weakened by the inflammatory process will open, unable to withstand the tension. Secondly, creating high pressure during continuous barium drinking will allow creating a trap for the contrast agent between the UES and LES to accurately

determine the width of the esophagus, its walls, tone and functional sphincters that occur in GERD.

METHOD. X-RAY EXAMINATION OF THE ESOPHAGUS AND ITS SPHINCTERS AT MAXIMUM PRESSURE IN THE STOMACH

This method can be part of an X-ray examination of the esophagus, stomach, and duodenum or as an independent study if the suspicion of GERD was not confirmed after endoscopy. The patient, lying on the X-ray table, continuously drinks barium suspension through a straw from a jar standing

at his head. When the barium runs out (200-250 ml), he immediately raises his straightened legs. At this moment, an x-ray is taken from the pharynx to the body of the stomach. It should be noted that a delay between the last swallow and the x-ray may necessitate a repeat examination because the x-ray will only show traces of barium in the esophagus. After

the first radiograph, the subject gets up, but after 5 minutes he lies down again on the X-ray table. A second radiograph is taken at rest to determine the completeness of barium evacuation into the stomach and the possibility of free reflux (Figure 3).

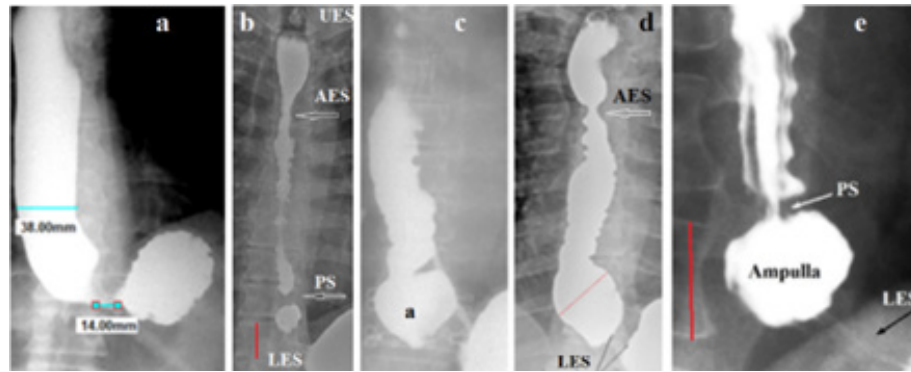


Figure 3. Radiographs of patients with GERD performed at high pressure in the stomach. **(a).** A sharp expansion of the esophagus (3.8 cm with a norm of 1.5 cm), and a significant shortening of the LES (1.4 cm with a minimum norm of 3.2 cm). **(b).** The patient takes only liquid food with frequent vomiting after meals. Signs of severe esophagitis are combined with high tone of the esophagus (narrow lumen). LES is 2 cm long with the presence of folds. The proximal sphincter (PS) is 0.7 cm long. An expanded segment of the esophagus is determined between upper esophageal sphincter (UES) and aortal esophageal sphincter (AES). **(c).** Expansion of the esophagus and the phrenic ampulla {a}, shortening of the LES, uneven contours of the esophagus. **(d).** Typical functional narrowing at the level of the aortic arch in a patient with extraesophageal symptoms that disappeared after taking a 1.9 cm tablet. This is the aortic esophageal sphincter (AES) that I described, which occurs in GERD because of acid retention at the site of an anatomical narrowing of the esophagus [49]. **(e).** The functional proximal sphincter (PS) has contracted above the phrenic ampulla. It occurs in GERD to close the ampulla proximally. This allows pressure in the ampulla to be higher than in the stomach to expel the bolus into the stomach. The difference in the shape of the folds in the esophagus and LES (2 cm long) is due to different width and tones [50,51].

Radiometric analysis of radiographs

This method allows using mathematics to analyze the condition of the esophagus and LES. The expansion of the esophagus by more than 1.5 cm indicates GERD. However, the inflammatory process may be accompanied by increased tone of the esophagus, which leads to narrowing of its lumen. The most reliable and permanent sign of GERD is shortening of the LES below the minimum age norm. In all radiographs of adult patients, the LES was significantly shorter than 3.2 cm. Projection increase should always be considered. For example, in Figure 3e, the LES looks quite long. Considering that the height of D-9 is 1.9 cm, therefore the length of the LES is 1.7 cm, which is almost 2 times less than the norm (3.2 cm). Secondly, despite the presence of long folds, this reduced sphincter cannot be a CD, the length of which is 1 cm. Thirdly, this sphincter cannot be a CD, also because after 30 seconds of abdominal compression it cannot remain contracted. The width of the ampulla is 2 cm, and it cannot be a displaced stomach, because the LES has not displaced,

but has decreased in length. The ampulla is proximally overlapped by the abbreviated proximal sphincter, 0.5 cm long, which cannot be the LES, displaced into the chest. These data confirm the results of the studies of Chandrasoma and DeMeester, which show that the folds above the stomach are not related to the stomach. In GERD, the folds are into the esophagus and LES [44]. They differ in shape because the width and tone of these sections are different. Radiometric analysis and histological studies have also proven: (1). The esophagus does not shorten either during swallowing or during GERD. (2). In GERD, the LES shortens because of the opening of its intra-abdominal portion. (3). The LES does not shift cranially. (4). The dilatation of the esophagus above the LES, called the phrenic ampulla, occurs only with GERD. (5). The phrenic ampulla, regardless of its size (<2 or >2), is not a hiatal hernia. (6). The short constriction above the ampulla is a contraction of the functional PS. (7). Longitudinal folds above the stomach are in the LES and indicate an inflammatory process [19,26,44,50].

Advantages of the proposed method

1. The test is simple and safe. It takes only a few minutes, does not require X-ray observation, is accompanied by minimal X-ray exposure, and does not require special training of a radiologist.
2. It is scientifically based, as it is based on the etiology, pathogenesis and pathological physiology of GERD, and diagnosis is based on symptoms that distinguish pathology from the norm.
3. Due to the contraction of both esophageal sphincters during barium intake, tight filling of the esophagus was possible for the first time. This allows measurement of the width of different parts of the esophagus and the length of the LES, PS as well as visualization of AES.

Radiological symptoms of the GERD

Radiological symptoms of the GERD can be divided into the functional, as well as associated with changes of the esophagus or of the LES.

- A. Functional symptoms of the GERD:** (1) Contraction of the LES with high gastric pressure. (2) Reflux of gastric contents into the esophagus. (3). Incomplete cleansing of the esophagus from the contrast agent.
- B. Changes in the esophagus with GERD:** (1). Dilation of the esophagus more than 1.5 -1.7 cm. (2). The presence of a phrenic ampulla regardless of its width. (3). Longitudinal folds of the esophagus. (4). Asymmetrical finely wavy contours. (5). Functional symmetrical narrowing above the ampulla (PS) or at the level of the aortic arch (AES). (6). Peptic asymmetrical constriction, as well as Schatzki ring [50].
- C. The LES changes in GERD:** (1) The shortening of the LES is less than the minimum age limit. (2) Longitudinal folds at the level of the LES. (3) Small gas bubble in the stomach. (4). Obtuse angle of His (Figure 4).

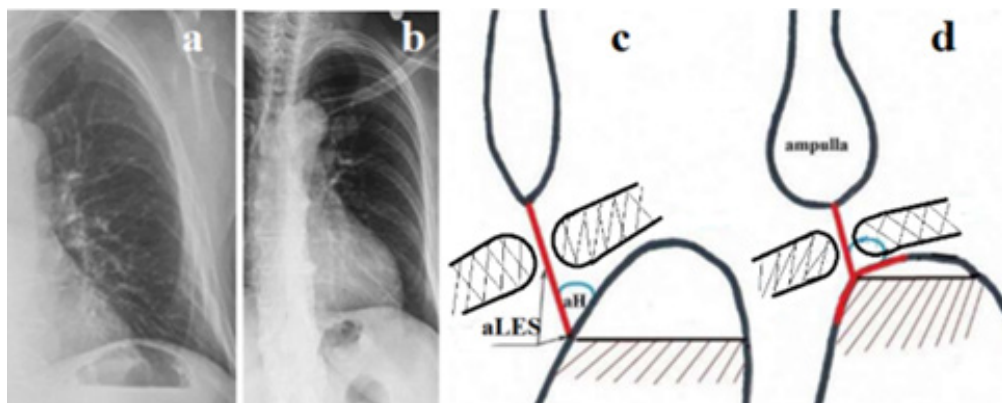


Figure 4. (a-b). Radiographs of the left dome of the diaphragm of a healthy person (a) and a patient with GERD (b). (c). Scheme of the EGJ with normal LES function (red). The angle of His (aH) is acute. Large gas bubble in the stomach. (d). In GERD, the LES is shortened because the abdominal part of the LES (aLES) is not functioning. This leads to an increase in the angle of His and a decrease in the gas bubble of the stomach due to belching during transient relaxation of the weakened part of the LES.

As shown by histological studies of Chandrasoma and DeMeester, GERD begins with the penetration of hydrochloric acid into the intra-abdominal part of the LES. It follows that, at least up to this point, acid does not penetrate the esophagus, which contradicts the idea of the possibility of physiological reflux in healthy individuals [44]. The same authors found that damage to the LES by acid leads to the opening of its intra-abdominal part. This part ceases to participate in the antireflux function. My radiological studies are completely consistent with the histological studies of Chandrasoma. These studies irrefutably prove: (1). Any recurrent (not accidental) episode of reflux damages the

LES and the esophagus; (2). Damage to the LES leads to its shortening and a decrease in its antireflux function; (3). An increase in the angle of His is a result of shortening of the LES and is not a predisposing factor for GERD; (4). Weaknesses of the LES causes belching, which is not seen in healthy people. Most children and adolescents do not know what belching is. (5) A reduction in the gas bubble in the stomach is evidence of weakness of the LES and can be used to screen for GERD.

MATERIAL

Clinical characteristics of patients

The maximum provocation method was used to examine

60 patients, with a slight predominance of women (55%). Except for 3 patients under the age of 20 years, the remaining patients were aged from 53 to 76 years (62 ± 4). All patients had GERD symptoms that they could not control, including 53 patients who received PPI. In 39 cases, patients underwent endoscopy from 1 to 4 times. In only one case, erosion was found in the esophagus, the benign nature of which was confirmed by histological examination. A small diaphragmatic hernia was described in two patients. In 18 patients, gastritis was diagnosed with endoscopy. Thus, only one of 39 patients was diagnosed with erosive esophagitis, confirming the diagnosis of GERD. In 38 (97%) patients, endoscopic examination without histology did not reveal evidence in favor of GERD. Even though taking PPI did not relieve patients from debilitating symptoms, only

2 patients were referred for pH monitoring. Each of them had a DeMeester score below 4. Analysis of medical history revealed a surprising pattern. The disease always began with heartburn. After some time, pain syndrome was recorded more often, from a pressing feeling behind the sternum to pain in the epigastrium. Heartburn occurred only after eating excess food. Despite occasional heartburn, abdominal pain, or belching, patients considered themselves healthy for a long period. In some patients, symptoms returned after many years and more often than in the early period, extraesophageal symptoms (hoarseness or alteration of voice, sensation of foreign body in throat, importunate cough, etc.) were bothered. Figure 5 provides examples of low pain sensitivity of the esophagus with complete incompetence of the LES (chalasia of EGJ).

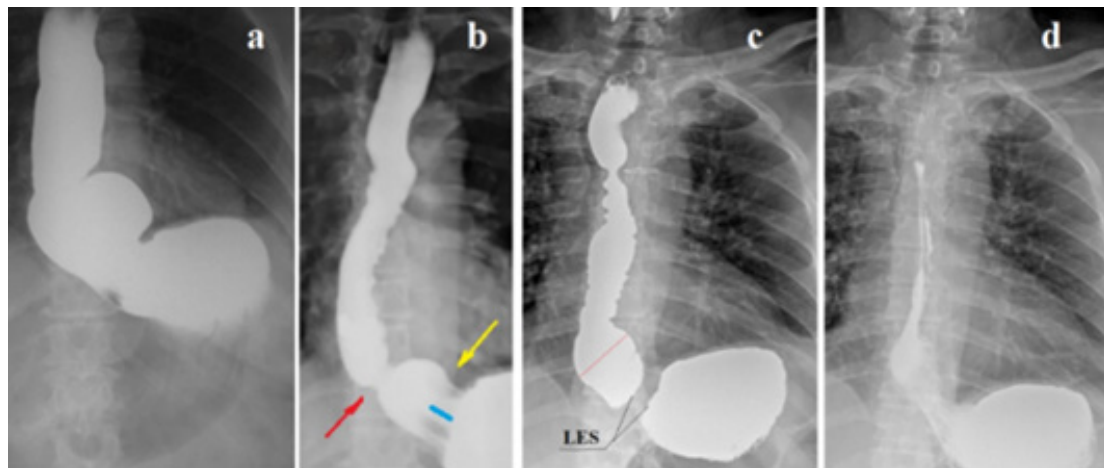


Figure 5. Radiographs of patients with chalasia EGJ. (a-b). A 68-year-old woman has been ill since her youth, when heartburn appeared. She was diagnosed with asthma when she was young. The bronchospasm attacks passed. Recently, small amount of milk in coffee causes severe heartburn after 15-30 minutes. She takes 20 mg of PPI per day, which is enough to prevent heartburn. Repeated endoscopy always revealed only a “hiatal hernia.” (a). During maximum provocation, a sharp dilation of the esophagus is visible, especially in its ampullary region, as well as a sharp dilation of the esophageal opening of the diaphragm. (b). After 5 minutes, free reflux from the stomach into the esophagus is determined. (c-d). A 72-year-old man complained of a debilitating cough, change in voice, and a sensation of a foreign body in the throat for 4 months. Very rarely small pieces of food appear in the mouth. For a month he woke up at night because he is choking on saliva. He does not feel any acid or bitterness in his mouth. He has no heartburn, pain, or dysphagia. About 15 years ago he had heartburn, which went away only after swallowing a tablet with a diameter of about 3 cm. Since then, he considered himself healthy. (c). A sharp shortening of the LES (1 cm), expansion of the esophageal ampulla and symmetrical narrowing of the esophagus at the level of the aortic arch (arrow) are detected. (d). After 5 minutes, free reflux of barium from the stomach into the esophagus is determined. The patient swallowed a tablet with a diameter of 1.9 cm. After this, he stopped choking on saliva at night. This is a typical example of the formation of a functional sphincter (AES) over the aortic narrowing of the esophagus.

These typical cases show that (1) in the process of ontogenesis, the clinical symptoms of GERD can change significantly; (2) over time the esophagus loses pain sensitivity, which can be explained by the damage to the sensitive elements in the esophageal mucosa by the gastric juice; (3) lactose triggers GERD symptoms without reaching the colon. Symptoms are felt more quickly with chaliasia of EGJ, since excess hydrochloric acid, as soon as it appears in the stomach, immediately enters the esophagus.

RESULTS

In 59 of 60 patients with clinical symptoms, that may be in reflux, the diagnosis of GERD was not in doubt, including 38 patients in whom endoscopy did not reveal any changes in the esophagus, and in 2 patients in whom Demeester score was $< 4\%$. In only one case radiological findings did not confirm the diagnosis of GERD (Figure 6.a).

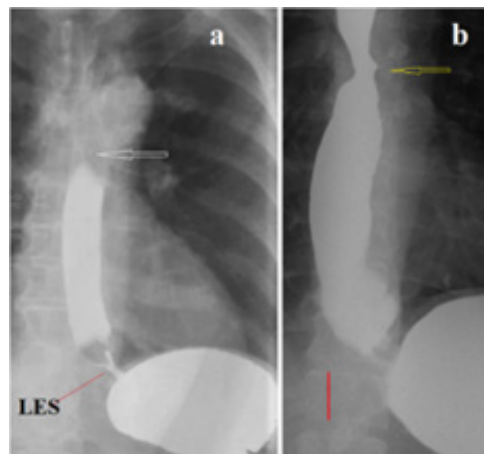


Figure 6. (a). A 71-year-old woman in the past few months, several non-esophageal complaints have developed (voice change, copious sputum, cough after drinking, difficulty breathing, chest pain, and severe weakness). Prior to this, there were never any symptoms from the respiratory and digestive systems. On the radiograph, the anterior point of the traveling peristaltic wave is shown by an arrow. The esophagus is not dilated (1.7 cm) with smooth wall without ampullary expansion. The LES is open. It is significantly shorter than normal, but all sphincters shorten during opening. The diagnosis of GERD was not confirmed. **(b).** A woman of 63 years old considers herself sick for 10 years with the onset of severe pain in the epigastrium. Over the course of 10 years, gastritis was diagnosed 4 times by gastroscopy. Two years ago, every morning, she was worried about a painful cough and a sore throat. Several times at night, she woke up with attacks of suffocation and with a feeling of strong acid in her mouth. At pH study Demeester score was 3.2. High pressure in the stomach led to a contraction of the LES, the length of which (1 cm) is significantly less than the minimum normal limit (3.2 cm). The esophagus is dilated (2.8 cm) with an uneven left contour. The phrenic ampulla is 3.3 cm wide. A sharp asymmetric narrowing at the level of the aortic arch is detected (AES), which was not detected during subsequent gastroscopy. Relief came after swallowing a dense tablet with a diameter of 2.2 cm. Six months later, she asked for a second tablet.

First, all patients with clinical symptoms ГЭРБ этот диагноз был подтвержден рентгенологически. This indicates that the so-called functional disorders of the esophagus are nothing more than GERD. Secondly, the diagnosis of GERD was established in 2 (3%) of 59 patients in whom the DeMeester score was $< 4\%$. This confirms previous evidence that reflux of gastric contents with a pH $< 4\%$ for one hour out of a 24-hour study period cannot fail to cause esophageal injury. In 38 (64%) patients whom GERD was not detected by endoscopy, despite the frequent detection of gastritis, and duodenitis. Damage to the stomach and duodenum indicate hypersecretion of hydrochloric acid. Since the mucous

membrane of the esophagus does not have protection, unlike the mucous membrane of the stomach and duodenal bulb, the very fact of these diagnoses is evidence of GERD. Third, the X-ray method is based on the contrast between the pathological and normal physiology of the EGJ, which distinguishes it from other diagnostic methods. Fourth, the X-ray examination does not change the physiology of the EGJ, since it does not use intraesophageal instruments that affect its physiology. Fifthly, this study is visual and accurate as it uses mathematical analysis. It follows that x-ray examination with maximum provocation has a higher diagnostic accuracy than pH monitoring and endoscopy.

DISCUSSION

I for the first time determined the length of the LES in people of different ages using X-ray examination. These figures are probably close to the true ones since they coincide with the results of manometric studies [20-24], and the three-dimensional model EGJ by Yassi et al [48]. The present study found a shortening of the LES less than the minimum normal limit in all patients with GERD symptoms. This is consistent with the scientific understanding of the pathophysiology of GERD. Chemically aggressive stomach contents primarily damage the function of the LES, resulting in the opening of its intra-abdominal portion, which ceases to perform an antireflux function [23,24,44]. During an increase in pressure in the stomach, only the proximal part of the LES contracts. Thus, in GERD, shortening of the LES always occurs. The degree of shortening of the LES depends on both the degree of its damage and the magnitude of the provocation. Therefore, to accurately determine the functioning length of the LES I used maximum provocation of dual origin. (a). Rapid uninterrupted drinking of a large volume of contrast agent. (b). With the simultaneous creation of the greatest possible pressure in the stomach, which was carried out by raising straightened legs. It turned out that in healthy individuals this provocation did not affect the bolus passage through the EGJ. In patients with GERD, a reflex increase in the tone of the UES and LES led to their contraction, which was an important diagnostic sign of GERD. In addition, the length of the LES could be used to judge the degree of its damage. Filling the esophagus between two closed sphincters allows one to judge the actual width of the esophagus, as well as better identify functional and peptic narrowing in it. The second radiograph, taken 5 minutes later in a calm state, determines the possibility of free reflux and the degree of clearing of the esophagus from the contrast agent. As a result of using this method in 60 patients with at least one of the symptoms of GERD, the radiological diagnosis of GERD was beyond doubt in 59 (98%), which made it possible to apply pathogenetic treatment for GERD. In one case, where GERD was excluded, there was no pain syndrome. The study was performed due to the possibility of non-esophageal symptoms of GERD.

Before X-ray examination, pH monitoring was performed in 2 patients (3%). In both cases, the DeMeester score was <4%, which according to Lyon consensus 2.0 is a sign of functional disorder (reflux hypersensitivity, functional heartburn, etc [52]. However, in these 2 patients, as in the remaining 59 patients, organic damage to the EGJ was detected with a length of the LES less than the minimum limit of normal (3.2 cm).

The modern stage in the development of gastroenterology began with articles by DeMeester et al [16,17]. In 1976

they published an article proposing a normal range for esophageal pH monitoring. It was defined as $\text{pH} < 4$ for 4% of the 24 hours of monitoring 5 cm proximal to the LES. To do this, the authors examined 15 individuals who believed that they had no problems with the digestive system. Since then, this boundary has been called the "DeMeester score", and the proposed method of pH monitoring has long been considered the gold standard for diagnosing GERD. However, pH monitoring had no theoretical basis. The study of pH in the esophagus initially suggested the possibility of physiological reflux. It contradicted previous scientific research. Moreover, this is contrary to common sense, because it is impossible even to assume that the acid, which leads to the development of ulcerative lesions of the stomach and duodenal bulb, the mucous membrane of which has protection, may not cause a pathological process, being in the esophagus for about an hour throughout the day. Moreover, the esophagus has only mechanical protection provided by the EGJ. Based on histological studies of Chandrasoma, DeMeester et al. it has been shown that reflux begins in the penetration of hydrochloric acid into the abdominal part of the LES, which weakens and opens because of damage. Until this time, acid does not enter the esophagus. Acid enters the esophagus in a later period, when the squamo-oxyntic gap increases more than 15 mm [44]. It follows that reflux as a normal phenomenon, i.e., physiological reflux can't be. Based on pH monitoring, it is believed that pathological reflux in infants is diagnosed when the reflux index is $> 10\%$ [51]. It follows that at reflux index $< 10\%$ when for 2.3 hours out of 24 hours of monitoring, an acid bolus with $\text{pH} < 4$ is in the esophagus, GERD can be excluded. This is contrary to studies by Salvatore et al. Esophagitis was present in 17 of 44 (39%) infants who underwent endoscopy with esophageal biopsy for suspected GERD. 38% of infants with a pathologic pH study had a normal esophageal biopsy and 53% of infants with histologic esophagitis had a normal pH study. Discordance between pH study and biopsies occurred in 14 of 44 (32%) patients" [53]. This study showed that neither endoscopy nor pH monitoring were accurate enough to reject the diagnosis of GERD, which is confirmed by our data.

Demeester et al defined the "normal" limit based on a survey of 15 individuals who denied typical symptoms of reflux disease. However, it is known that the overall prevalence of esophageal disorders among supposed health individuals by GI endoscopy was 17.3% -20% [12,36]. In addition, it is known that the diagnostic accuracy of endoscopy is also not high. From which it follows that a significant percentage of people who consider themselves healthy are patients with GERD. To select individuals without GERD as a control, it was necessary to perform an X-ray examination and endoscopy with histology. As a result of a violation of

the scientific research methodology, it turned out that ambulatory 24-hour esophageal pH measurement has a false negative rate of 15% to 30% [12,13,36]. Therefore, pH monitoring diagnoses only severe forms of GERD. Almost 30% of patients with GERD who do not have frequent, annoying complaints are not examined because they do not fall under the Montreal definition of disease ("condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications") and these patients do not receive pathogenetic treatment until they develop a severe form that is difficult to treat. A significant number of patients with GERD with troublesome or atypical symptoms, who have a Demeester score below the norm, are diagnosed with functional disorders (hypersensitive esophagus, functional heartburn, irritable bowel syndrome and functional dyspepsia) and these patients also do not receive pathogenetic treatment. It follows from this that pH monitoring cannot serve as a criterion of truth [54,55].

According to the Lyon consensus 2.0 expert decision, determined by voting using the Delphi method, the patients who had typical GERD symptoms and AET < 4% without erosion were divided according to symptom association probability (SAP) and symptom index (SI). Patients who had pH-impedance monitoring both positive SAP ($\geq 95\%$) and SI ($\geq 50\%$) were classified as RH (reflux hypersensitivity). Patients who had both negative SAP (< 95%) and negative SI (< 50%) were classified as FH (functional heartburn). HC (healthy control) had normal UGE, 24-hour pH-impedance monitoring and high-resolution manometry [52,56]. Experts who claim that accurate diagnosis of GERD is possible only with pH monitoring, 24-hour pH-impedance monitoring and high-resolution manometry, do not refer to the laws of physiology, the state of the LES and completely ignore numerous articles that pH monitoring has more than 30% false-negative conclusions. This means that in patients with RH and FH, hydrochloric acid with a pH < 4, was present in the esophagus for an hour out of 24 hours. In the same review, the authors provide evidence of the effectiveness of PPI treatment in more than 50% of patients with RH. The Nissen fundoplication improved or resolved reflux symptoms in 85% of RH patients even 5 years after the surgery, which was like patients with pathological acid exposure. These data refute the assertion that weakly acidic reflux (AET < 4%) is physiological, i.e., does not damage the esophagus. The authors state that several studies demonstrated esophageal hypersensitivity to esophageal balloon distension compared to those with NERD, Barrett's esophagus or asymptomatic healthy subjects. In evaluating these data, the authors ignore the duration of the disease and the degree of esophageal damage. It is known that "GERD is typically heralded by the substernal burning pain of heartburn" [57]. However, about

17% of patients with erosive esophagitis, i.e., with a more severe form of GERD, consider themselves healthy [13]. This suggests that damage to the esophagus by acid reduces sensitivity to pain. Shieh et al showed that patients with achalasia of the esophagus after POEM surgery 26 (41.9%) had erosive esophagitis, but only 12 had GERD symptoms [58]. Barrett's esophagitis is a later and more severe stage of GERD. Thus, heartburn is an early, reliable symptom of GERD because of the normal pain response of the esophageal wall. More severe forms of GERD are less responsive to damage because of the loss of pain-sensitive nerve elements in the esophageal wall. Thus, functional heartburn is not a factor contributing to GERD, but a result of damage to the LES and the esophageal wall [59]. The two experts' consensuses, Rome IV criteria and the Lyon consensus, are the bedrock of RH diagnosis. Recently, Savarino et al. stated that "recent pathophysiological and therapeutic data suggest the need for a return to including reflux hypersensitivity in the GERD spectrum [60]. This statement debunks the scientific value of the recommendations that arise from voting using the Delphi method.

Science is based on irrefutable evidence. Medicine is no exception. It develops thanks to the analysis of assumptions, which are called hypotheses. If, during hypotheses testing, its accuracy is confirmed, it becomes a theory. But if, during the research, at least one irrefutable piece of evidence is found that contradicts the hypothesis, then the hypothesis must either be rejected or changed. Numerous irrefutable pieces of evidence have been presented above that the hypothesis about the possibility of functional reflux, which allegedly does not damage the LES and esophagus, is false. Therefore, all research methods (pH monitoring, pH-impedance monitoring) based on a false hypothesis have no diagnostic value.

Since all studies are conducted exclusively with pH monitoring, voting participants using the Delphi method are forced to ignore some of the scientific achievements of previous generations to explain the full spectrum of clinical manifestations of GERD. At the same time, numerous explanations (hypotheses) are proposed that have no evidence. The Delphi voting methodology is designed to solve organizational problems, not to make scientific decisions. Secondly, it is very important to know who selects the voting participants and by what principles. In a review, Hungin et al experts from general practice, gastroenterology and gastropsychology rethought the "ladder" approach to reflux-like symptom management [61]. Turning to Hungin's articles, I found the following ideas about GERD: "none of these ('excessive acid' into the oesophagus; 'failure of the valve' at the gastro-oesophageal junction; 'delayed gastric emptying'; and 'damage' at the lower oesophagus) holds

true. GORD IS NOT NORMALLY RELATED TO EXCESSIVE ACID. The “excess acid” explanation is clearly flawed, as acid secretion levels are normal in people with GERD. There is no consistency from symptom association analyses when symptoms are evaluated against pH monitoring. It is likely that no such entity as GORD actually exists” [62]. This position shows how reliance on pH monitoring undermines scientific understanding of the etiology, pathogenesis and pathophysiology of GERD.

Kahrilas’ review article states that GERD is thought to develop to the increase in reflux by “significantly increasing the rate of transient lower esophageal sphincter relaxations (TLESRs)”. Surprisingly, in the same article, Kahrilas changes his opinion about the frequency of TLESRs: - “Patients with GERD have an equal frequency of TLESRs compared with normal individuals, although they have a higher percentage of TLESRs associated with reflux” [63]. He associates TLESRs with the increase in pressure in the stomach, ignoring the reliable scientific fact that, normally, the increase in pressure in the stomach causes an increase in the tone of the LES [19,26,34,51]. The diagnostic technique for GERD presented in this article convincingly proves that the increase in pressure in the stomach causes a contraction of the LES. With GERD, unlike the norm, the LES, weakened by the inflammatory process, relaxes, unable to withstand prolonged tension. It follows that TLESRs are a manifestation of weakness of the damaged LES and are observed only in GERD. The false idea of the possibility of TLESRs in healthy people is due to the recognition of GERD patients as healthy based on the DeMeester score < 4%. The statement by Masui et al. that the normal number of belches per day can reach 13 [65] is the result of examining patients with a DeMeester score <4%. Most children, adolescents, and young adults never belch. It follows that the air swallowed with food is utilized in the intestine. Belching occurs only in patients with GERD during relaxation of the damaged LES, as shown in Figure 4. To somehow explain the discrepancy between endoscopic data and pH monitoring, Leon consensus 2.0 stated that: - “later studies have demonstrated grade A oesophagitis in 5%–7.5% of healthy subjects” [52]. It is impossible to list such “scientific” achievements of experts from different gastroenterological consensuses in this article.

In my previous studies, I have proven that the erroneous idea of esophageal shortening is because in patients with GERD, during shortening of the LES, which leads to shortening of the esophagus + LES complex, it was considered as shortening of the esophagus. Clips attached to the esophageal mucosa changed their relationship to the peristaltic wave, but did not move relative to the bony landmarks [51]. Convincing histological studies by Chandrasoma and DeMeester have proven two dogmas to be incorrect: (1) that cardiac

epithelium normally lines the proximal stomach; and (2) that the gastroesophageal junction is defined by the proximal limit of rugal folds [44]. It follows that the LES does not move cranially, and the dilation of the esophagus in GERD, which is called a hiatal hernia, is a phrenic ampulla, regardless of its size. This ampulla during contraction is proximally blocked by a functional sphincter (proximal sphincter - PS), which provides high pressure in the ampulla to open the LES so that it is higher than the gastric pressure. Over time, the PS turns into a wide fibrous ring, clearly visible during gastroscopy. And in an allergic reaction, which is called eosinophilic esophagitis, it turns into a narrow rigid ring, called the Schatzki ring [50,55].

An analysis of the literature and our own research shows that GERD is a result of hypersecretion of hydrochloric acid, which is provoked in some of the population by genetically determined factors (lactose intolerance, allergy, histamine intolerance, etc.). GERD is always accompanied by other acid-dependent diseases (gastritis, duodenitis, ulcers, cholestasis). GERD begins with the penetration of hydrochloric acid and pepsin into the intra-abdominal part of the LES, which leads to chemical damage to its wall, an inflammatory reaction and opening. At this period, reflux into the esophagus is not observed, which excludes the possibility of functional GER. Gradually, because of shortening of the LES, the strength and duration of its contraction decrease, which leads to involuntary relaxation of the LES and penetration of a chemically aggressive refluxant into the esophagus. The inflammatory process in the esophagus causes its lumen to expand, especially the last peristaltic wave, which is called the phrenic ampulla. In the proximal part of the ampulla, a functional sphincter (PS) appears, which, by closing the ampulla, allows it to create high pressure, sufficient to open the LES and higher than the gastric pressure. This allows the ampulla to inject a bolus into the stomach, as well as close proximally and not let the refluxant pass in the cranial direction. The PS gradually turns into a wide fibrous ring or a narrow Schatzki ring in allergic esophagitis. As a result of chronic gastritis, the amount of hydrochloric acid decreases, but it continues to destroy food proteins and is therefore dangerous for the esophagus. With age, the amount of lactose taken in, which causes hypersecretion of hydrochloric acid, sharply decreases. Chronic esophagitis causes damage to the nerve elements in the esophageal wall, resulting in decreased pain sensitivity to chemical damage. The earlier the diagnosis is made and pathogenetic treatment is started, the greater the chances of preventing the progression of the disease.

CONCLUSION

X-ray examination of the esophagus with provocation of

maximum pressure in the stomach, provides high accuracy of the diagnosis of GERD (98%). The most reliable sign of GERD was shortening of the LES less than the lower limit of the age norm. At the same time, high diagnostic accuracy of clinical symptoms was proven, which allows starting not "ladder", but complex treatment of the disease, regardless of the clinical symptoms. The proposed diagnostics showed the absence of functional diseases, including 2 (3%) cases, in whom the DeMeester score was <4%. In doubtful cases, endoscopy and/or x-ray examination with maximal gastric pressure are recommended to clarify the diagnosis.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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