INTRODUCTION

Gastro-esoghageal reflux disease is the most common esophageal disorder in children of all ages. GER signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus. Although occasional episodes of reflux are physiologic, exemplified by the regurgitation of normal infants, the phenomenon becomes pathologic (GERD) in children who have more frequent episodes or persistant, and thus produce esophagitis or esophageal symptoms, or in those who have respiratory sequelae ***(Richard et al., 2009).***

The lower esophageal sphincter (LES), supported by the crura of the diaphragm at the gastro-eophageal junction, together with valve-like functions of esophageo-gastric junction anatomy form the anti-reflex barrier ***(Behrman et al., 2009).***

Transient LES relaxation (TLESR) is the major primary mechanism allowing reflux to occur. Gastric distention (postprandially, or due to abnormal gastric emptying or air sallowing) is the main stimulus for TLESRs. Straining during the TLESR makes reflux more likely, as do positions that place the gastro-eophageal junction below the air-fluid in the stomach ***(Robert et al., 2009).***

Infant reflux becomes symptomatic during the first few months of life, peaking at about four months and resolving in

most by 12 months and nearly all by 24 months. Symptoms in older children tend to be chronic, waxing and waning, but completely resolving in no more than half, resembling adult pattern ***(Hal et al., 2009).***

Treatment of GERD includes various measures, conservative therapy and life style modification form the foundation of GERD therapy. Dietary measures for infants include normalization of feeding techniques, volumes, and frequency if abnormal. Positioning measures in infants (birth to 12 months of age), supine positioning may prompt regurgitation. Pharmacotherapy includes antacids which are the most commonly used anti-reflux therapy by acid neutralization, histamine-2 receptor antagonists (H2RAs) acting by selective inhibition of histamine receptors on gastric parietal cells, proton pump inhibitors (PPIs) acting decreasing gastric secretion, prokinetic therapy acting by decreasing LES pressure, surgery usually fundoplication is effective therapy for intractable GERD in children ***(Vandenplas et al., 2009).***

Approximately 80% of patients have a recurrent but non progressive form of GERD that is controlled with medications. Identifying the 20% of patients who have a progressive form of the disease is important, because they may develop severe complications, such as strictures or Barrett esophagus ***(Sherman et al., 2010).***

Aim of the Work

The aim of this study was to define the possible outcome of patients diagnosed with GERD after three years of completion of their treatment.

ANATOMY AND PHYSIOLOGY OF THE ESOPHAGUS

Anatomy of esophagus:

The esophagus is a 25-cm long muscular tube that connects the pharynx to the stomach. The length of the esophagus at birth varies between 8 and 10 cm and measures about 19 cm at age 15 years.

The esophagus extends from the lower border of the cricoid cartilage (at the level of the sixth cervical vertebra) to the cardiac orifice of the stomach at the side of the body of the 11th thoracic vertebra. The upper limit in the newborn infant is found at the level of the fourth or fifth cervical vertebra, and it ends higher, at the level of the ninth thoracic vertebra.

In its vertical course, the esophagus has 2 gentle curves in the coronal plane. The first curve begins a little below the commencement of the esophagus and inclines to the left as far as the root of the neck and returns to the midline at the level of fifth thoracic vertebra. The second curve to the left is formed as the esophagus bends to cross the descending thoracic aorta, before it pierces the diaphragm. The esophagus also has antero-posterior curvatures that correspond to the curvatures of the cervical and thoracic part of the vertebral column ***(Gray, 2008).***

The esophagus has 3 constrictions in its vertical course, as follows:

- The first constriction is at 15 cm from the upper incisor teeth, where the esophagus commences at the crico-pharyngeal sphincter; this is the narrowest portion of the esophagus and approximately corresponds to the sixth cervical vertebra.
- The second constriction is at 23 cm from the upper incisor teeth, where it is crossed by the aortic arch and left main bronchus.
- The third constriction is at 40 cm from the upper incisor teeth, where it pierces the diaphragm; the lower esophageal sphincter (LES) is situated at this level.

These measurements are clinically important for endoscopy and endoscopic surgeries of the esophagus.

The esophagus has been subdivided into 3 portions, as follows:

- The cervical portion extends from the crico pharyngeus to the suprasternal notch.
- The thoracic portion extends from the suprasternal notch to the diaphragm.
- The abdominal portion extends from the diaphragm to the cardiac portion of the stomach ***(Beasley, 1997)***.

The esophagus passes through the right crus of the diaphragm. In its abdominal course, it is covered with the

peritoneum of the greater sac anteriorly and on its left side, and it is covered with the lesser sac peritoneum on the right side. It comes to lie in the esophageal groove on the posterior surface of the left lobe of the liver and curves sharply to the left to join the stomach at the cardia. The right border continues evenly into the lesser curvature, whereas the left border is separated from the fundus of the stomach by the cardiac notch ***(Vollweiler and Vaezi, 2005).***

- **Blood supply**

The cervical portion is supplied by the inferior thyroid artery.

The thoracic portion is supplied by bronchial and esophageal branches of the thoracic aorta.

The abdominal portion is supplied by ascending branches of the left phrenic and left gastric arteries. ***(Gray, 2008)***

- **Venous drainage**

Venous blood from the esophagus drains into a sub-mucosal plexus. From this plexus, blood drains to the peri-esophageal venous plexus. Esophageal veins arise from this plexus and drain in a segmental way similar to the arterial supply, as follows:

- From the cervical esophagus, veins drain into the inferior thyroid vein.

- From the thoracic esophagus, veins drain into the azygos veins, hemiazygos, intercostal, and bronchial veins.
- From the abdominal portion, esophagus veins drain into the left gastric vein; the left gastric vein is a tributary of the portal system. ***(Larsen, 2001)***

- **Lymphatic drainage**

The esophagus has an extensive, longitudinally continuous, submucosal lymphatic system. The esophagus has 2 types of lymphatic vessels. A plexus of large vessels is present in the mucous membrane, and it is continuous above with the mucosal lymphatic vessels of pharynx and below with mucosal lymphatic vessels of gastric mucosa. The second plexus of finer vessels is situated in the muscular coat. Efferent vessels from the cervical part drain into the deep cervical nodes. Vessels from the thoracic part drain to the posterior mediastinal nodes and from the abdominal part drain to the left gastric nodes. Some vessels may pass directly to the thoracic duct.

Lymphatic drainage of the esophagus contains little barrier to spread, and esophageal lymphatics are densely interconnected. Hence, esophagus carcinoma can spread through the length of the esophagus via lymphatics and may have nodal involvement several centimeters away from the primary lesion ***(Beasley, 1997)***.

- **Nerve supply**

Recurrent laryngeal branches of the vagus nerve supply the striated muscle in the upper third of the esophagus, and cell bodies for these fibers are situated in the rostral part of the nucleus ambigous. Motor supply to the non-striated muscle is parasympathetic, and cell bodies for these fibers are situated in the dorsal nucleus of vagus. These fibers reach the esophagus through the vagus and its recurrent laryngeal branches. They synapse in the esophagus wall in the ganglia of sub-mucosal plexus (Meissner) and myenteric plexus (Auerbach). The myenteric is situated between the outer longitudinal and inner circular muscle fibers. From these plexuses, short, postganglionic fibers emerge to innervate the mucous glands and smooth muscle fibers within the walls of the esophagus.

Vasomotor sympathetic fibers that supply the esophagus arise from the upper 4-6 thoracic spinal cord segments. Fibers from the upper ganglia pass to the middle and inferior cervical ganglia and synapse on postganglionic neurons. The axons of these neurons innervate the vessels of the cervical and upper thoracic esophagus. Postsynaptic fibers from the lower ganglia pass to the esophageal plexus to innervate the distal esophagus. Afferent visceral pain fibers travel via the sympathetic fibers to the first 4 segments of the thoracic spinal cord.

Histologically, the esophagus has the following Four concentric layers:

- Mucosal layer
- Sub-mucosal layer
- Muscular layer
- Adventitial layer ***(Seybt et al., 2009).***

Mucosa forms the innermost layer and is formed by a non-keratinizing stratified squamous epithelium that is continuous with that of the pharynx. Mucosal epithelium changes from squamous cell epithelium to columnar cell epithelium at the gastro-esophageal junction. This junction has been termed the "Z line" or squamo-columnar junction.

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The third layer is formed by circular and longitudinal muscle fibers. The longitudinal layer is generally thicker than the circular layer; both are described as follows:

- Inner circular muscle fibers: These fibers are continuous superiorly with the fibers of the crico-pharyngeal part of

the inferior constrictor and inferiorly with oblique fibers of the stomach.

- Outer longitudinal muscle fibers: The longitudinal muscle fibers form a continuous coat around the whole of the esophagus except postero-superiorly, 3-4 cm below the cricoid cartilage; here, they diverge as 2 fascicles that ascend obliquely to the anterior aspect of the esophagus.

The proximal one-third of the esophagus consists primarily of striated muscle. Smooth muscle predominates in the distal portion.

The fourth and the outermost fibrous layer is formed by external adventitia of irregular, dense connective tissue containing many elastic fibers.

The esophagus has no serosa, which makes it unique to the rest of the gastro-intestinal tract ***(Postma et al., 2009).***

Physiology of the Esophagus:

The primary peristalsis in the cervical segment involves both central and peripheral mechanisms. The primary peristalsis consist of inhibition (called deglutitive inhibition) followed by excitation.

The secondary peristalsis is entirely due to peripheral mechanisms and also involves inhibition followed by excitation.

The lower esophageal sphincter (LES) is characterized by tonic muscle that is different from the muscle of the esophageal body.

The LES, like the esophageal body smooth muscle, is also innervated by the inhibitory and excitatory neurons. The LES maintains tonic closure due to its myogenic property.

The LES tone is modulated by the inhibitory and the excitatory nerves. Inhibitory nerves mediate LES relaxation and the excitatory nerves mediate reflex contraction or rebound contraction of the LES ***(Doty, 2010).***

Clinical disorders of esophageal motility can be classified on the basis of disorders of the inhibitory and excitatory innervations and the smooth muscles.

The main function of the esophagus is to transport swallowed food into the stomach. How the esophagus performs this function has been a subject of speculation and investigations for a long time. The esophagus consists of two distinct parts which are the cervical and thoracic parts, which are composed of striated and smooth muscles, respectively.

Failure to appreciate that the neuromuscular apparatus and neuronal circuits for peristalsis are different in the striated and smooth muscle portions of the esophagus led to confusion and contradictions in some early studies. Experimental evidence for a swallowing center and sequential activation of motor neurons to

elicit esophageal peristalsis was first established in the striated muscle ***(Larsen, 2001).***

The smooth muscle portion of the esophagus has myenteric plexus similar to the small intestine. However, peristalsis in the smooth muscle portion of the esophagus is very different than the intestine; the esophagus, but not intestine, can produce peristalsis at will (primary peristalsis). Therefore, peristalsis in the smooth muscle of the esophagus, as in the striated muscle of the esophagus, was also assumed to be due to sequential activation of cholinergic excitatory nerves. However, the mechanism of peristalsis in the esophageal smooth muscle turned out to be very complicated involving both central and peripheral mechanisms.

Another important function of the esophagus is to prevent gastro-esophageal reflux. It has always been assumed that some kind of barrier at the gastro-esophageal junction was present to prevent back flow of stomach contents into the esophagus. However, existence of a well defined lower esophageal sphincter (LES) was a matter of debate in the past. Although anatomists failed to find a well defined LES, a physiological sphincter was discovered on intraluminal pressure recordings. It was also found that the LES relaxed on swallowing.

These observations stimulated investigations into the neuromuscular basis of basal tonic closure and LES relaxation associated with or unassociated with swallowing ***(Kronecker and Meltzer, 2008).***

The neural mechanism of primary peristaltic contraction in the smooth muscle of the thoracic esophagus is orchestrated by the premotor neurons in solitary tract, which send projections to the caudal and rostral parts of the dorsal motor nucleus of vagus.

The caudal part of the dorsal motor nucleus of vagus contains neurons of the inhibitory pathway to the esophagus, whereas the rostral part houses the excitatory pathway neurons to the esophagus. The inhibitory pathway neurons are activated first; this results in inhibition of all ongoing activity in the esophagus and relaxation of the LES. This is followed by sequential activation of neurons to distal areas of the esophagus.

The sequence of inhibition followed by excitation can be documented with membrane potential studies as a wave of hyperpolarization followed by depolarization. The peristaltic behavior is the result of a progressive increase in the duration of hyperpolarizations along the esophagus.

The gradient of increasing inhibition distally along the esophagus that precedes peristaltic contraction is also called the latency gradient, or deglutitive inhibition ***(Meyer, 1986).***

Primary peristalsis expresses itself differently at different phases of the swallowing process.

Esophageal peristalsis that occurs in the thoracic esophagus without the associated pharyngeal contraction is known as secondary peristalsis.

Its physiologic role is to clear the esophagus of food residues and refluxed materials by moving them to the stomach. Secondary peristalsis, which is elicited by esophageal distention, is executed entirely by a local intramural reflex.

The LES normally relaxes as a part of the peristaltic reflex. Under certain circumstances, the LES may relax without associated peristaltic contraction.

This inappropriate LES relaxation is called transient LES relaxation (TLESR), and it may be elicited by gastric vagal afferent stimulation or stimulation of afferents in the superior laryngeal nerve with stimuli that are below the threshold for activating swallowing.

Transient LES relaxation may be part of a belch reflex and has been implicated as an important mechanism of gastro-esophageal reflux ***(Cohen, 2005).***

GASTROESOPHAGEAL REFLUX DISEASE

Gastro-esophageal reflux (GER) refers to the passage of gastric contents into the esophagus with or without regurgitation or vomiting. GER is a normal physiologic process which can occur several times per day in healthy infants, and to a lesser frequency in children, and adults ***(vandenplas, 2009)***.

GER can be a daily, normal physiological occurrence in infants, children and adolescents. Most episodes of GER in healthy individuals last <3 minutes occur in the postprandial period, and cause few or no troublesome symptoms ***(Sicherer and Sampson, 2011).***

Gastro-esophageal reflux disease (GERD) refers to the presence of troublesome symptoms and/or complications of persistent GER ***(Sherman, 2009).***

Younger children are generally more suggestible; so queries from parents or clinicians regarding a specific symptom may be biased toward affirmative responses. Thus, in younger patients reliance on a parent or caregiver is generally necessary, although symptom reporting by these surrogates may decrease the validity of diagnosis ***(Jaffe et al., 2009***).

Validated symptom questionnaires related to specific age groups are needed for achieving reliability in the child at any age,