Diplomarbeit

Evaluation of the effect of the hormone status on the motility of the esophagus, as well as the gastrointestinal symptoms, of patients with a reflux associated disease

eingereicht von

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Zusammenfassung

Hintergrund

Die gastroösophageale Refluxkrankheit (GERD) tritt auf sobald der Rückfluss von Mageninhalt in die Speiseröhre Symptome und/oder Komplikationen verursacht (1). Die Hauptursache der GERD liegt an einer insuffizienten Antireflux-Barriere, die am gastroösphagealen Übergang lokalisiert ist. Die Ursachen der Dysfunktion sind multifaktoriell, wie z.B. eine Hiatushernie, eine Dysfunktion des unteren Ösophagus Sphinkter, defekte Druckbarriere und nicht-Sphinkter-assoziierte Ursachen. Einige Autoren (2) (3) (4) glauben, dass die Pathophysiologie der GERD durch Änderungen der Hormonlevel hervorgerufen werden könnte. Darüber hinaus sind teilweise die Ursachen für Motilitätsstörungen, wie z.B. Achalasie und die Auswirkungen der verschiedenen Hormone auf gastrointestinale Symptome, unbekannt. Das Ziel dieser Studie war, den Einfluss der Hormone, Thyroidea stimulierendes Hormon (TSH), Triiodidthyronin (FT3), Tetraiodidthyronin (FT4), Gastrin, Vasoaktives intestinales Peptid (VIP) und Calcitonin, auf die Refluxkrankheit, auf die Motilität der Speiseröhre und auf gastrointestinale Symptome zu untersuchen.

Methoden

Dies war eine prospektive Studie mit einer Kohorte von 100 Patienten mit Symptomen einer GERD. Alle Patienten unterzogen sich routinemäßig folgenden Untersuchungen: einer Hochauflösende Manometrie (HRM), einer 24h-pH-Impendanz-Messung, und einer Gastroskopie. Zur Beurteilung der Lebensqualität mussten die Patienten den Gastrointestinale-Lebensqualität-Index (GIQLI) Fragebogen beantworten. Für die Beurteilung der Symptome wurden der Reflux-Symptom-Index (RSI) und die Symptom-Check-List (SCL) herangezogen. Aus dem SCL wurden vier verschiedene Symptomkomplexe entnommen, um Symptome spezifisch für Reflux (Sodbrennen, Reflux, Brustschmerzen), nicht-typische Reflux-Symptome (Husten, Heiserkeit, Asthma, Geschmacksstörungen), Blähungs-Symptome (Völlegefühl, Blähungen) und gastrointestinale Symptome (Diarrhö, Obstipation, Winde) zu beurteilen. Weiters wurden Blutabnahmen durchgeführt, um die Höhe von TSH, FT3, FT4, Calcitonin, VIP und Gastrin zu analysieren.

Nach der HRM wurden die Patienten gemäß der Chicago Klassifikation in drei Gruppen unterteilt. Gruppe I (N=16) repräsentierte Patienten mit leichten Motilitätsstörungen. Gruppe II (N=22) enthielt Patienten mit gestörter ösophagogastraler Abflussstörung oder mit einer erheblichen Motilitätsstörung. Die Gruppe III (N=48) repräsentierte normale Patienten. Anhand der Ergebnisse der 24h-pH-Impedanz-Messung wurden die Patienten in ‚Patienten mit GERD' und ‚ohne GERD' eingeteilt.

Ergebnisse

Vollständige Daten waren in 86/100 Fällen vorhanden. Diese 86 Patienten setzten sich aus 44 Männern und 42 Frauen mit einem mittleren Alter von 56 Jahren zusammen. Motilitätsstörungen hatten 38 von 86 Patienten, 16 Patienten in Gruppe I und 22 in Gruppe II.

Die 86 Patienten hatten einen DeMeester Mittelwert von 20,6. Ein pathologischer DeMeester Wert war bei 45 Patienten vorhanden, mit einem Mittelwert von 35. Es gab keine Korrelationen zwischen dem DeMeester Werten und den Hormonwerten. Die 86 Patienten hatten einen mittleren Unteren Ösophagus Druck von 23,6mmHg, aber es wurden keine Korrelationen mit den Hormonen gefunden. Hingegen wurde eine starke gegensinnige Relation zwischen Calcitonin und dem Integralen Relaxationsdruck (IRP) des gastroösophagealen Übergangs gefunden (r= -0,492; p=0,000).

Es wurden keine Korrelationen zwischen den Hormonwerten und GIQLI, RSI und SCL gefunden. Aber positive Korrelationen bestanden sowohl zwischen VIP und den GI-Symptomen (Diarrhö, Obstipation, Winde) (r=0,298; p=0,011), als auch zwischen FT3 und Dysphagie (r=0,283; p=0,016).

Innerhalb der Gruppe II, korrelierten TSH und FT4 mit den Ergebnissen des SCL Fragebogens. FT4 korrelierte sowohl mit den Typische-Reflux-Symptomen (p=0,002), als auch mit den GI-Symptomen (p=0,039). TSH korrelierte ebenfalls mit den Typischen-Reflux-Symptomen (p=0,007). Eine Regressionsanalyse bestätigte, dass diese Ergebnisse kein Zufall waren.

Außerdem bestand innerhalb Gruppe II eine Korrelation zwischen VIP und den Blähungs-Symptomen des SCL (p=0,072).

Schlussfolgerung

Diese Studie zeigt, dass die Hormone TSH, FT3, FT4, Calcitonin, VIP und Gastrin die Motilität der Speiseröhre nicht beeinflussen. Allerdings könnte Calcitonin einen Effekt auf die Funktion des gastroösophagealen Verschlussmechanismus haben. Darüber hinaus scheinen sowohl die Schilddrüsenhormone TSH, FT3 und FT4, also auch VIP gastrointestinale Symptome zu beeinflussen. Weitere Studien sind notwendig um im Detail die Rolle dieser Hormone zu klären und wie diese Erkenntnisse ihren Weg in die klinische Praxis finden könnten.

Abstract

Backround

The gastroesophageal reflux disease (GERD) evolves when the backflow of gastric content into the esophagus leads to symptoms and/or complications (1). Identified as the main source of GERD is the dysfunctional antireflux barrier, which lies at the gastroesophageal junction. The reason for the dysfunction are multifactorial, like hiatal hernias, dysfunction of the LES, defect pressure barrier and non-sphincter associated reasons. Previously some authors (2) (4) (3) suggested that the pathophysiology of GERD may be provoked by alterations of the hormone levels of the patients. Furthermore, the reason for motility disorders like achalasia and the influence of hormones on gastrointestinal symptoms are partly unknown. The aim of the study was to evaluate, if the hormones Thyroid stimulating hormone (TSH), Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4), gastrin, Vasoactive Intestinal Peptide (VIP) and calcitonin have an influence on GERD, motility disorders and gastrointestinal symptoms.

Methods

This was a prospective study with a cohort of 100 patients with symptoms of GERD. All patients routinely underwent: high-resolution manometry (HRM), 24h-pH-Impedance-Monitoring and gastroscopy. For the evaluation of quality of life the Gastrointestinal quality of life index (GIQLI) was used, for evaluation of symptoms Reflux-symptom index (RSI) and symptom check list (SCL) were used. Out of the SCL four different scores were extracted to assess symptoms specific for reflux (heartburn, regurgitation, chest pain), non-typical reflux symptoms (cough, hoarseness, asthma, distortion of taste), gas-bloating-symptoms (fullness, bloating), and gastrointestinal symptoms (diarrhea, constipation, flatulence). Furthermore, blood samples were taken to analyze the levels of TSH, FT3, FT4, Calcitonin, VIP and Gastrin. After HRM the patients were subdivided into three groups according to the Chicago Classification. Group one represented patients with minor motility disorders. Group two included patients with EGJ outflow obstruction or major motility disorders. The third group represented “normal” patients. According to the results of 24h-pH-Impedanz-Monitoring the patients were divided in ‘patients with GERD’ and ‘patients without GERD’.

Results

Complete data was available from 86 of 100 patients and consisted of 44 men and 42 women with a median age of 56 years. Motility disorders were found in 38/86 patients. In group I 16 patients and 22 patients in group II.

The 86 patients had a median DeMeester score of 20,6. A pathological DeMeester was found in 45 patients with median score of 35, and respectively patients with GERD and without GERD. There have been no correlations between the DeMeester score and the hormones. Of the 86 patients, the median LES pressure was 23,6 mmHg, but no correlations were found between the different hormone levels and the LES-pressure. But a strong inverse relation between calcitonin and the Integrated Relaxation Pressure (IRP) of the esophagogastric junction (EGJ) was found (r= -0,492; p=0,000).

No correlations were found between hormone levels and the mean scores of GIQLI, RSI and SCL. But positive correlations were found between VIP and GI-Symptoms (r=0,298; p= 0,011), as well as correlations between FT3 and dysphagia (r=0,283, p=0,016).

Within the group II, TSH and FT4 correlated with outcomes of the SCL-questionnaire. FT4 correlated with the Typical-symptoms (p=0,002), as well as the GI-symptoms (diarrhea, constipation, flatulence) (p=0,039). TSH correlated with the Typical-symptoms (p=0,007). A regression analysis confirmed that these outcomes were no coincidence.

Further within group II a correlation between VIP and the SCL-Gas-Bloat-Symptom (p=0,072) was found.

Conclusion

This study demonstrates that the hormones TSH, FT3, FT4, Calcitonin, VIP and Gastrin do not affect the motility of the esophagus. However, Calcitonin could have an effect on the function of the EGJ. Furthermore, thyroid hormones TSH, FT3 and FT4, as well as VIP seem to influence gastrointestinal symptoms. Further studies are needed to clarify in detail the role of these hormones and how these findings could find their way into clinical praxis.

Content

Abbreviations

AGA: American Gastroenterological Association

ATP: Adenosine triphosphate

BE: Barrett's Esophagus

CCK: Cholecystokinin

COX: Cyclooxygenase

DCI: Distal Contractile Integral)

DMN: Dorsal motor nucleus of the vagus

EER: Extresophageal Reflux

EES: Extraesophageal Symptoms

ERCP: endoscopic retrograde cholangiopancreaticography

ERD: erosive reflux disease

GEFV: Gastroesophageal flap valve

GERD: Gastroesophageal reflux disease

GIP: Glucose-dependent insulin-releasing peptide

GIQLI: Gastrointestinal Quality of Life Index

GRP: Gastrin Releasing Peptide

HREPT: High-Resolution Esophageal Pressure Topography

HRM: High-Resolution-Manometry

IRP: Integrated Relaxation Pressure

LMN: Lower motor neurons

MUSE^{TM}: Medigus Ultrasonic Surgical Endostapler

NA: Nucleus ambiguus

NERD: non-erosive reflux disease

NO: Nitrogen Monoxide

PPI: Proton Pump Inhibitor

PPI: Proton Pump Inhibitor

RSI: Reflux Symptom Index

SAP: Symptom-Association-Probability

SCL: Symptom Check List

SI: Symptom-Index

SIH: Somatostatin

TRH: Thyroid Releasing Hormone

VIP: Vasoactive intestinal peptide

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Introduction

1. The esophagus

The esophagus is a 23-26-centimeter-long muscular tube, that connects the pharynx with the stomach. The origin lies right below the cricoid cartilage and its end at the cardia of the stomach, where it runs through the esophagus hiatus of the diaphragm. (5)

Functionally the esophagus is divided into the upper sphincter, the so-called body of the esophagus and the lower sphincter. Topographically it is distinguished in a cervical, a thoracic and an abdominal part, Fehler! Verweisquelle konnte nicht gefunden werden.. (5)

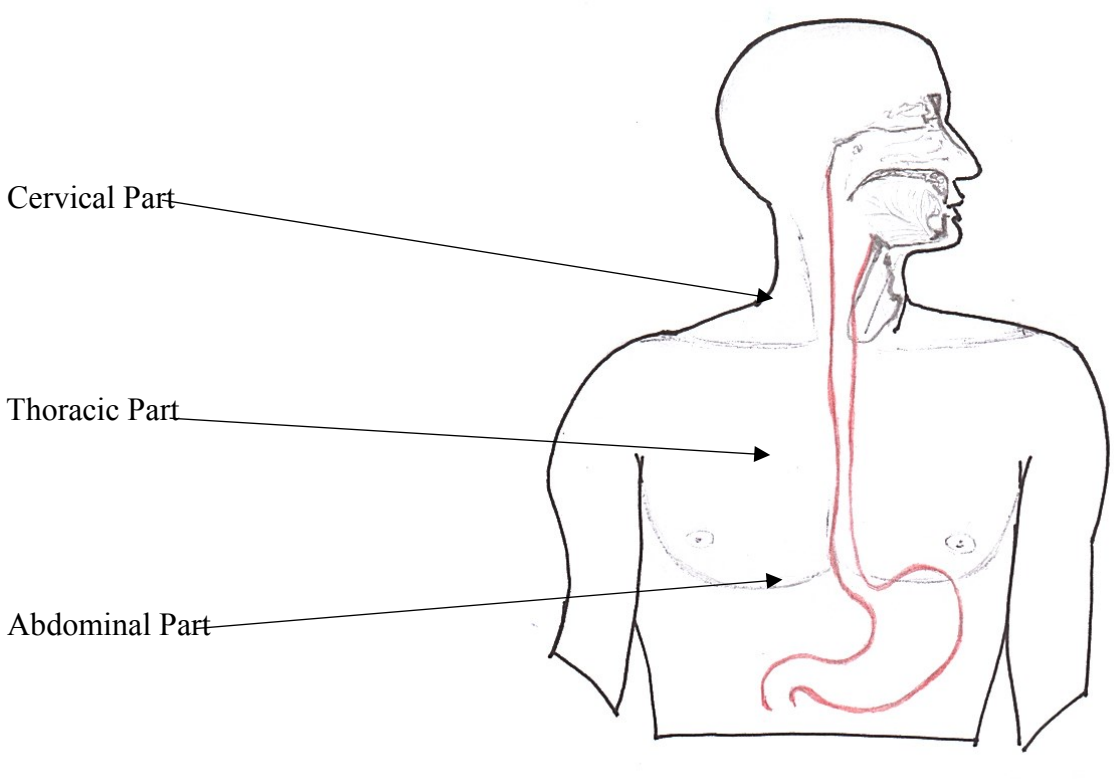

Figure 1: Parts of the esophagus.

There are three narrow parts that occur throughout the esophagus. The first one is called the mouth of the esophagus and follows the laryngeal part of the pharynx. Because of rhythmical contractions it stays closed when the tube is at rest. The so-called lip of the esophagus lies at the highest point of this tightness and presses itself against the cricoid cartilage. The second narrow part is located, where the aortic arch lies to the left and the left bronchus lies in the front of the tube. The narrowness of the diaphragm, is the third and last tight part. It

is placed three centimetres above the cardia and is the result of the contraction of the strong sphincter. (5)

The upper and lower esophagus sphincters are two important structures and play roles in many mechanisms concerning the esophagus, like swallowing and the anti-reflux barrier. The lower sphincter enters the stomach in a particular way through the diaphragm. The geometry of this structures is called the angle of His, **Figure 3**.

1.1 Blood supply

The subclavian artery provides the blood supply for the upper esophagus, directly or through the thyrocervical trunk. The middle gets fed by the rami esophageal, coming from the aorta and the intercostal arteries. The supply for the lowest part is served by the left gastric artery and the inferior phrenic artery. The venous provision for the upper third serves the inferior thyroid veins, the following section is taken care by the azygos and hemizygous veins. The left gastric vein transfers the blood from below to the portal vein and further to the vena cava. (5)

1.2 Innervation

When it comes to the innervation, the vagal nerve plays a significant role. The rami esophageal, coming from the recurrent laryngeal nerve, reach the superior part of the esophagus. Below the tracheal bifurcation, the vagal nerves from both sides lay out along the esophagus. This creates an interweaving, called the esophageal plexus. Fibres from the aortic and thoracic plexus as well as fibres from the sympathetic trunk arrive at the plexus esophagus. A very important nerval plexus for the motor function lies in between the muscular sheet, termed the myenteric plexus. (5)

1.3 Esophageal tissue

The overall fine structure of the esophageal tissue consists of a mucosa membrane and a muscular layer.

The lumen is coated with the mucosa, which is a multilayer squamous uncornified. Within this layer lies not only lymph follicle and pads of veins, but also smooth muscle cells. This epithelium has a sharp border at the transition of the cardia, which is called ora serrata.

Between the two main components, the tunica muscularis mucosae and the mucosa, exists another very thin layer of tissue, the tela submocosa. It contains mucous glands, a vegetative plexus as well as lymph and blood vessels. It also keeps the individual sheets, the tunica muscularis and the mucusa, relocatable. (5)

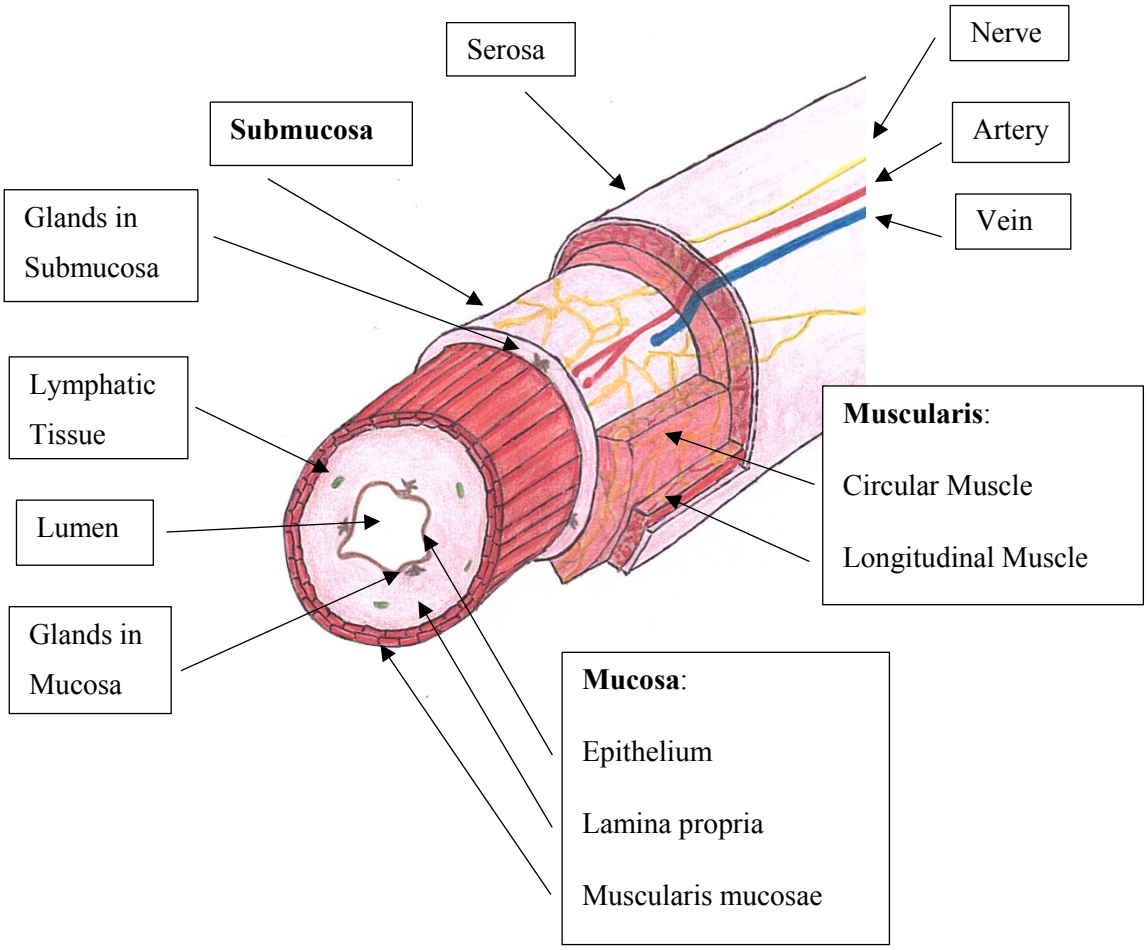

Figure 2: Layers of the esophageal tissue. Mucosa, Submucosa and Muscularis.

The muscular part of the esophagus is quiet a complex construct of helically and steeply passing muscle bundles. These muscular columns get thicker on their way down. In cross section the composition of esophageal muscle appears internally circular-shaped and externally longitudinal-shaped. In the cranial third of the tube the muscles are striated but the caudal third consists only of smooth muscles. (5)

2. Swallowing

In general, the act of swallowing happens in three stages. The oral phase, the pharyngeal and the laryngeal phase. As soon as the chyme reaches the pharynx, a peristaltic wave is initiated. Solid food arrives at the stomach in less than ten seconds, fluids in approximately one second. During the peristaltic wave, areas of 2-4 centimetres' length are contracting. Additional contractions follow because of the pressure against the wall of the esophagus. (5)

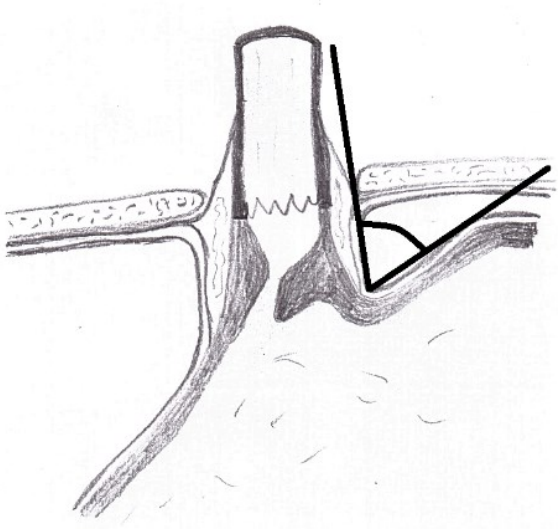

Figure 3: Transition of the esophagus into the stomach and the Angle of His.

At the crossover of esophagus and stomach, the closure mechanism plays a significant role in physiological terms as well as in terms of diseases. On one hand, the closing must be strong enough to prevent the backflow of gastric content in the esophagus, on the other hand it must allow the arriving of food at the right time at the stomach. This task is not performed by a sphincter like in the common idea. The interaction of multiple factors leads to a sufficient closure of the bottom of the esophagus.

First, there exists a higher pressure in the lower esophagus than in the stomach, **Table 1**. In general, along the whole tube occurs a strong longitudinal tension. Because of this not only would the esophagus be shortened if you cut it, but also the tube stays closed. Another fact that pays its tribute, is the way the esophagus joins the gut. It happens in an angled way, called the angle of His, **Figure 3.** (5) The extension of this angle into the lumen forms the gastroesophageal flap valve (GEFV) (6) (7) (8).

Table 1: Pressure of the UES, LES and the stomach.

Location	Pressure at Rest
Upper esophageal sphincter	37mmHg
Lower esophageal sphincter	19mmHg
Stomach	6mmHg

The act of swallowing can be differentiated in „primary peristalsis" and „secondary peristalsis ". The difference lies in the origin of its trigger. Primary peristalsis is induced by swallowing itself and secondary peristalsis is generated by local reflexes (9).

Primary peristalsis is coordinated by the swallowing centre in the brainstem and its vagal efferents. These fibres arise from two nuclei, the nucleus ambiguus (NA) (10) and the dorsal motor nucleus of the vagus (DMN) (11).

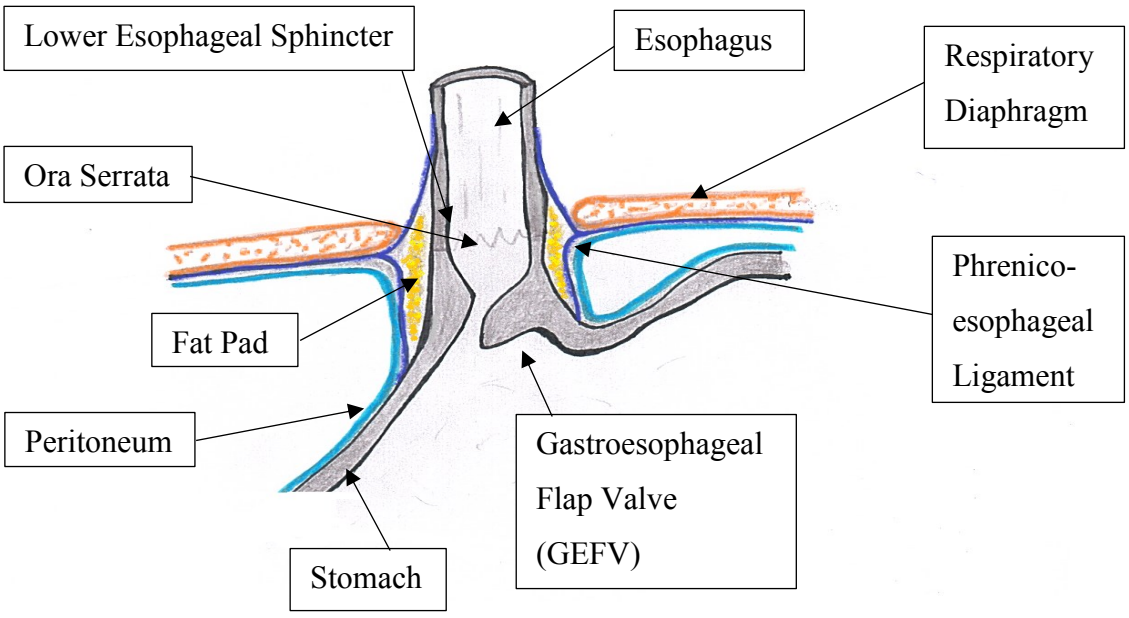

Figure 4: Transition of the esophagus into the stomach.

Vagal lower motor neurons (LMN), which originate from the NA control the reflexes of the striated muscles. The LMNs send cholinergic innervation to motor end plates. These efferents are inhibited by myenteric nitrergic neurons. Preganglionic neurons fulfil parasympathetic motor and secretory functions.

Concerning the smooth muscles, a parallel pathway, both inhibitory and excitatory, exists and is composed of cholinergic preganglionic neurons. These neurons stimulate the postganglionic ones by the way of nicotinic and muscarinic receptors. Consecutively the inhibitory part of the postganglionic neurons releases ATP, VIP and NO. The excitatory part frees Ach and substance P. Fehler! Verweisquelle konnte nicht gefunden werden..

Secretory activities by the vagal efferents are exercised directly or through liberation of regional mediators or circulating hormones.

The essential part of primary peristalsis is the loosening of the LES to the level of intragastrical pressure. This state of relaxation continues for approximately 8-10 seconds. Subsequently an aftercontraction happens in the ventral part of the LES, which is the result of the peristaltic contraction in the body of the esophagus. These events allow the bolus to be swallowed, even though this immense pressure is prevailing in the LES. Furthermore the antireflux barrier returns immediately afterwards. (9)

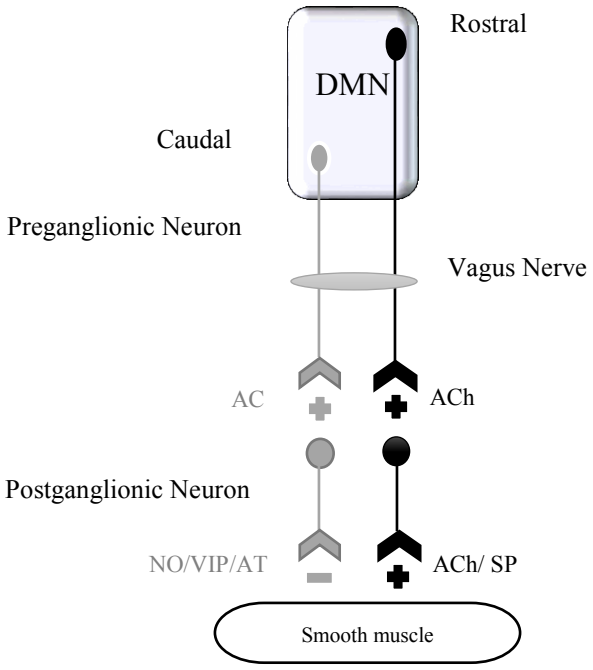

Figure 5: Vagal efferent. Parallel excitatory and inhibitory pathways.

3. Gastric juice

The composition of the gastric juice is various, depending on the activity of the stomach. Is the stomach at rest, it produces a basis-secretion, which is similar to plasma. During the digestion process, the stomach produces a different secretion. (10)

Digestives enzymes

The most important digestive enzyme is pepsin. It is produced in the gastric chief cells as pepsinogen. In the presence of H^+ -ions and a pH level lower than 3, pepsinogen gets activated by already existing pepsin. (10)

The production of gastric acid

Responsible to produce gastric acid are the oxyntic cells in the stomach. At rest, the cells contain secretory vesicles, which can fuse and form a canalicular membrane with the lumens of the glands. In this membrane, the H^+-K^+-ATPase, the so-called proton pump, is located. This proton pump represents the last step in producing the gastric juice, shown in **Figure 6**. At rest, the secretion of gastric juice is minimal. Because of ingestion the total volume per day is about 2-3 litre. (10)

The control of gastric acid production

A complicated system of neuronal, paracrine and endocrine stimuli manages the secretion of acid in the gut. On top of the oxyntic cells exist independent receptors, which can activate secretion. The most relevant stimulators for this secretion are acetylcholine, gastrin, and histamine. The most important physiological inhibitor is somatostatin (SIH). SIH can reduce the secretion of acid directly by antagonizing histamine. Additionally, a negative feedback for the acid secretion from duodenum and jejunum exists, which is activated by lipids as well as acid and increased duodenum-osmolality. Here endocrine mechanisms and reflexes play an important role: (10)

- Secretin (from the S-cells in the duodenum) inhibits gastrin and support the SIH-liberation.
- Glucose-dependent insulin-releasing peptide (GIP) (from the K-cells in the duodenum and jejunum) inhibits gastrin-liberation.
- Prostaglandin E_2 (PGE_2) inhibits parietal cells as well as reduces liberation of histamine and gastrin.

Some more factors pay their tribute to inhibition of acid secretion: (10)

- Cholecystokinin (CCK) (from the I-cells in the duodenum) directly inhibits parietal cells.
- Vasoactive intestinal peptide (VIP) (from the NANC neurons) inhibits gastrin liberation.
- Glucagon (from the A-cells from the stomach and duodenum) inhibits gastrin liberation.
- Calcitonin (from the thyroid gland) as well inhibits liberation of gastrin.
- Neurotensin (from the N-cells in the ileum) inhibits acid secretion.
- Peptide YY (from ileum and colon) as well inhibits acid secretion.

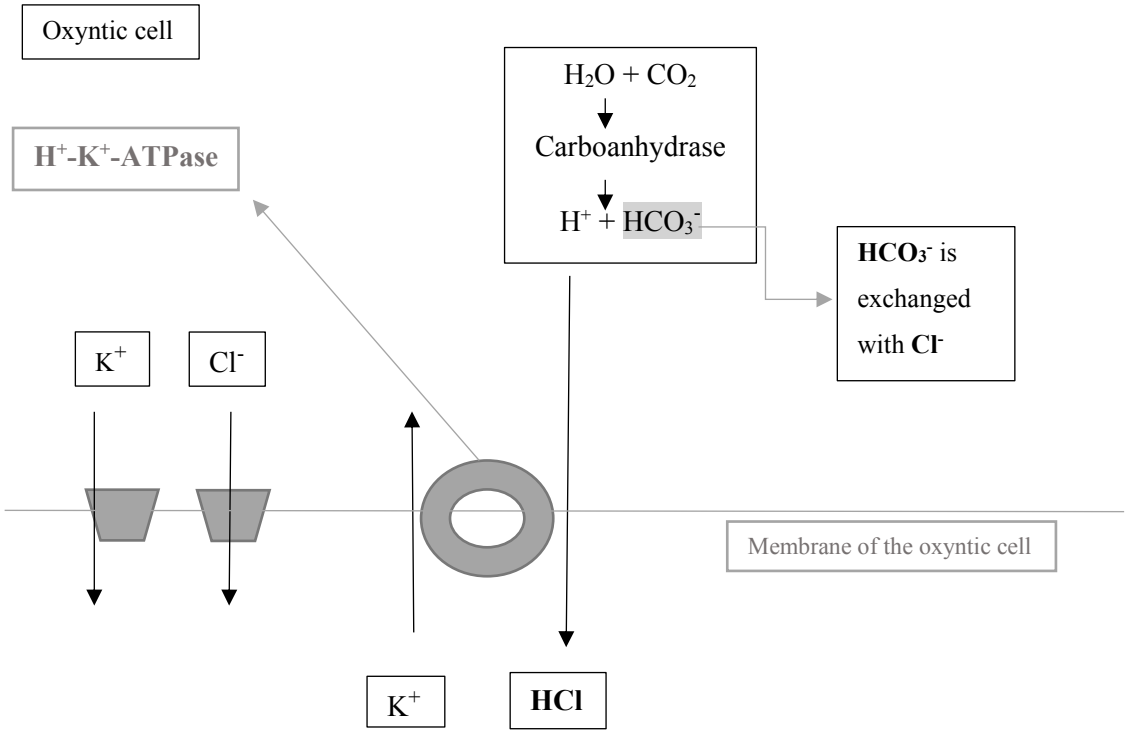

Figure 6: Basolateral Membrane of the Oxyntic Cell, HCl-production. From (10)

Worth mentioning is also the fact, that secretion can be differentiated between basal and stimulated secretion. The basal secretion follows a circadian rhythm, with its maximum during the night and its low point in the morning. The stimulated secretion happens in three phases, the cephalic phase, the gastric phase and the intestinal phase. During ingestion, the secretion is compound 15% by the basal, 30% by the cephalic, 50% by the gastric and 5% by the intestinal phase. (10)

The gastric mucosa shield

The gastric mucosa is protected from hydrochloric acid (HCl), pepsin and bile acid, with different mechanism. A layer of mucus, approximately 180µm thick, containing bicarbonate blocks the intrusion of H^+-ions and pepsin. It follows that on the surface of the epithelium a pH level of 7 exists and on top of the mucus a pH level of 1-2 is possible. The production of mucus and bicarbonate is increased by the vagal nerve and prostaglandins (PGE_1, PGE_2, PGI_2). In addition, prostaglandins inhibit the acid secretion of the oxyntic cells and they increase the mucosal perfusion, which makes them an important protector of the gastric mucosa. The key enzyme in the biosynthesis of prostaglandins is the cyclooxygenase (COX), which exists in two different isoforms in the gastrointestinal tract, COX-1 and COX-2. (10)

4. Hormones

4.1. Thyroid stimulating hormone, Triiodothyronine & Tetraiodothyronine

The hypothalamus-hypophyses-thyroid system

The neuroendocrine control system is not as distinctive as in other endocrine glands. The stimulation of the hypophyses Thyroid stimulating hormone (TSH or Thyrotropin) over the hypothalamic Thyrotropin releasing hormone (TRH) is very important. (10)

In the Hypophyses TRH stimulates the biosynthesis and secretion of TSH. In the thyroid gland TSH controls not only all synthesis and secretion processes, but also its metabolism (like hormone production, storage and release, blood supply, intake of iodide). (10)

Tetraiodothyronine (T4) represents the main product of the thyroid gland, only a small amount of Triiodothyronine (T3) is liberated by the thyroid, mostly it is generated in the liver and by deiodination of T4 at the target cells. In the blood, they are bound to carrier proteins. With a transporter, the hormones actively get transferred into the target cell. T4 is deiodinated to T3, which regulates transcription in a lot of cells. The generated proteins effect the transcription of various other genes. The molecular mechanism for a lot of metabolic effects of thyroid hormones are still unknown. (10)

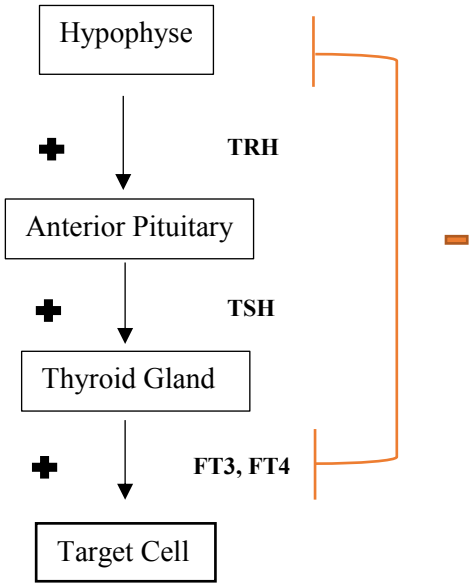

Figure 7: The hypothalamus-hypophyses-thyroid system and its negative feedback mechanism.

Thyroid hormones have an important effect on the growing of the bones and other protein synthesis correlated repining processes (like the nervous system). When it comes to the metabolic effects of the thyroid hormones, a very relevant one is the increase of the basal metabolic rate. This means increased temperature and oxygen consumption in all tissues, except the brain, the gonads and the spleen. (10)

FT3 is also stimulating all steps of the carbohydrates metabolism, e.g. absorption of the carbohydrates into the digestive tract.

Thyroid hormones as well have a permissive effect on the sympathetic nerve system, especially on the β-adrenergic-receptor.(10)

4.2. Calcitonin

Calcitonin is produced in the C-cells, which are parafollicular cells in the thyroid, but also in the parathyroid and the thymus. When the level of the plasma calcium is rising over standard this hormone is set free. Subsequently calcium is incorporated into the skeleton. In the kidneys calcitonin leads to a forced excretion of phosphate and resorption of calcium. Furthermore calcitonin inhibits liberation of gastrin.(10)

4.3. Gastrin

Gastrin is generated by the G-cells in the antrum of the stomach and in the duodenum. Its function is the direct stimulation of acid secretion, increase of the digestive peristalsis in the antrum, stimulation of the ECL-cells and stimulation of mucosa-growth in the stomach, the duodenum and the colon.(10)

The liberation of gastrin happens because of luminal amino acids, expansion of the stomach, and gastrin-releasing-peptide (GRP), which is a peptide generated in the vagal nerve. Additional calcium in the plasma and noradrenaline can increase the secretion of gastrin. (10)

The liberation of gastrin is inhibited by somatostatin (SIH), which is produced by the D-cells of the stomach and the duodenum. The D-cells additionally are stimulated by luminal acid exposure, which leads to SIH-secretion. Cholinergic agonists inhibit SIH-secretion, which means that the vagal nerve stimulates acid secretion indirectly. Gastrin on the other hand stimulates the SIH-secretion in the way of negative feedback. (10)

4.4. Vasoactive Intestinal Peptide (VIP)

VIP represents a neurotransmitter and neuromodulator in the enteric nerve system and is produced by neurons, as well as mast cells and granulocytes. The functions of this hormone are varied. In the intestine VIP relaxes the smooth muscles, but also inhibits the acid production in the stomach. Furthermore, it stimulates the transport of water into the bile, as well as the liberation of pancreatic enzymes, hydrocarbonate and chloride in the intestine (Boushy and Drucker 2003). Apart from that, VIP is a regulator of the immune system and of the dendritic cells and has strong anti-inflammatory qualities (Delago et al. 2004). (13)

5. Gastroesophageal-Reflux-Disease

5.1. Definition

Gastroesophageal Reflux disease (GERD) is a chronic disease (14). In European countries it appears very commonly with a prevalence from 10% to 20% (15).

In healthy people, gastroesophageal reflux is a physiological situation in the human body and it occurs unnoticed. If problems/symptoms or morphological lesions evolve, GERD is present. That means gastroesophageal reflux leads to GERD, if the contact of the aggressive stomach-content with the esophageal mucosa is prolonged. Two mechanisms are responsible

for this situation. First the accumulation of the number of refluxes and second the delay of the esophageal clearance.

5.2. Pathophysiology

In general GERD develops because of a dysfunction of the anti-reflux barrier. The barrier consists of the lower esophagus sphincter, the diaphragm and the geometry of the gastroesophageal junction. Normally the LES builds a pressure barrier (20mmHg) and usually this barrier only loosens during the act of swallowing.

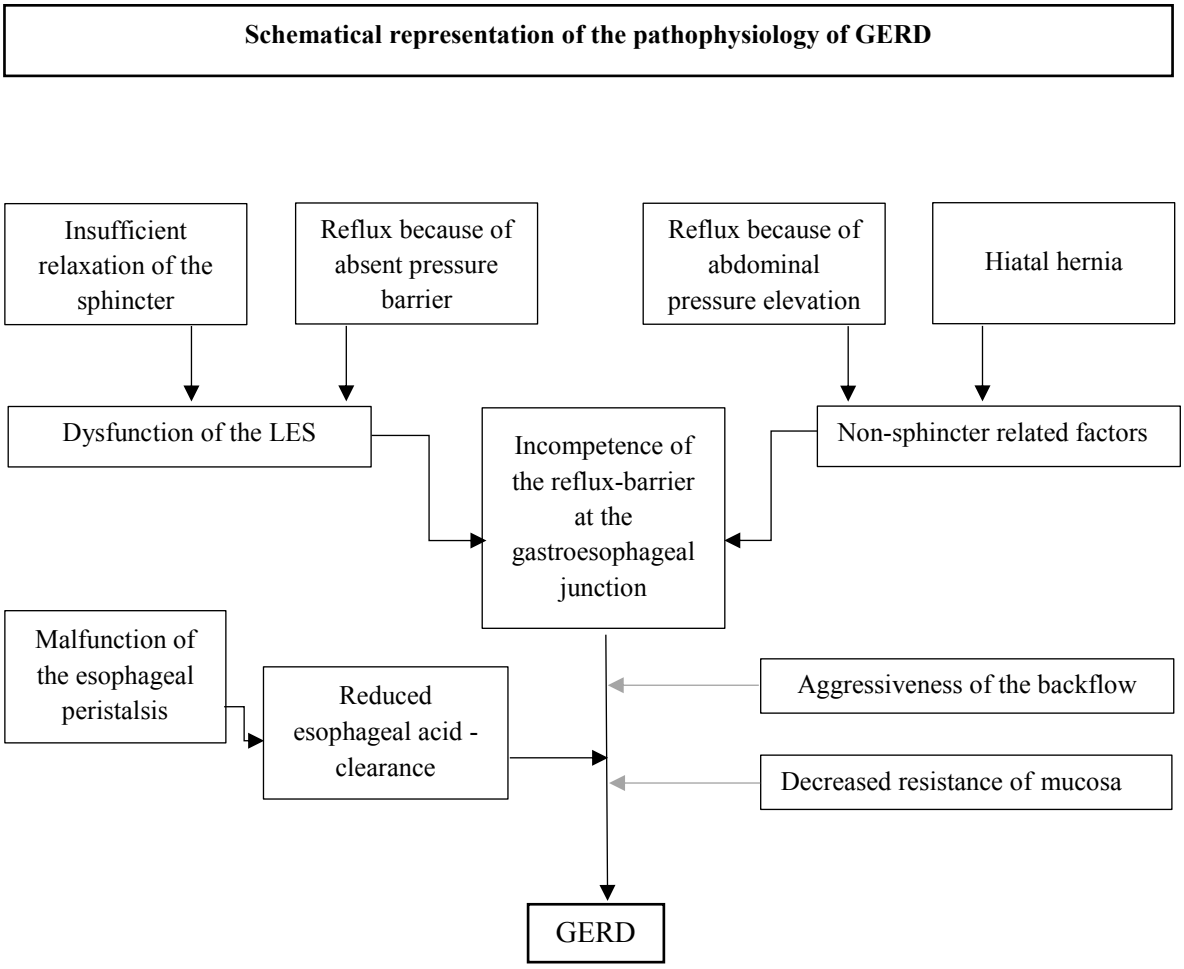

Figure 8: Pathophysiology of gastroesophageal reflux disease, from (16)

There are three factors, that lead to a dysfunctional barrier:

1. Transient relaxation of the sphincter
2. Defect pressure barrier
3. Non-sphincter associated reasons

Ad 1) Transient relaxation of the sphincter

Patients with GERD show cumulative pressure losses of the LES, which are not related with the act of swallowing. In healthy people, as well as in patients with GERD, most of the reflux events happen during transient relaxations of the LES.

Distension of the stomach seems to be the major trigger that leads to Transient relaxation. Afferents in the vagus, that trigger Transient relaxations through the DMN and the efferents of the vagus (vago-vagal reflex), is initiated by the distension-activated expansion of the stomach-wall. (17)

The reason why transient relaxations of the sphincter occur more often in patients with GERD then in healthy people is yet unknown. (16)

Ad 2) Defect pressure barrier

Another factor, that pays its less important tribute in the malfunction of the sphincter, is the free reflux because of a continuous low pressure-level. (16)

The explanation for this cause is undiscovered. Chronic inflammatory processes do not play a role in this case. The healing of the reflux-esophagitis induced by medication and/or surgical therapy do not make a difference in the defect pressure barrier between the esophagus and the stomach, neither does it lead to a normalization of a motility disorder of the esophagus.(18)

Ad 3) Non-sphincter associated factors

Factors that also contribute to a malfunction of the sphincter, can be a functional disorder of the diaphragm, a hiatus hernia or an increased intraabdominal pressure. (16)

Clearance disorder of the esophagus

Patients with GERD show a defect clearance of the esophagus with a prolonged contact of mucosa with the aggressive content of the stomach (19). The disorder of primary and secondary peristalsis is one of the most important reasons for a failed clearance. Another key role plays the concentration of acid, pepsin and bile acid in the reflow. This is also the target for one of the most effective therapies for GERD, the reduction of acid with proton pump inhibitors. (16)

Of course, other circumstances such as stress, obesity, pregnancy, and diet as well as drugs affect the whole process of GERD (20) (21) (22).

5.3. Clinical Presentation

GERD in general has a highly diverse clinical presentation. This is explained by the large variety of origins, that this disease has. (14)

The manifestation differs between esophageal (typical) and extra-esophageal (atypical) symptoms, which were categorized with the Montreal-Classification, shown in **Figure 9**(1).

When it comes to esophageal symptoms, heartburn (as well-known as retrosternal burning and substernal burning) is the most usual and often manifestation. Second most frequent symptom in GERD is regurgitation of contents from the stomach and the duodenum, that reach the hypopharynx or/and the mouth. This appears in 33-86%. (14)

Extraesophageal Symptoms (EES) cover chronic cough, hoarseness, sore throat, burning and globus sensations, and dental erosions (22). The phrase extraesophageal reflux (EER), or laryngophareal reflux (LPR) is defined as syndromes induced by backflow to structures above the UES, the laryngopharynx. (23)

Based on endoscopic findings, further distinction, concerning the presentation of GERD, can be made. The disease can present itself with or without macroscopic esophagitis, or in serious cases with strictures, haemorrhage, or Barrett's esophagus (BE) (24). The phrase non-erosive reflux disease (NERD) represents patients with GERD, but without esophagitis, and the phrase erosive reflux disease (ERD) represent patients with GERD and esophagitis. (25)

Martínek et al could show with their study in 2008, that patients with NERD and mild to moderate ERD have similarities in acid exposure time and motility abnormalities. This

shows that mild to moderate ERD is not “a more severe” disease but rather “a more complicated” one. (24)

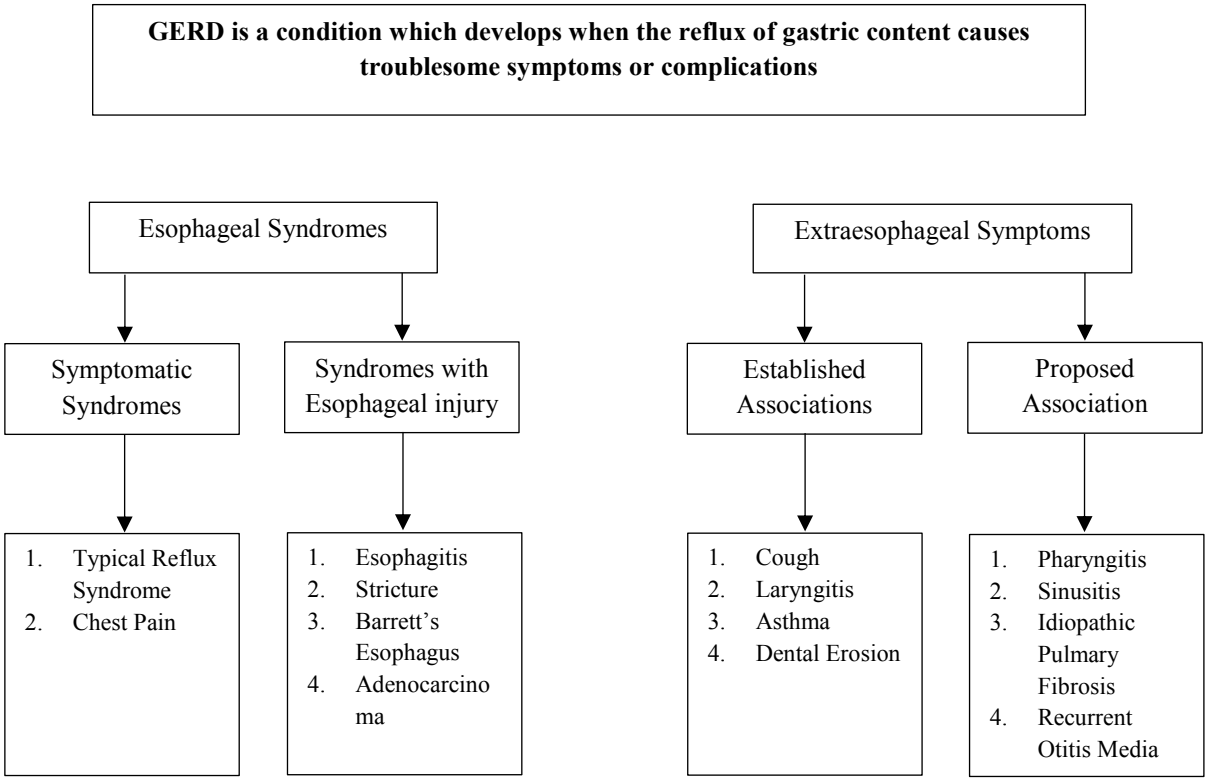

Figure 9: Montreal-Classification. An overall definition of GERD and its constituent symptoms. From (1)

5.4. Therapy

Like Fuchs et al. resumed in their consensus statement for the management of gastroesophageal reflux disease, “The aim of therapy is to resolve the symptoms, treat and prevent complications, and improve the patient’s quality of life” (14).

Three different approaches to GERD can lead to a serious improvement, in different levels of intensity, for this common problem.

5.4.1. Lifestyle

In general, big meals and lying down (within 3h) after eating should be avoided. Furthermore, fatty or spicy food, chocolate, coffee, peppermint, citrus fruits, tomatoes, carbonated drinks, and alcohol may generate more reflux events and GERD associated

symptoms. (26) (20) (22) (27) Also sleeping with the head elevated and stopping to smoke should be considered (28) (29).

Adjustments in lifestyle and diet may help some patients, but alone they relatively show no effect (14). Consequently, lifestyle changes can be an addition to standard therapy.

5.4.2. Medical Therapy

The ambition of medical therapy is to reduce the typical symptoms of GERD. The improvement of these factors is followed by the healing of gastroesophageal mucosa injuries and an increased quality of life. (14) (30) (31) (32)

H_2receptor antagonists (H_2RAs)

Histamine causes (over the H_2 receptor) an increase of secretion of gastric juice. Not only more gastric acid is secreted, but also more pepsin. (10) In some cases H_2RAs can improve LPR and may help patients with less serious forms of GERD (23). But in general, H_2RAs lost their clinical relevance, because they are less efficient in acid suppression than PPI. Patients easily become refractory to H2RAs. This makes the therapy useless for long-term use and add-on. (14) (33) (34) (35)

Proton pump inhibitors (PPI)

Medical therapy with PPI should be the first approach when it comes to GERD (14). They are the strongest inhibitors of the basal and stimulated gastric acid secretion. Because they block the terminal process of secretion, the acid excretion is inhibited, independently of its stimulus (acetylcholine, histamine, gastrin). (36) Responsible for this terminal process is the H^+/K^+ adenosine triphosphates pump of the oxyntic cell. Because of the pump-deactivation, PPI provide a very effective symptomatic relief and heal esophagitis in most of the patients. (14) (22) (20) (37) (38) (39) Omeprazole, lansoprazole, pantoprazole, esomeprazole, and rabeprazole in regular doses have shown similar ratio of remission of erosive esophagitis (40) (41), but it is known that GERD patients with hiatal hernia need higher doses than patient without (42). Furthermore, patients should take their medication between 30 and 60 min prior eating, because PPI are best resorbed when food is not present (39) (14).

5.4.3. Surgical Therapy

Before surgery or any other invasive therapy is considered, there must be evidence, that the patient needs a long-term treatment of GERD. After accurate diagnostic testing, antireflux surgery should be offered patients with ongoing low quality of life, continuous painful or problematic symptoms, and/or aggravation of the disease, regardless of proper PPI therapy. (14)

Fuchs et al. (2014) summarised in their recommendation for management of gastroesophageal reflux disease a list of criteria, drawn from literature, which shows the most important and most frequently mentioned conditions, that lead to an indication for antireflux surgery (14):

- Typical symptoms for GERD (43) (14)
- Documented correlation between symptoms and reflux (44) (14)
- Year-long reflux history (45) (46) (47) (14)
- Reduced quality of life (48) (49) (50) (14)
- Positive PPI response (43) (14)
- Need for PPI dosage increase (51) (37) (52) (53) (14)
- Hiatal hernia (45) (54) (55) (14)
- Documented esophagitis in the past before PPI (45) (54) (52) (56) (14)
- Proven LES incompetence (45) (46) (57) (58) (54) (47) (14)
- Documented acid reflux (45) (57) (54) (49) (50) (59) (60) (14)

Techniques

Recreation of a functional anti-reflow barrier is the motive of surgical therapy.

“The Reconstruction of the anti-reflux barrier consists of three fundamental components: [1] proper length of the intra-abdominal esophagus, [2] crural repair, and [3] fundoplication.”, Fuchs et al. (2014). (14)

There are two main procedures, the total (360°) Nissen fundoplication, Fehler! erweisquelle konnte nicht gefunden werden., and the partial (180°-270°) Toupet fundoplication, **Figur 11**(14). The most frequent operation worldwide is the Nissen fundoplication, whereas the Toupet fundoplication is suggested for preventing postoperative unwanted effects, which accompany a total fundoplication. Koch et al. (2011) have shown,

that one year after surgery there is no specific distinction in the outcomes between the two types of operation. (61)

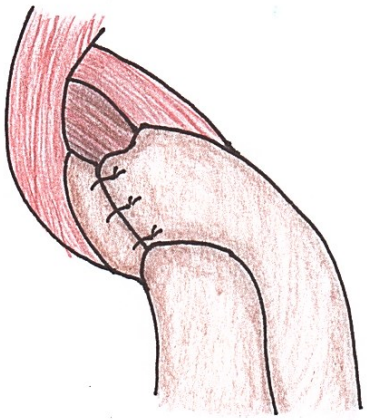

Figure 10: Nissen fundoplication

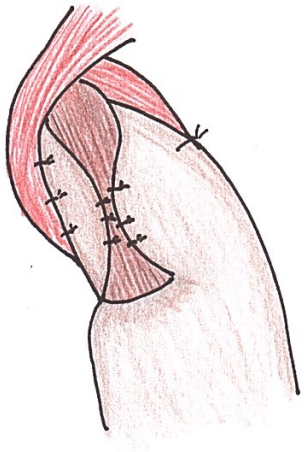

Figure 11: Toupet fundoplication

5.5. Motive and aim of the study

The gastroesophageal reflux disease evolves when the backflow of gastric content into the esophagus leads to painful and damaging symptoms and/or complications (1). Identified as the main source is the dysfunctional antireflux barrier, which lies at the gastroesophageal junction. This junction is mainly compound by the lower esophageal sphincter (LES), the crural diaphragm, and the geometry of these components (7) (6)

The initial standard therapy is at first a medical one with proton pump inhibitors. Gold-standard for surgical therapy, is the fundoplication after Nissen or Toupet (62) (63). The pathophysiology of GERD is complex, multifactorial and not completely understood. The function of LES, motility disorders and symptoms of GERD may be provoked by alterations of the hormone levels of the patients.

Ilhan et al. (2014) have shown, the presence of a hypothyroidism leads to a shortened time of relaxation, in regard to the total duration as well as to the percentage of the ratio between contraction and relaxation of the musculature of the esophagus (2). Furthermore Yaylali et al. (2009) has shown in a study with 30 patients, that hypothyroidism can lead to a reduction of the motility of the esophagus and further to a gastrointestinal dysfunction (3). Apart from this, an animal experiment with opossums, performed by Goyal et al. (1976), has shown that an increased level of gastrin may modulate the pressure level of the LES (64). Farre´ et al. has shown in another animal experiment with pigs, that the vasoactive intestinal peptide (VIP) can directly provoke a relaxation of the LES (4). And according to Hotz et al. (1981),

calcitonin inhibits the secretion of gastric acid as well as of pepsin and pancreas enzymes, the release of gastrin and the hormonally stimulated contraction of the LES (65). This all together encourage the assumption, that numerous hormones can have an influence on the pathophysiology of GERD. So far, no study was performed using modern diagnostic tools to evaluate if hormones have an influence on GERD, motility disorders of the esophagus and symptoms of the gastrointestinal tract. The aim of the study was to find out the role of the hormones in the pathophysiology of GERD, motility disorders of the esophagus and gastrointestinal symptoms. This could mean a further step towards diagnosing and treating these diseases.

Material and methods

1. Study design

The motivation for this study was the substantial number of patients, who suffer from reflux associated symptoms, even after adequate therapy, and that we still do not understand the pathophysiology of GERD in detail. Furthermore, the reasons for motility disorders like achalasia are still unknown. These diseases could be provoked by alterations of the hormone levels in the blood. Former trials encouraged the assumption, that numerous hormones may have an influence on reflux associated symptoms, the esophageal motility and the LES. The main aim of this study was to figure out, if hormones influence gastrointestinal symptoms, especially GERD symptoms, the LES and the motility of the esophagus.

This study was approved by the competent institution ethics committee and was performed according to the declaration of Helsinki (revised version of Fortaleza 2013). The regulations of the Austrian Data Protecting Act and the upper Austrian Hospital Act had been fulfilled.

This was a prospective trial with one cohort, which existed of patients with suspected gastroesophageal reflux disease. Also, a minimal invasive intramural intervention (blood samples for determining hormone levels) took place. The patients had to be willing to participate and gave signed informed consent. The study was planned with 100 patients. According to the results of the High-Resolution Manometry patients were subdivided into three groups of esophagus motility, **Figure 12**.

Group I (n= 16)

The group I represents all patients with minor motility disorders, for example, weak peristalsis or frequent failed peristalsis.

Group II (n= 22)

Group II constitute all patients with EGJ functional outflow obstruction, for example achalasia, or major motility disorder.

Group III (n=48)

In this group, all "normal" patients, meaning without motility disorder and functional outflow obstruction, are included.

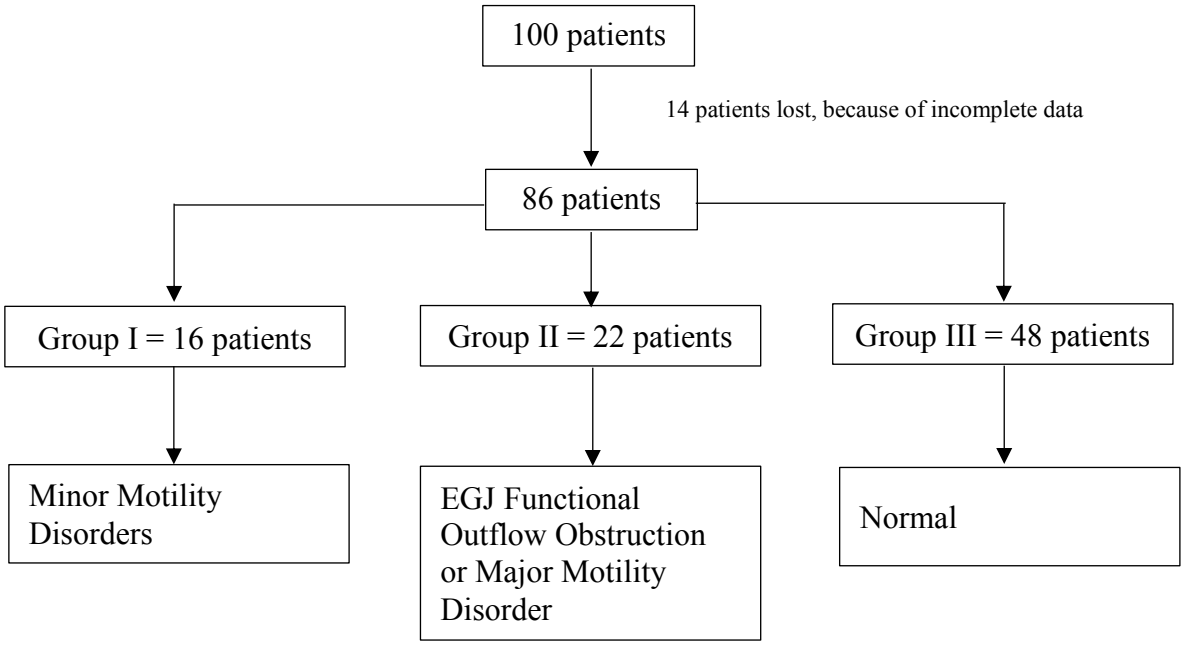

Figure 12: Patients-distribution.

Furthermore, patients were divided according to the results of 24h-pH-measurnemt into patients with pathologic distal acid exposer (GERD) and normal distal acid exposer.

Inclusion criteria:

- Patients with symptoms of GERD
- Eligibility for all diagnostic procedures
- Signed informed consent form

- Age between eighteen and eighty

Exclusion criteria:

- Pregnancy
- Language barrier
- Previous surgery of stomach and esophagus
- Presence of contraindication for any procedure

2. Process

All patients were interviewed by a specialist. If the patients were suitable for the study they got an appointment for hospitalized evaluation of GERD.

Before any procedures were conducted, patients must undergo PPI abstinence for a period of at least ten days.

During hospitalization, the following examinations, which are detailly described below, were performed: High-Resolution-Manometry (HRM), Esophagogastroduodenoscopy, 24-hour-pH-impendance-monitoring, Furthermore, the patients got three different questionnaires (GIQLI, RSI, and SCL). During these routine diagnostic explorations, blood samples are taken for the determination of the levels of the following hormones:

1. Thyroid Stimulating Hormone, TSH (µU/ml)
2. Free Triiodothyronine, FT3 (pmol/l)
3. Free Tetraiodothyronine, FT4(pmol/l)
4. Gastrin (pmol/l)
5. Calcitonin (pg/ml)
6. Vasoactive Intestinal Peptide, VIP (pmol/l)

3. Gastroduodenoscopy

With endoscopic exploration, a macroscopic view of the esophagus, the stomach and the very beginning of the duodenum, is presented. During this procedure, especially the mucosa gets examined, to detect any alterations, like inflammations, bleeding, ulcers, deformations and others. But also, other pathologies, like tumors, hernias or esophagal varices would be very important to find or to rule out. If something like a tumor or an altered tissue appears, a biopsy can be taken for further microscopic analysis.

Figure 13: Gastroduodenoscopy-Tower. © Barmherzige Schwestern hospital, Linz

Before this procedure patients should not eat or drink 6 to 8 hours in order to have an empty digestive system. This is important to assure a good quality of this examination. If needed, patients can get a light anesthesia with Propofol. The patient lies on his left side and the endoscope gets inserted through the mouth. Little by little the esophagus gets explored. In a rapid succession, the endoscope is guided through the stomach and the pylorus to the very beginning of the duodenum. Air gets inflated for a better view. When the endoscope gets retracted, the stomach as well as the gastroesophageal junction are carefully investigated. The air is aspirated and the endoscope gets pulled out.

In the process of evaluating GERD, upper endoscopy normally is the first procedure to perform. Endoscopic guidelines exist, which are published by different societies. For example, the AGA (American Gastroenterological Association) suggests three criteria for endoscopic examinations. First criteria is to prevent wrong diagnosis, second to detect complications, and third to figure out the causes and consequences of treatment failure. (8)

A reflux-screening using only endoscopy on its own, is not sensitive enough for diagnosing GERD. Even if the result is normal, the absence of GERD is not proofed. To be certain, more examinations are necessary, like high resolution manometry and 24h-pH-measurement.

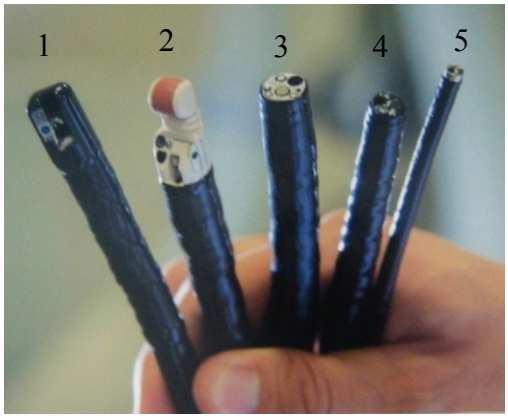

Figure 15:

1) *Endoscope for endoscopic retrograde cholangiopancreaticography (ERCP)*
2) *Endosonography*
3) *Coloscopy*
4) *Esophagogastroduodenoscopy*
5) *Esophagogastroduodenoscopy for children*

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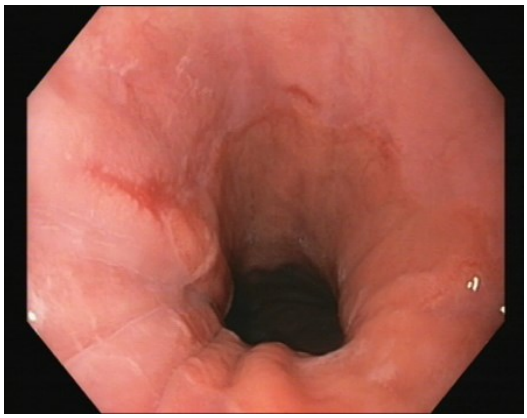

Figure 14: Endoscopic view of the esophagus with esophagitis

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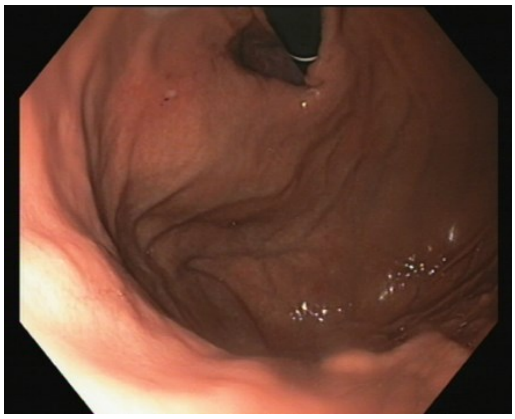

Figure 17: Retroflex-view of the stomach.

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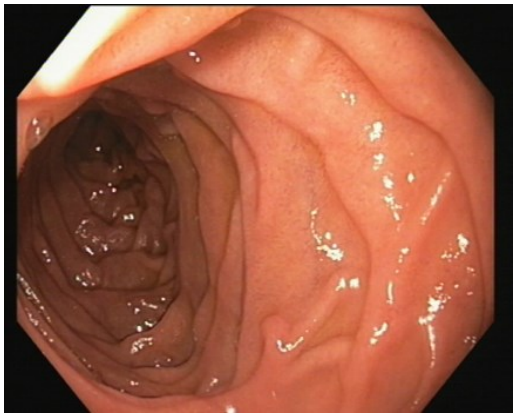

Figure 16: Endoscopic view of the duodenum.

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4. High Resolution Manometry (HRM)

With High Resolution Manometry motility disorders of the esophagus are easily recognized. This established method evaluates the function of the upper and lower esophageal sphincter, as well as the esophageal peristalsis, by measuring different pressure levels throughout the esophagus. This procedure has its roots in conventional manometry. This technique uses four to eight pressure channels to record the esophageal peristalsis.

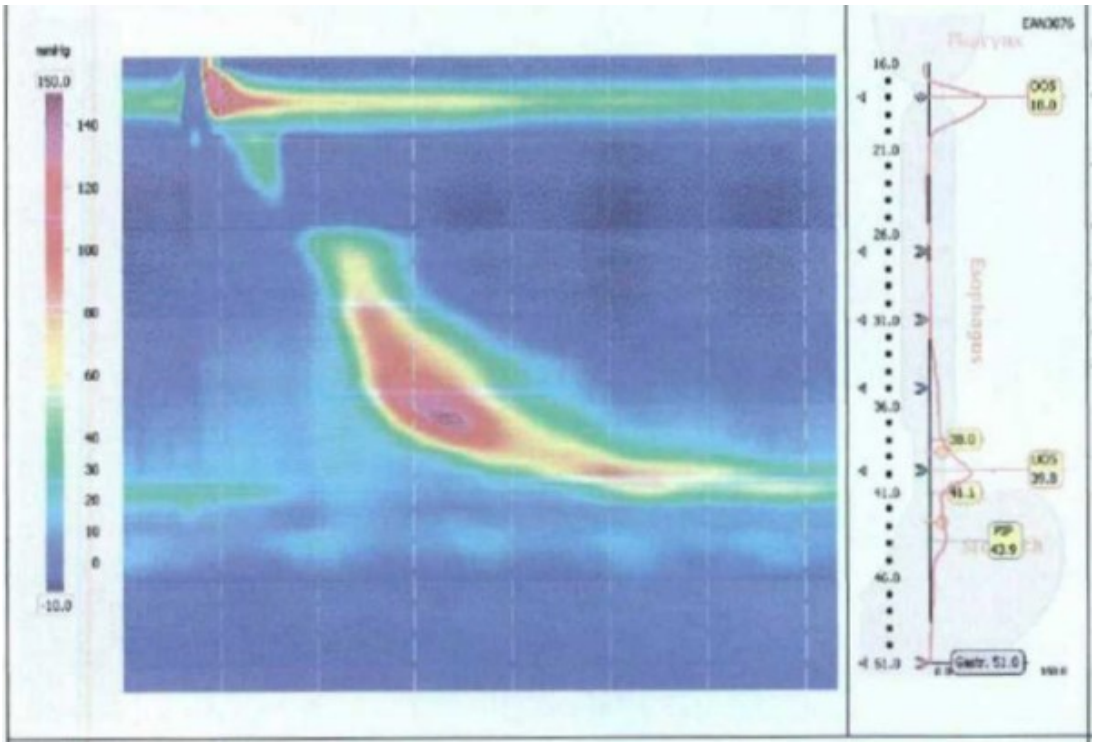

Figure 18: High Resolution Manometry with catheter. © Barmherzige Schwestern hospital, Linz

More sensors (20-36), that are closely spaced and the display of pressure levels in the way of contour plots, led to HRM. This concept is called the Clouse-contour-plot. It can be compared to a topographical surface map, where the altitudes are represented by colors. A colored bar is created by replacing every pressure level with a distinct color. Using interpolation, the colored bars are combined and this results in a contour plot or rather a high-resolution esophageal pressure topography (HREPT). Through this contour plot a lot of useful information is shown. Landmarks like the UES and the LES, for example, guarantee a correct positioning of the catheter.

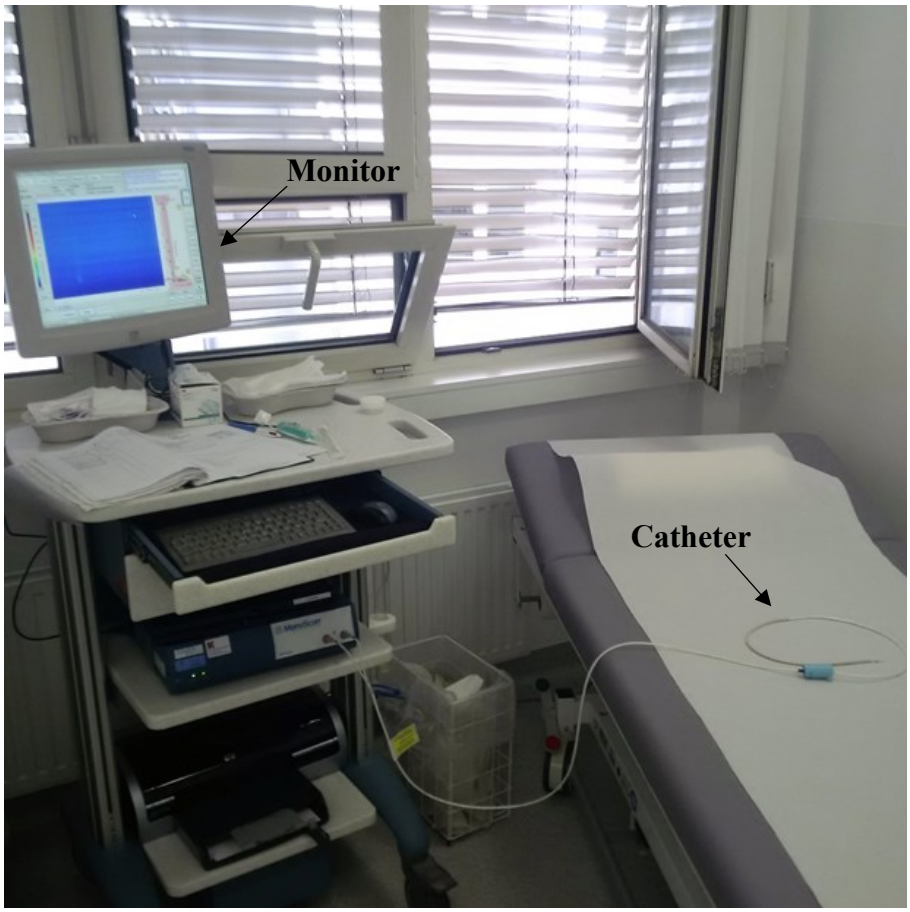

Figure 19: High Resolution Manometry with catheter. © Barrmherzige Schwestern hospital, Linz

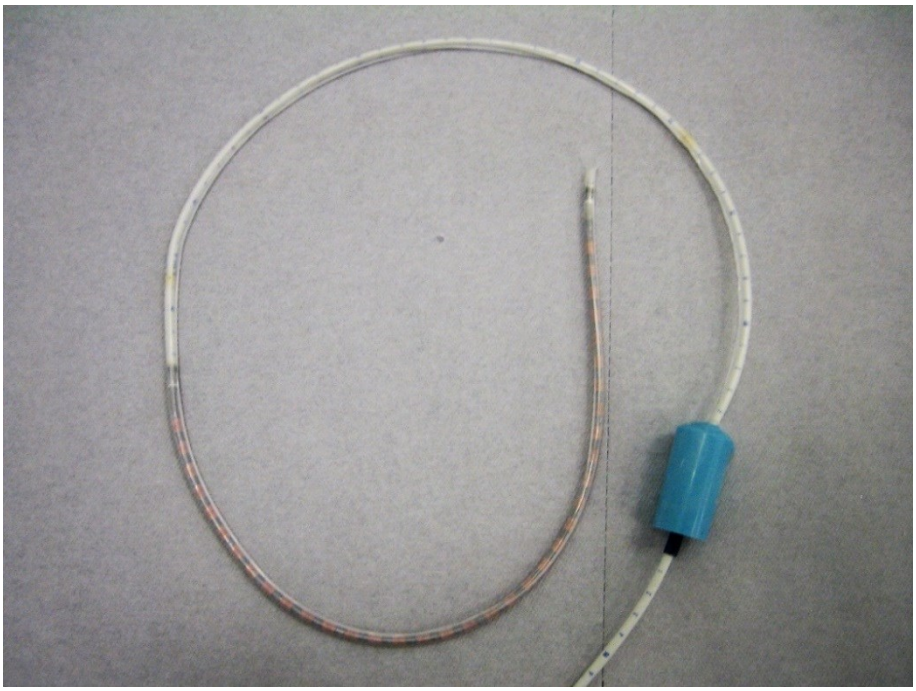

Figure 20: Close-up of the catheter, HRM. © Barrmherzige Schwestern hospital, Linz

2009, the first version of the Chicago Classification was created. Because of the continuous new clinical and investigational publications, other updated versions of the CC followed in 2012 and 2014. Up to this date the latest version is the CC v0.3.

Concerning the esophageal motility, disorders have been divided into achalasia (with three subtypes), EGJ outflow obstruction, major disorders and minor disorders and have been new defined. Consequential an updated hierarchical algorithm for clinical application have been designed.

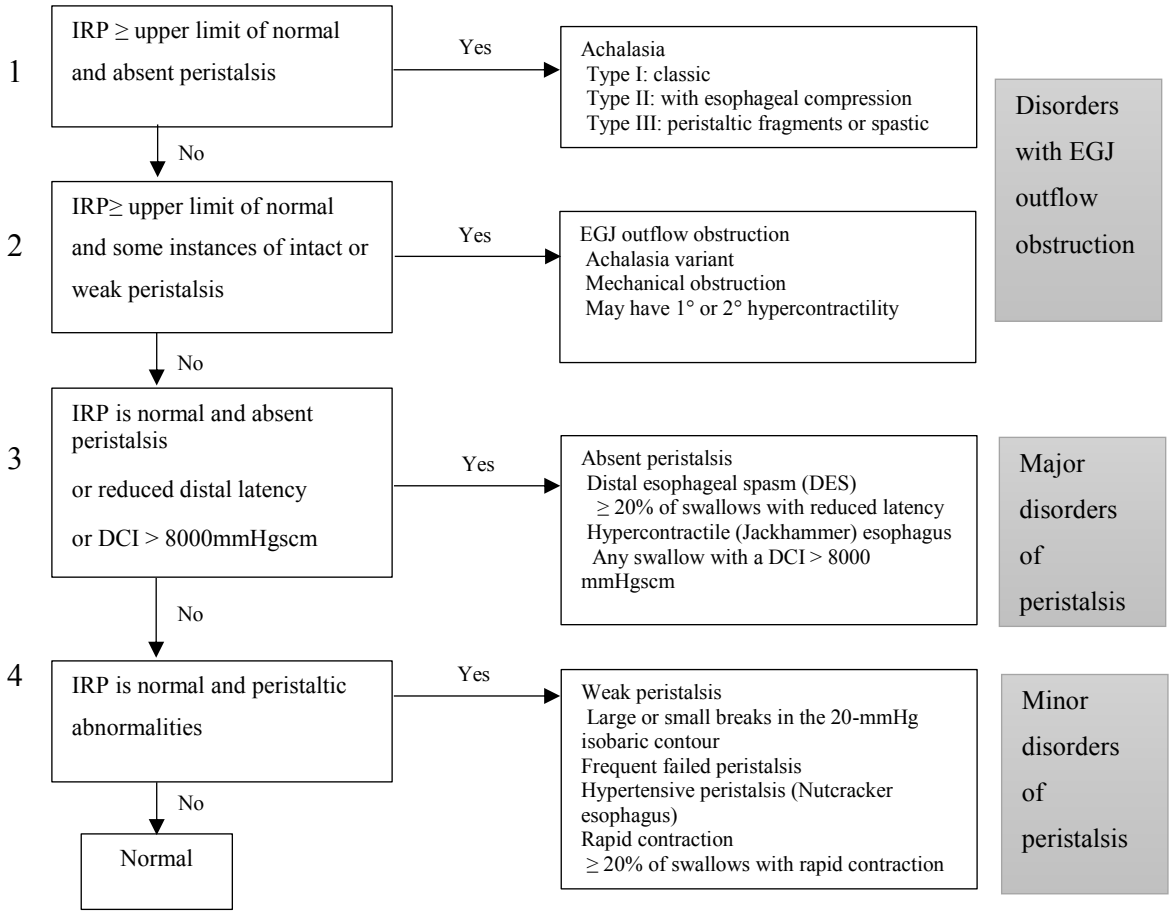

Figure 21: Hierarchical Analysis of Esophageal Motility - Chicago Classification 2012

*Table 2: Esophageal pressure topography metrics. All pressure referenced to atmospheric pressure except the integrated relaxation pressure (IRP), which is referenced to gastric pressure. *unclear relevance – Chicago Classification*

Pressure Topographic Metrics	
Metric	**Description**
IRP (mmHg) Integrated Relaxation Pressure	Mean EGJ pressure measured with an electronic equivalent of a sleeve sensor for 4 contiguous or non-contiguous seconds of relaxation in the ten-second window following deglutitive UES relaxation
DCI (mmHgscm) Distal Contractile Integral	Amplitude x duration x length (mmHgscm) of the distal esophageal contraction greater than 20 mmHg ffrom proximal to distal pressure troughs.
CPD (time, position) Contractile Deceleration point	The inflection point along the 30-mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the phrenic ampulla.
CFV (cm/s) Contractile Front Velocity *	Slope of the tangent approximating the 30mmHg isobaric contour between proximal and the CPD
DL (s) Distal Latency	Interval between UES relaxation and the CPD
Peristaltic breaks (cm)	Gaps in the 20-mmHg isobaric contour of the peristaltic contraction between UES and EGJ, measured in axial length

Table 3: Esophageal pressure topography scoring of individual swallows – Chicago Classification

Esophageal pressure topography	
Integrity of contraction	
Normal Contraction	20mmHg isobaric contour without large or small break
Weak contraction	a. Large break in the 20mmHg isobaric contour (>5cm in length) b. Small break in the 20mmHg isobaric contour (2-5cm in length)
Failed contraction	Minimal (<3cm) integrity of the 20mmHg isobaric contour distal to the proximal pressure trough
Contraction pattern (for intact or weak peristalsis with small breaks)	
Premature Contraction	DL > 4,5s
Hypercontractile	DCI > 8000mmHgscm
Rapid contraction	CFV > 9cm/s
Normal contraction	Not fulfilling any of the above criteria
Intrabolus pressure pattern (30mmHg isobaric contour)	
Panesophageal pressurization	Uniform pressurization extending from the UES to the EGJ
Compartmentalized esophageal pressurization	Pressurization extending from the contractile front to a sphincter
EGJ pressurization	Pressurization restricted to zone between the LES and CD in conjunction with hiatal hernia
Normal pressurization	No bolus pressurization > 30mmHg

Table 4: Chicago classification of esophageal motility

Esophageal Motility	
Diagnosis	**Diagnostic Criteria**
Achalasia	
Type I Achalasia	Mean IRP > upper limit of normal, 100% failed peristalsis
Type II Achalasia	Achalasia with esophageal compression: mean IRP > upper limit of normal, no normal peristalsis, panesophageal pressurization with ≥20% of swallows
Type III Achalasia	Mean IRP > upper limit of normal, no normal peristalsis, preserved fragments of distal peristalsis or premature (spastic) contractions with ≥20% of swallows
EGJ Outflow Obstruction	Mean IRP > upper limit of normal, some instances of intact peristalsis or weak peristalsis with small breaks such that the criteria for achalasia are not met ¥
Motility Disorders	
Distal esophageal spasms	Normal mean IRP
Hypercontractile esophagus (Jackhammer)	At least one swallow DCI > 8000mmHgscm with single peaked or multipeaked contraction ¥¥
Absent Peristalsis	Normal mean IRP, 100% of swallows of failed peristalsis
Peristaltic abnormalities	
Weak peristalsis with large peristaltic defects	Mean IRP < 15mmHg and >20% swallows with large breaks in the 20mmHg isobaric contour (>5cm in length)
Weak peristalsis with small peristaltic defects	Mean IRP < 15mmHg and >30% swallows with small breaks in the 20mmHg isobaric contour (2-5cm in length)
Frequent failed peristalsis	>30%, but <100% of swallows with failed peristalsis
Rapid contraction with normal latency	Rapid contractions with ≥20%of swallows, DL >4,5s
Hypertensive peristalsis (Nutcracker esophagus)	Mean DCI >5000mmHgscm, but not meeting criteria of hypercontractile esophagus
Normal	Not achieving any of the above criteria

¥ May be a variant from of achalasia, indicative of wall stiffness consequent from a infiltrative disease, or manifestation of hiatal hernia in which case it can be subtyped to CD or LES.

¥¥ The locus of the multipeaked contraction can be in either of the distal two contractile segments or very rarely in the LES, but is usually in the third contractile segment. May coexist with EGJ outflow obstruction.

5. 24h-pH-Impedance-Measurement

The combined measurement of 24-ph-metry and pH-impedance monitoring allows a objectification of a gastroesophageal reflux and is in fact a very sensitive standard method. (66)

Before this procedure patients should not eat or drink for 6 hours. The catheter gets inserted through the nose and is placed five centimeters above the LES – the position of the sphincter is defined in a previous procedure, the HRM. When symptoms occur during the measurement, the patient must press specific buttons for individual symptoms. After the test, during interpretation, the correlations between symptoms and refluxes are analyzed.

The monitoring shows all types of reflux, it as well defines the pH of the refluxes (acid and weakly acid, non-acid) (8) (59). If the exposition time of acid lies over five percent, it is a sign for GERD. (67) Another pathological sign is the number of the reflux episodes. If more than seventy-three episodes take place, it counts as pathological. Furthermore, these episodes are differentiated between acid (pH<4), weakly-acid (pH 4-7) and non-acid (pH>7).

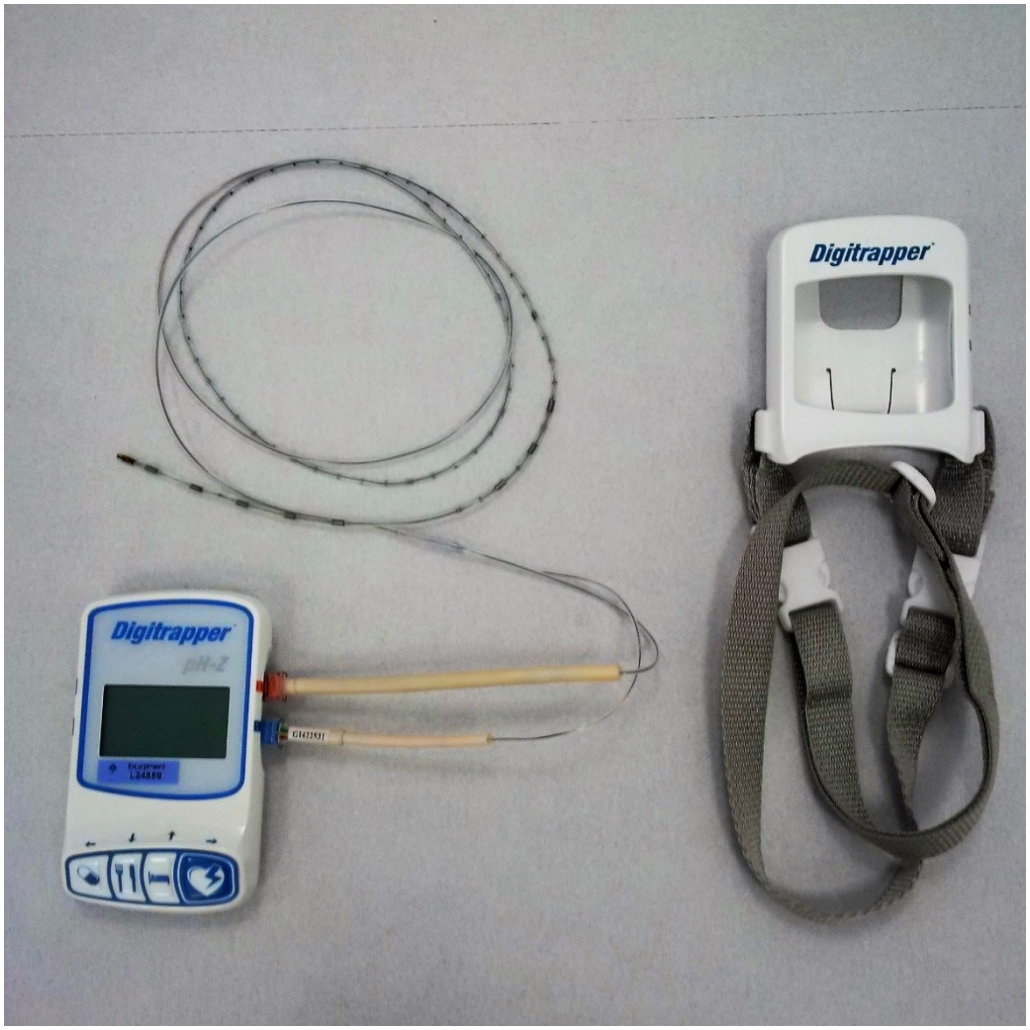

Figure 22: 24h-pH-measurement with pH-impedance- and pH-catheter on the left. Support device for patient on the right. © Barrmherzige Schwestern hospital, Linz

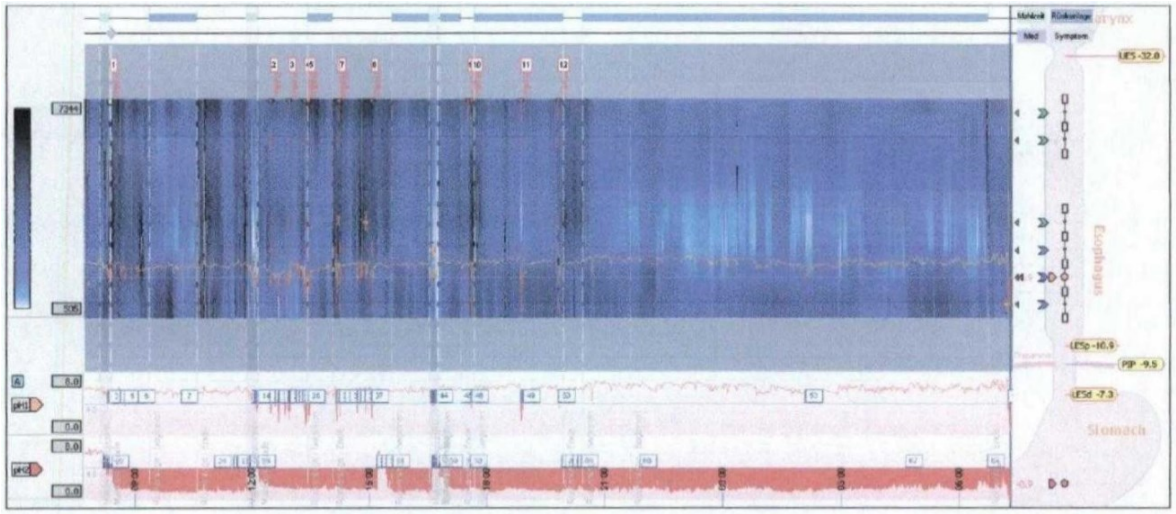

Figure 23: PH-Impedance-Monitoring. Dual-channel monitoring presents information of the proximal and the distal esophagus. © Barrmherzige Schwestern hospital, Linz.

The De Meester-Score determines the frequency and the temporal expansion of the reflux episodes, in upright and horizontal position, as well as their relation to food intake. This score is calculated from: 1) the values of the percentage of time with pH<4 during the total measuring period – upright and horizontal, 2) the number of refluxes >5 minutes, 3) the duration of the longest reflux episode and 4) the total number of refluxes. (68) The De Meester-Score is normal when it lies under 14,72, is an important reference value. (69)

Table 5: Normal value of 24h-pH-measurement, from (68)

Time slot with pH<4, total	≤ 5,8%
Time slot with pH<4, upright position	≤ 8,2%
Time slot with pH<4, horizontal position	≤ 3,5%
Total number of reflux episodes	≤ 46
Number of reflux episodes >5 minutes	≤ 4
Longest reflux episodes	≤ 19 minutes

When evaluating 24h-pH-measurments, a major step is the "symptom-reflux-correlation". This shows, if a temporal relation between reflux episodes and symptoms exist. If a symptom occurs in a time range between 2 and 5 minutes after a reflux episode, symptom and reflux episode correlate. (68)

For quantification of the "symptom-reflux-correlation" three parameters exist – the Symptom Index (SI), the Symptom Sensitivity Index (SSI) and the Symptom Association Probability (SAP).

Symptom Index (SI)

The SI indicates the number of reflux-correlated symptoms in relation to the total number of occurred symptoms. High or rather positive values (SI ≥50%) indicate that the symptoms are most likely reflux-correlated. (68)

Symptom Sensitivity Index (SSI)

The SSI describes the percentage of the symptom-associated-reflux-episodes referred to the total number of reflux episodes. This represents the sensitivity of the esophageal mucosa to the acid backflow. A positive SSI lies over 10%. (68)

Symptom Association Probability (SAP)

The SAP calculates the possibility of the connection between reflux and symptoms. The 24 hours are segmented into two-minutes-periods. A contingency table is created and with the Fisher's-Exact-Test the coincidence of the relation between reflux episodes and symptoms is checked. Lies the SAP over 95% the possibility of a random encounter of reflux and symptom is less than 5%. (68)

All in all, the 24h-pH-measurement is necessary for objectivation of the reflux disease.

6. Questionaires

Every patient receives three different kind of questionnaires, which are standardized and gather information about the complaints and the quality of life of each person. The reflux symptom index (RSI) after Belafsky includes reflux symptoms with focus on atypical symptoms (70). The symptom check list (SCL) as well covers atypical symptoms, but further typical symptoms and intake manners of PPI. (71) Original questionnaires shown in the *Appendix*.

6.1. Gastrointestinal Quality of Life Index (GIQLI)

The GIQLI was developed (Eypasch et al. 1995) to conceive the quality of life in patients with GERD (72). Confirmed and recommended by the European Study Group for Antireflux Surgery, the GIQLI is a well-accepted questionnaire (73).

The answers for the 36 questions are graded from 0 to 144. The average score in healthy people is 122,6. Higher scores, mean higher quality of life.

The GIQLI questionnaire is subdivided into 5 subsets:

1. Gastrointestinal symptoms (0-76 points)
2. Emotional status (0-20 points)
3. Physical functioning (0-28 points)
4. Social functioning (0-16 points)
5. Stress of medical treatment (0-4 points)

Patients were also asked for the frequently or on demand use of acid-blocking medication. (74)

6.2. Reflux Syndrome Index (RSI)

Belafsky et al. have developed a nine-item questionnaire, the reflux syndrome index. The maximum score amount to 45 points. Each individual question can be scaled from 0 (no problem) to 5 (severe problem). A result of >13 is considered to be pathological. (70)

The following list shows the items, the patients had to grade within the RSI questionnaire:

1. Hoarseness or a problem with the voice.
2. Clearing your throat.
3. Excess throat mucous or postnasal drip.
4. Difficulty swallowing food, liquids, or pills.
5. Coughing after you ate or after lying down.
6. Breathing difficulties or choking episodes.
7. Troublesome or annoying cough.
8. Sensations of something sticking in your throat or a lump in your throat.
9. Heartburn, chest pain, indigestion, or stomach acid coming up. (75)

6.3. Symptom Check List (SCL)

The SCL asks for 14 specific symptoms, namely heartburn, regurgitation, epigastric pain, cough, hoarseness, asthma, dysphagia, fullness, diarrhea, flatulence, constipation, belching, bloatedness, and distortion of taste.

To assess the intensity of the symptoms, all symptoms were scored as a product of severity (0-4) and frequency (0-4). For each symptom, the patients were asked two questions: `How much does this problem bother you?' and `How often do you have this problem?' The severity was classified from 0 (not at all) to 4 (very severe). The frequency was classified as (0) if the symptoms were absent, (1) if symptoms occurred once a week, (2) if symptoms occurred several times a week, (3) if symptoms occurred daily, and (4) if symptoms were permanent. To get the ultimate result the frequency of each symptom is multiplied by its degree, resulting in scores from 0 to 16 for each symptom, with a total max score of 224 and a minimum score of 0. Higher scores indicate more severe symptoms.

Additionally, four different scores were extracted to assess symptoms specific for:

- Typical reflux symptoms: reflux heartburn, regurgitation, chest pain
- Non-typical reflux symptoms: cough, hoarseness, asthma, distortion of taste
- Gas-Bloating-Symptoms: fullness, bloating
- Gastrointestinal Symptoms: diarrhea, constipation, flatulence (74)

7. Blood samples

The blood samples were taken on the first day of hospitalization. We evaluated the levels of six different hormones in the patient's blood:

1. Thyroid Stimulating Hormone, TSH (µU/ml)
2. Free Triiodothyronine, FT3 (pmol/l)
3. Free Tetraiodothyronine, FT4(pmol/l)
4. Calcitonin (pg/ml)
5. Gastrin (pmol/l)
6. Vasoactive Intestinal Peptide, VIP (pmol/l)

The hormones were quantified with two different tests, the ElectroChemiLuminescenceAssay (ECLIA) and the RadioImmunoAssy (RIA).

7.1. ECLIA – Electrochemiluminescence (Cobas®)

Figure 24: Electrochemiluminescence (Cobas®)

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TSH, FT3, FT4 and Calcitonin were all determined with a technology called ECLIA (Electrochemiluminescence), which represents an immunological in vitro test. The analytical method is based on two marked antibodies, which together build a sandwich-complex. One antibody is marked with biotin and one is marked with ruthenium. When Streptavidin is added, the sandwich-complex can bind to the solid phase, **Figure 25**. On the lotion, a voltage is created and triggers a specific reaction - this makes the antibody-complex detectable.

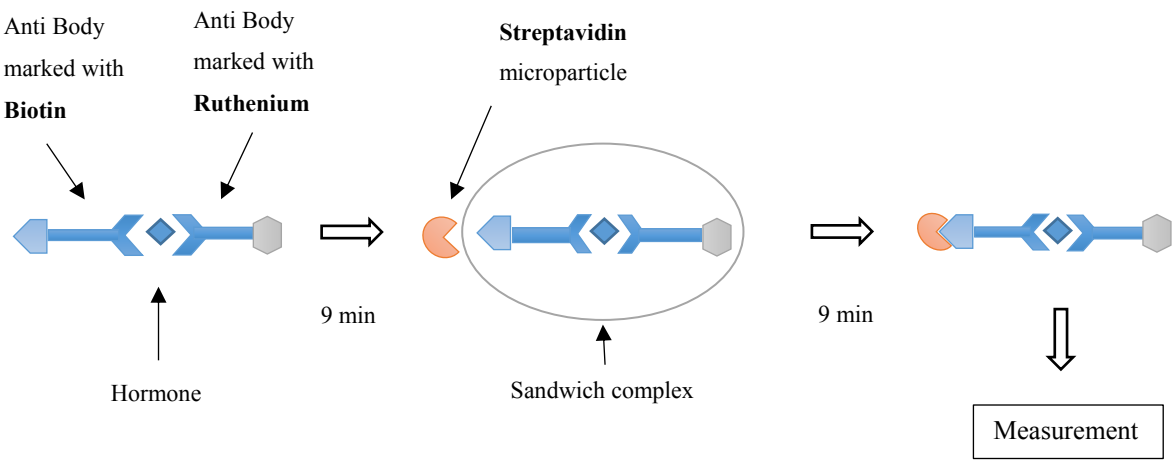

Figure 25: Principle of measurement, Sandwich-Assay.

7.2. RIA – RadioimmunoAssy

VIP and gastrin were both detected with RIA (RadioimmunoAssy). The hormones get pipetted by hand. A tracer, Iodine ^{125}, is added and binds to the hormones. With the Automatic Gamma Counter, the hormones get quantified.

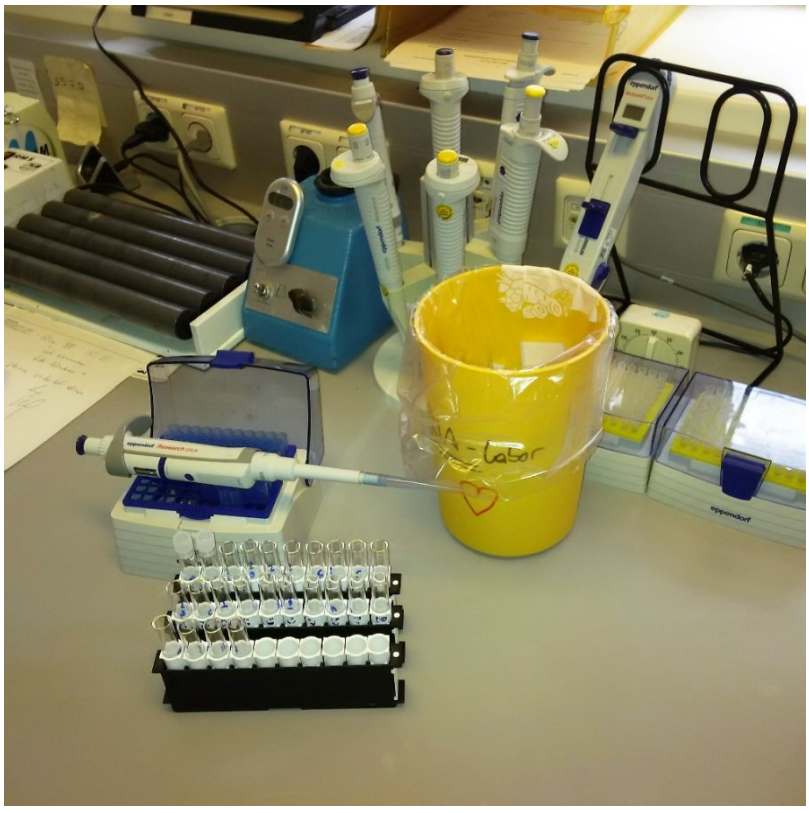

Figure 26:

Workstation for the RIA analysis. Nuclear Labor.

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8. Statistical methods

Data analysis was carried out using SPSS, statistical analysing software. The following test methods were used: Comparison of the mean values of the data was carried out with the t-test. The relations between the evaluated hormones and the remaining data were tested with the correlation by Pearson. For regression analysis, linear regression was utilized. In some cases, descriptive statistic was used.

Results

Complete data was available in 86/100 patients and was evaluated. These patients consisted of 44 men and 42 women from 24 to 88 years (mean age 56 years). Demographic data of these patients is summarized in **Table 6**. Minor motility disorders (Group I) were present in 16 patients, 22 patients had EGJ functional outflow obstruction or major motility disorders (Group II) and 48 patients were normal (Group III). The normal and mean values of the evaluated hormones are summarized below, **Table 7**.

Table 6: Demographic data.

Patients	**86**
Women	**42**
Men	**44**
Median Age	**56 years**

Table 7: Hormone values

Hormone	Normal Value	Mean Value
TSH	0,4 – 4 µU/ml	1,5 µU/ml
FT3	2,8 – 8 pmol/l	5,1 pmol/l
FT4	10 – 25 pmol/l	15,9 pmol/l
Calcitonin	< 10 pg/l	4 pg/l
VIP	< 30 pmol/l	16,3 pmol/l
Gastrin	< 60 pmol/l	30,1 pmol/l

1. Influence of the hormones on LES pressure

The median LES pressure of the 86 patients was 23,6 mmHg. No correlations were found between the different hormones and the LES-pressure. But a strong inverse relation between calcitonin and IRP was found (r= -0,492; p=0,000), see **Table 8**.

Table 8: Comparison of the hormones and HR-manometry data

		DCI, Manometry	Interbolus-pressure, Manometry	LESP	Wave Amplitude	IRP
TSH	Correlation	,037	-,064	,043	,071	-,112
	Significance	,740	,566	,700	,523	,314
	N	82	83	83	82	83
FT3	Correlation	,029	,019	,163	,072	,142
	Significance	,794	,864	,141	,519	,200
	N	82	83	83	82	83
FT4	Correlation	-,067	,052	,011	-,027	-,049
	Significance	,550	,643	,919	,811	,659
	N	82	83	83	82	83
Calcitonin	Correlation	-,022	,058	-,119	,024	-,492
	Significance	,843	,602	,284	,830	,000
	N	82	83	83	82	83
VIP	Correlation	,041	,018	,022	-,027	-,011
	Significance	,715	,872	,845	,810	,920
	N	82	83	83	82	83
Gastrin	Correlation	-,017	,025	-,030	,009	,055
	Significance	,881	,821	,787	,933	,620
	N	82	83	83	82	83

2. Influence of the hormones on the results of the questionnaires (symptoms)

No correlations were found between hormones and the main parameters GIQLI, RSI and SCL. But positive correlations were found between VIP and GI-Symptoms (r=0,298; p= 0,011), as well as correlations between FT3 and dysphagia (r=0,283, p=0,016), see **Table 9**.

Table 9: Comparison of hormones and questionnaires (symptoms)

		GIQLI	RSI_	SCL_	Typical Symptoms	Atypical Symptoms	GI-Symptoms	Gasbloat-Symptoms	Dysphagia	Regurgitation
TSH	Corr.	,077	-,056	-,040	-,164	-,009	,050	,019	-,020	,014
	Sign.	,512	,649	,737	,169	,942	,677	,873	,868	,908
	N	74	69	72	72	72	72	72	72	72
FT3	Corr.	-,060	,071	,029	-,124	,130	-,023	-,168	,283*	,051
	Sign.	,609	,563	,807	,300	,276	,848	,158	,016	,669
	N	74	69	72	72	72	72	72	72	72
FT4	Corr.	-,009	-,045	,130	,207	,011	,072	,034	-,005	,072
	Sign.	,936	,711	,277	,082	,926	,549	,774	,969	,545
	N	74	69	72	72	72	72	72	72	72
Calcitonin	Corr.	,072	-,093	-,046	-,059	,003	-,067	-,041	-,089	,001
	Sign.	,541	,445	,703	,624	,982	,574	,735	,460	,991
	N	74	69	72	72	72	72	72	72	72
VIP	Corr.	-,030	,001	,131	,122	-,022	,298*	,157	,003	-,070
	Sign.	,802	,993	,273	,307	,854	,011	,188	,979	,559
	N	74	69	72	72	72	72	72	72	72
Gastrin	Corr.	,147	-,017	-,101	-,219	,123	-,045	-,157	-,172	-,129
	Sign.	,211	,892	,400	,064	,305	,710	,188	,149	,279
	N	74	69	72	72	72	72	72	72	72

3. Influence of the hormones on GERD

The 86 patients had a median DeMeester score of 20,6. A pathological DeMeester score existed in 45 patients, with median of 35. Comparison of hormones and pathological DeMeester Score and comparison and comparison of hormones and non-pathological DeMeester Score was performed. No correlations were found. Furthermore, no correlations between the total DeMeester score and the hormones were found, **Table 10**, **Table 11** and **Table 12**.

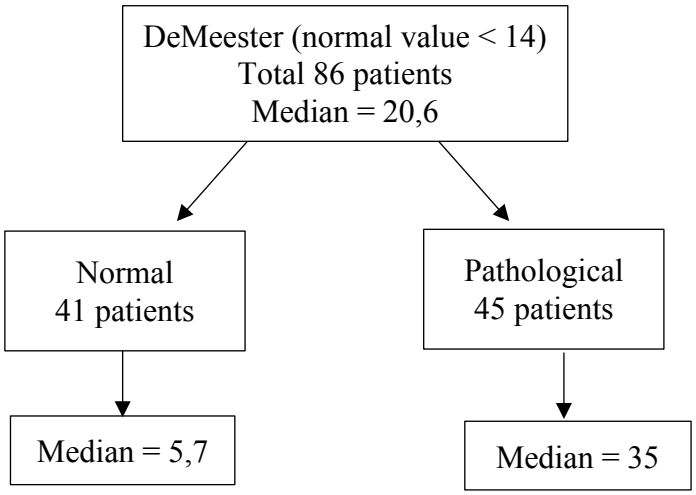

Figure 27: Contribution of the values of DeMeester-score

Table 10: Comparison of hormones and pathological DeMeester Score.

		TSH	FT3	FT4	Calcitonin	VIP	Gastrin
De_Meester	Correlation	,003	-,138	,080	-,129	,061	,216
	Significance	,984	,366	,600	,399	,693	,153
	N	45	45	45	45	45	45

Table 11: Comparison of hormones and non-pathological DeMeester Score.

		TSH	FT3	FT4	Calcitonin	VIP	Gastrin
De_Meester	Correlation	-,294	-,144	,135	,155	,155	-,263
	Significance	,062	,367	,400	,334	,333	,096
	N	41	41	41	41	41	41

Table 12: Comparison of hormones and the total DeMeester

		TSH	FT3	FT4	Calcitonin	VIP	Gastrin
De_Meester	Correlation	-,109	-,084	,078	,000	,098	-,116
	Significance	,318	,440	,476	,997	,370	,287
	N	86	86	86	86	86	86

4. Influence of the hormones on Motility disorders

4.1 Comparison of the mean values of the evaluated hormones between Group I&II and Group III

Further a comparison of the hormone-mean-values between the patients with motility disorders (Group I and II), and the normal patients (Group III) was carried out. No significant difference in the hormone levels between the groups were found; see **Table 13** to **Table 18**. This leads to the assumption, that the evaluated hormones do not influence the above-mentioned disorders.

Table 13: Comparison of TSH-mean-values between Group III and Group I&II

	TSH	
	Group II n=48	Group I & II n=38
Mean	1,54	1,42
Standard deviation	0,69	1,02
Significance	**No significance p=0.539**	

Levene Test: F=2,752; p=0,101

Table 14: Comparison of FT3-mean-values between Group III and Group I&II

	FT3	
	Group III n=48	Group I & II n=38
Mean	4,87	5,35
Standard deviation	0,57	2,22
Significance	**No significance p=0.196**	

Levene Test: F=2,492; p=0,118

Table 15: Comparison of FT4-mean-values between Group III and Group I&II

	FT4	
	Group III n=48	Group I & II n=38
Mean	16,23	15,42
Standard deviation	2,71	4,22
Significance	**No significance p=0.302**	

Levene Test: F=0,543; p=0,463

Table 16: Comparison of Calcitonin-mean-values between Group III and Group I&II

	Calcitonin	
	Group III n=48	Group I & II n=38
Mean	2,98	2,30
Standard deviation	3,07	3,10
Significance	**No significance p=0.315**	

Levene Test: F=0,355; p=0,553

Table 17: Comparison of VIP-mean-values between Group III and Group I&II

	VIP	
	Group III n=48	Group I & II n=38
Mean	15,83	16,77
Standard deviation	5,88	9,29
Significance	**No significance p=0.583**	

Levene Test: F=1,049; p=0,309

Table 18: Comparison of Gastrin-mean-values between Group III and Group I&II

	Gastrin	
	Group III n=48	Group I & II n=38
Mean	27,27	27,21
Standard deviation	12,58	11,55
Significance	**No significance p=0.981**	

Levene Test: F=0,002; p=0,961

4.2 Comparison of the mean values of the evaluated hormones between Group II and III

The comparison of the hormone-mean-values between the patients with EGJ outflow obstruction or Major motility disorders (Group II) and the normal patients (Group III) have shown no significant differences **Table 19** to **Table 24**. The comparison between Group II and III shows a significance of p=0,043, regarding **calcitonin**.

Table 19: Comparison of TSH-mean-values between Group II and Group III

	TSH	
	Group II n=22	Group III n=48
Mean	1,27	1,54
Standard deviation	1,07	0,69
Significance	**No significance p=0.291**	

Levene Test: F=2,943; p=0,091

Table 20: Comparison of FT3-mean-values between Group II and Group III

	FT3	
	Group II n=22	Group III n=48
Mean	5,58	4,87
Standard deviation	2,93	0,57
Significance	**No significance p=0.117**	

Levene Test: F=5,659; p=0,020

Table 21: Comparison of FT4-mean-values between Group II and Group III

	FT4	
	Group II n=22	Group III n=48
Mean	15,00	16,24
Standard deviation	4,35	2,71
Significance	**No significance p=0.233**	

Levene Test: F=0,536; p=0,467

Table 22: Comparison of Gastrin-mean-values between Group II and Group III

	Gastrin	
	Group II n=22	Group III n=48
Mean	26,95	27,28
Standard deviation	11,63	12,58
Significance	**No significance p=0.918**	

Levene Test: F=0,146; p=0,703

Table 23: Comparison of VIP-mean-values between Group II and III

	VIP	
	Group II n=22	Group III n=48
Mean	16,19	15,83
Standard deviation	7,37	5,88
Significance	**No significance p=0.842**	

Levene Test: F=0,410; p=0,524

Table 24: Comparison between Group II and III, regarding Calcitonin.

	Calcitonin	
	Group II n=22	Group III n=48
Mean	1,68	2,98
Standard deviation	2,04	3,07
Significance	**p=0.043***	

Levene Test: F=5,758; p=0,019

4.3 Comparison of the mean values of the evaluated hormones between Group I and Group II

The statistical analysis came to the result, that the mean values of the individual hormones do not significantly differentiate between the patients with minor motility disorders (Group I) and the patients with EGJ outflow obstruction or major motility disorders (Group II), summarized in **Table 25** to **Table 30**.

Table 25: Comparison of means of TSH between Group I and II.

	TSH	
	Group II n=22	Group I n=16
Mean	1,27	1,62
Standard deviation	1,07	0,95
Significance	**No significance p=0.298**	

Levene Test: F=0,373; p=0,545

Table 26: Comparison of means of FT3 between Group I and II.

	FT3	
	Group II n=22	Group I n=16
Mean	5,58	5,07
Standard deviation	2,93	0,56
Significance	**No significance p=0.437**	

Levene Test: F=1,983; p=0,167

Table 27: Comparison of means of FT4 between Group I and II.

	FT4	
	Group II n=22	Group I n=16
Mean	15,00	15,96
Standard deviation	4,35	4,12
Significance	**No significance p=0.491**	

Levene Test: F=0,006; p=0,938

Table 28: Comparison of means of Calcitonin between Group I and II.

	Calcitonin	
	Group II n=22	Group I n=16
Mean	1,68	3,10
Standard deviation	2,04	4,03
Significance	**No significance p=0.160**	

Levene Test: F=6,458; p=0,015

Table 29: Comparison of means of VIP between Group I and II.

	VIP	
	Group II n=22	Group I n=16
Mean	16,19	17,54
Standard deviation	7,37	11,51
Significance	**No significance p=0.677**	

Levene Test: F=0,369; p=0,547

Table 30: Comparison of means of Gastrin between Group I and II.

	Gastrin	
	Group II n=22	Group I n=16
Mean	26,95	27,59
Standard deviation	11,63	11,80
Significance	**No significance p=0.874**	

Levene Test: F=0,480; p=0,49

4.4 Correlations between the evaluated hormones and Group II

But the study shows some interesting outcomes within the correlation-testing between the patients with functional outflow obstruction or major motility disorders (Group II) and the hormones VIP, FT4 and TSH.

For example, the correlation between VIP and the Gas-Bloat-Symptoms of the SCL (p=0,072) within Group II (EGJ functional outflow obstruction or major motility disorder) could lead to the assumption that an increased level of VIP does associate with more bloating-symptoms; **Table 31**.

Table 31: Correlation between VIP and SCL and SI, within Group II.

		SCL _ GB-Symptoms
VIP	**Correlation**	0,447
	Significance	0,072*
	N	17

*p<0,1

Table 32: Correlation between FT4 and SCL within Group II.

		SCL _ Typical Symptoms	SCL _ GI-Symptoms
FT4	**Correlation**	0,690	0,504
	Significance	0,002*	0,039**
	N	17	17

*p<0,1; **p<0,05

The correlation between **FT4** and the two SCL-fractions, Typical-symptoms and GI-symptoms, show that the higher the FT4 value, the higher the value of the two fractions, **Table 32**.

After a regression analysis between FT4 and the Typical-symptoms, as well as the GI-symptoms, we came to the following conclusion. The regression model can be classified as good (R^2=0,490). The coefficient of determination is not randomly achieved, but is a result of the relation of data (F-test=6,734; p=0,009). It is identified, that the Typical-symptoms and GI-symptoms are positively influenced by FT4. If the Typical-symptoms rise by 1 point, FT4 increases by 0,382 points. If the GI-symptoms rise by 1 point, FT4 increases by 0,275 points.

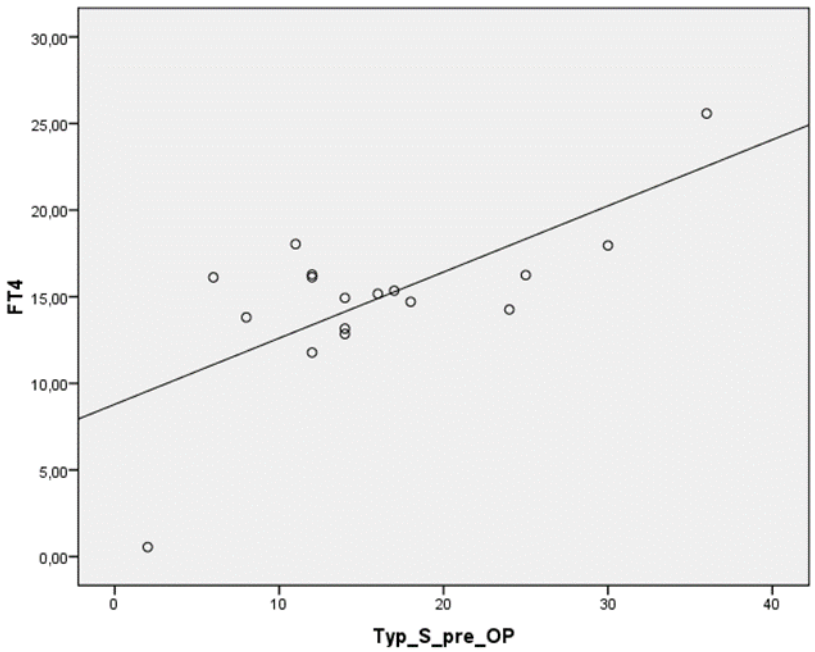

Figure 28: Regression Model between FT4 and the Typical-Symptom-Fraction of SCL.

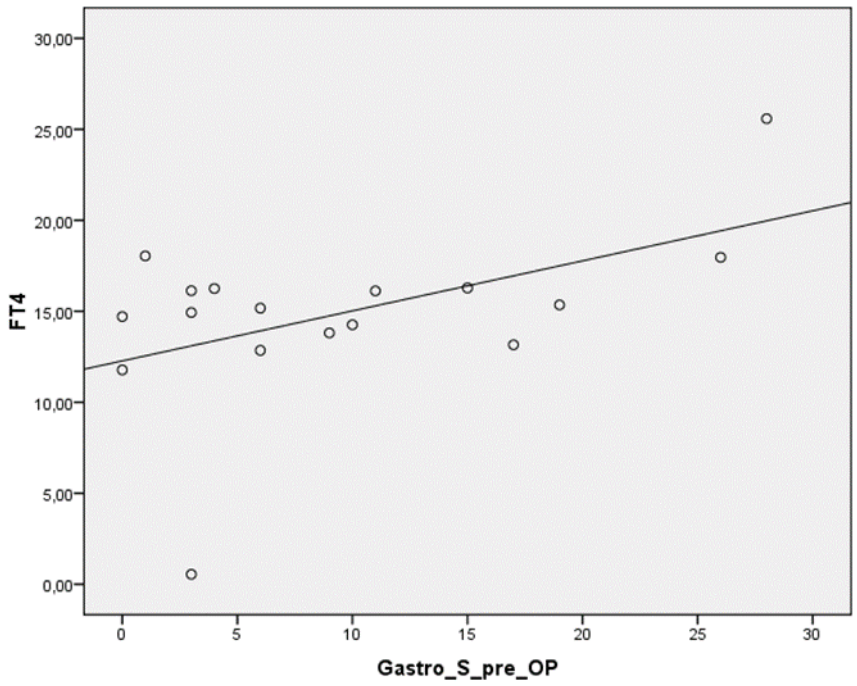

Figure 29: Regression-Model of FT4 with the GI-Symptoms-Fraction of SCL.

The correlation between **TSH** and the Typical-Symptoms of the SCL within Group II (patients with functional outflow obstruction or major motility disorders) shows, that the higher the Typical-symptom-value, the lower the TSH-value, **Table 33.**

Table 33: Correlation between TSH and SCL within Group II.

		SCL _ Typical Symptoms
TSH	**Correlation**	0,629
	Significance	0,007**
	N	17

**p<0,01

After a regression analysis between TSH and the Typical-symptoms, we came to the following conclusion. The regression model can be classified as acceptable (R^2=0,396). The coefficient of determination is not randomly achieved, but is a result of the relation of data (F-test=9,823; p=0,007). It is identified, that the Typical-symptoms are negatively influenced by TSH. If the Typical-symptoms rise by 1 point, TSH decreases by 0,083 points.

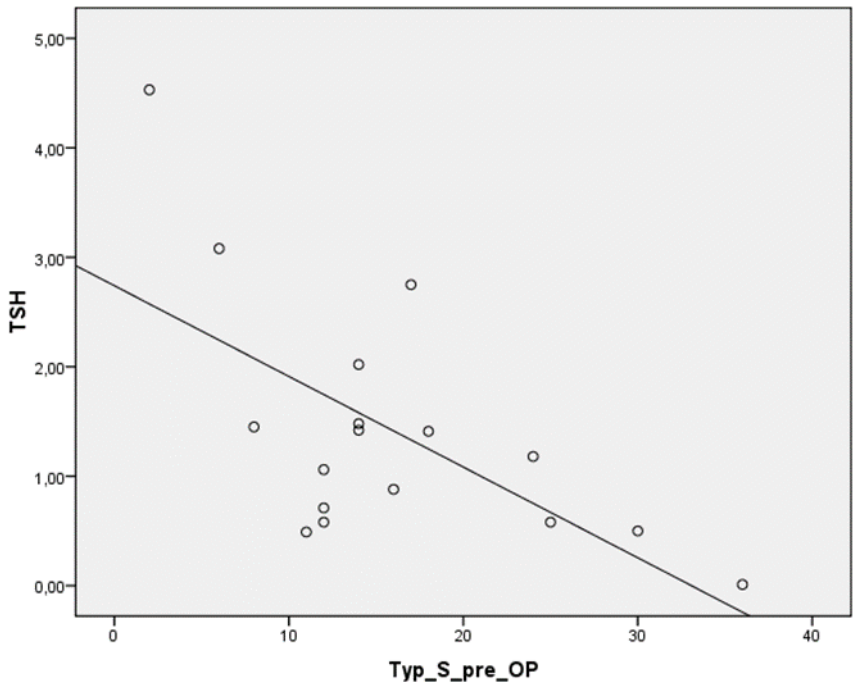

Figure 30: Regression-Model of TSH with the Typical-Symptom-Fraction of the SCL.

4.5 Subgroup analysis within Group II

We also performed a subgroup analysis, which produced some interesting results. The subgroup (n=7) consists of patients with EGJ outflow obstruction (Group II) with additional pathological DeMeester-Score with an average of 34,6 points. The results of this correlations are presented in **Table 34** and **Table 35**.

Table 34: Subgroup analysis, Group II with FT3.

		RSI	SCL total	SCL _ GI-Symptoms	SCl _ Atypical Symptoms
FT3	**Correlation**	0,789	0,851	0,938	0,920
	Significance	0,035*	0,015*	0,002**	0,020*
	N	7	7	7	7

*p<0,05; **p<0,01

Table 35: Subgroup analysis, Group II with FT4.

		SCL total	SCL _ Typical Symptoms	SCL _ Atypical Symptoms	SCL _ GI-Symptoms
FT4	**Correlation**	0,898	0,794	0,914	0,840
	Significance	0,006**	0,033*	0,004**	0,018*
	N	7	7	7	7

*p<0,05; **p<0,01

Discussion

The reasons for GERD are multifactorial, like hiatal hernias, dysfunction of the LES, defect pressure barrier and non-sphincter associated reasons. The pathophysiology of GERD as well as, the reason for motility disorders like achalasia and the influence of hormones on gastrointestinal symptoms are partly unknown. The aim of the study was to evaluate, if the hormones Thyroid stimulating hormone (TSH), Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4), Vasoactive Intestinal Peptide (VIP), gastrin and calcitonin have an influence on GERD, motility disorders and gastrointestinal symptoms. An answer to this issue would not only lead to a better understanding of GERD, but also may lead to development in diagnosing and therapy. Within our trial, we compared and correlated a large spectrum of parameters. Not only did we include a substantial number of hormones (TSH, FT3, FT4, Calcitonin, VIP, Gastrin), but also used the wide spectrum of diagnostic possibilities (HRM, 24h-pH-Monitoring, questionnaires). Like Farré et al. (2006) showed with his trial on pigs, that an increased level of VIP causes a relaxation of the LES, we could not find such a relationship for VIP, but a strong inverse relation between calcitonin and IRP was found. Concerning symptoms high VIP-levels lead to bloating symptoms. Another interesting finding was the correlation (p=0,072) between VIP and the Gas-Bloat-Symptoms (flatulence and fullness) from the SCL questionnaire.

The results further show that thyroid hormones, like TSH, FT3 and FT4, as well are corresponded to fractions of the SCL, like the Typical-symptoms, Atypical-symptoms and the GI-symptoms. In contrast to Yaylali et al. (2009), our results cause to assume that hyperthyreosis lead to reflux associated symptoms, not hypothyreosis. Also, a subgroup analysis (n=7) was performed, which consists of patients from the functional-obstruction-group with additional pathological DeMeester-Score. This score is a tool to quantify

gastroesophageal reflux and the results emphasize that FT4 and FT3 play a role in the development and/or in the persistence of a functional outflow obstruction and consequently of reflux symptoms. Our study further demonstrates that the remaining hormone status, does not have a significant influence on the motility of the esophagus.

With this study, we determined that thyroid hormones and VIP effect symptoms like diarrhea, constipation, flatulence, dysphagia, fullness and bloating. These outcomes highly suggest further investigations and a deeper look at the connection between thyroid hormones as well as VIP, gastrointestinal symptoms. We are well aware that this study has some limitations. First, because of the large number of parameters the results seem to be unspecific, consideration given that this was meant to be a trial with wide range. We are also conscious about the fact that maybe, despite of the large range of parameters, some factors, that also could play an important role, not have been taken in to consideration. A fact, that pursuing studies may want to acknowledge, is a more detailed preselection of patients. This would may be not only lead to more specific results, but also could lead to new scientific perspectives and therefore new ground for other approaches concerning this issue. Further the statistical methods do not deal with the numerous interweaving's of the several factors. This issue could be counteracted with collaborations of different disciplines. Also, it would be necessary to concentrate in detail on specific hormones to understand the whole mechanism that lead to GERD.

In conclusion, the results of this study show that the hormones TSH, FT3, FT4, Calcitonin, VIP and Gastrin do not affect the motility of the esophagus. However, Calcitonin could have an effect on the function of the EGJ. Furthermore, thyroid hormones TSH, FT3 and FT4, as well as VIP seem to influence gastrointestinal symptoms. These outcomes may not yet mean a change in the existing guidelines for screening, diagnosing or therapy, but they can lead to a wider spectrum or evolution of this fractions. Further trials will be necessary to develop these outcomes, so they can find their way into clinical praxis and consulting.

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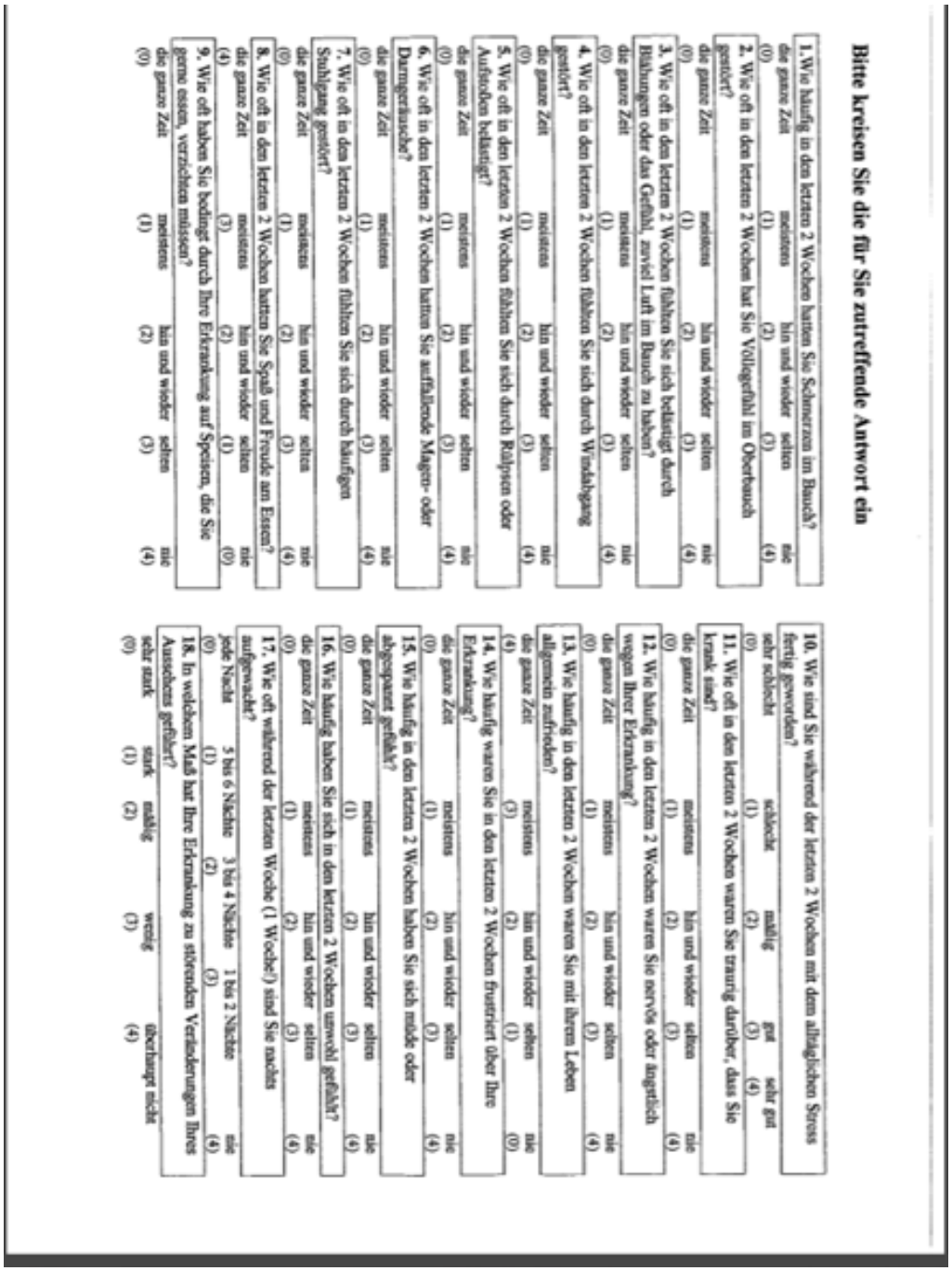
Appendix

Original questionnaires

Figure 31: Gastrointestinal Quality of Life Index, part 1



Bitte kreisen Sie die für Sie zutreffende Antwort ein

1. Wie häufig in den letzten 2 Wochen hatten Sie Schmerzen im Bauch?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

2. Wie oft in den letzten 2 Wochen hat Sie Völlegefühl im Oberbauch gestört?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

3. Wie oft in den letzten 2 Wochen fühlten Sie sich belästigt durch Blähungen oder das Gefühl, zuviel Luft im Bauch zu haben?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

4. Wie oft in den letzten 2 Wochen fühlten Sie sich durch Windabgang gestört?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

5. Wie oft in den letzten 2 Wochen fühlten Sie sich durch Rülpsen oder Aufstoßen belästigt?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

6. Wie oft in den letzten 2 Wochen hatten Sie auffallende Magen- oder Darmgeräusche?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

7. Wie oft in den letzten 2 Wochen fühlten Sie sich durch häufigen Stuhlgang gestört?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

8. Wie oft in den letzten 2 Wochen hatten Sie Spaß und Freude am Essen?

die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

9. Wie oft haben Sie bedingt durch Ihre Erkrankung auf Speisen, die Sie gerne essen, verzichten müssen?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

10. Wie sind Sie während der letzten 2 Wochen mit dem alltäglichen Stress fertig geworden?

sehr schlecht	schlecht	mäßig	gut	sehr gut
(0)	(1)	(2)	(3)	(4)

11. Wie oft in den letzten 2 Wochen waren Sie traurig darüber, dass Sie krank sind?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

12. Wie häufig in den letzten 2 Wochen waren Sie nervös oder ängstlich wegen Ihrer Erkrankung?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

13. Wie häufig in den letzten 2 Wochen waren Sie mit ihrem Leben allgemein zufrieden?

die ganze Zeit	meistens	hin und wieder	selten	nie
(4)	(3)	(2)	(1)	(0)

14. Wie häufig waren Sie in den letzten 2 Wochen frustriert über Ihre Erkrankung?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

15. Wie häufig in den letzten 2 Wochen haben Sie sich müde oder abgespannt gefühlt?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

16. Wie häufig haben Sie sich in den letzten 2 Wochen unwohl gefühlt?

die ganze Zeit	meistens	hin und wieder	selten	nie
(0)	(1)	(2)	(3)	(4)

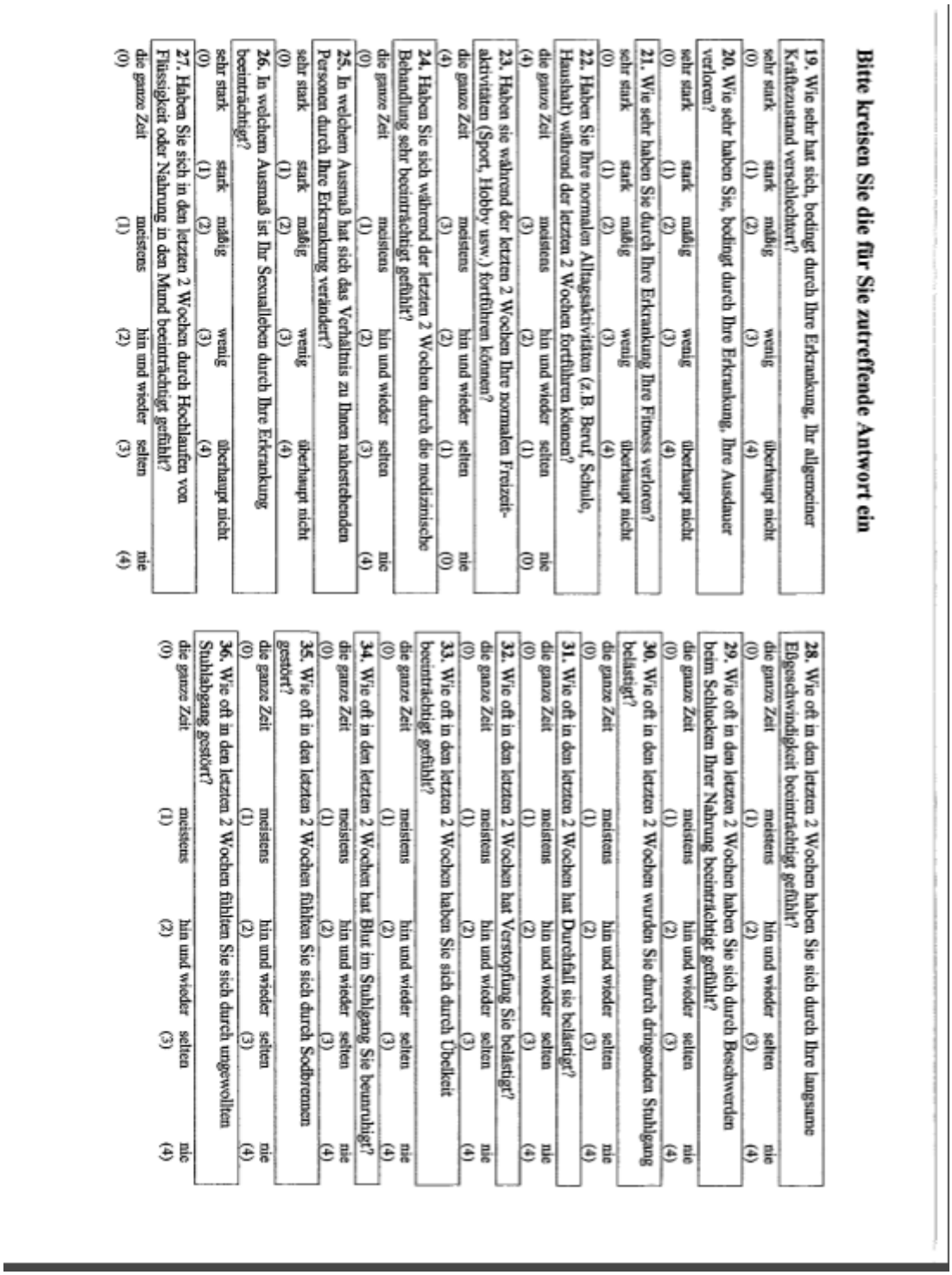
17. Wie oft während der letzten Woche (1 Woche!) sind Sie nachts aufgewacht?

jede Nacht	5 bis 6 Nächte	3 bis 4 Nächte	1 bis 2 Nächte	nie
(0)	(1)	(2)	(3)	(4)

18. In welchem Maß hat Ihre Erkrankung zu störenden Veränderungen Ihres Ausscheidens geführt?

sehr stark	stark	mäßig	wenig	überhaupt nicht
(0)	(1)	(2)	(3)	(4)

Figure 32: Gastrointestinal Quality of Life Index, part 2



Bitte kreisen Sie die für Sie zutreffende Antwort ein

19. Wie sehr hat sich, bedingt durch Ihre Erkrankung, Ihr allgemeiner Kräftezustand verschlechtert?

sehr stark (0) | stark (1) | mäßig (2) | wenig (3) | überhaupt nicht (4)

20. Wie sehr haben Sie, bedingt durch Ihre Erkrankung, Ihre Ausdauer verloren?

sehr stark (0) | stark (1) | mäßig (2) | wenig (3) | überhaupt nicht (4)

21. Wie sehr haben Sie durch Ihre Erkrankung Ihre Fitness verloren?

sehr stark (0) | stark (1) | mäßig (2) | wenig (3) | überhaupt nicht (4)

22. Haben Sie Ihre normalen Alltagsaktivitäten (z.B. Beruf, Schule, Haushalt) während der letzten 2 Wochen fortführen können?

die ganze Zeit (4) | meistens (3) | hin und wieder (2) | selten (1) | nie (0)

23. Haben sie während der letzten 2 Wochen Ihre normalen Freizeitaktivitäten (Sport, Hobby usw.) fortführen können?

die ganze Zeit (4) | meistens (3) | hin und wieder (2) | selten (1) | nie (0)

24. Haben Sie sich während der letzten 2 Wochen durch die medizinische Behandlung sehr beeinträchtigt gefühlt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

25. In welchem Ausmaß hat sich das Verhältnis zu Ihnen nahestehenden Personen durch Ihre Erkrankung verändert?

sehr stark (0) | stark (1) | mäßig (2) | wenig (3) | überhaupt nicht (4)

26. In welchem Ausmaß ist Ihr Sexualleben durch Ihre Erkrankung beeinträchtigt?

sehr stark (0) | stark (1) | mäßig (2) | wenig (3) | überhaupt nicht (4)

27. Haben Sie sich in den letzten 2 Wochen durch Hochlaufen von Flüssigkeit oder Nahrung in den Mund beeinträchtigt gefühlt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

28. Wie oft in den letzten 2 Wochen haben Sie sich durch Ihre langsame Eßgeschwindigkeit beeinträchtigt gefühlt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

29. Wie oft in den letzten 2 Wochen haben Sie sich durch Beschwerden beim Schlucken Ihrer Nahrung beeinträchtigt gefühlt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

30. Wie oft in den letzten 2 Wochen wurden Sie durch dringenden Stuhlgang belästigt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

31. Wie oft in den letzten 2 Wochen hat Durchfall sie belästigt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

32. Wie oft in den letzten 2 Wochen hat Verstopfung Sie belästigt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

33. Wie oft in den letzten 2 Wochen haben Sie sich durch Übelkeit beeinträchtigt gefühlt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

34. Wie oft in den letzten 2 Wochen hat Blut im Stuhlgang Sie beunruhigt?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

35. Wie oft in den letzten 2 Wochen fühlten Sie sich durch Sodbrennen gestört?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

36. Wie oft in den letzten 2 Wochen fühlten Sie sich durch ungewollten Stuhlabgang gestört?

die ganze Zeit (0) | meistens (1) | hin und wieder (2) | selten (3) | nie (4)

Figure 33: Reflux Symptom Index (RSI)

Fragebogen

Patientenidentifikations Nummer: _____

Zeitpunkt:	Erst-Untersuchung	O	Datum:
	Nach Fundoplicatio (3 Monate)	O	Datum:
	Nach Fundoplicatio (12 Monate)	O	Datum:

Teil 1: Beschwerden durch das Sodbrennen außerhalb und im Bereich der Speiseröhre: Fragebogen nach Belafsky et al.

Bitte kreisen Sie die Zahl ein, welche Ihre Beschwerden am besten beschreibt. Dabei ist Null keine Beschwerden und 5 ständige Beschwerden:

Wie haben sie die folgenden Beschwerden während des letzten Monats betroffen:

Heiserkeit / Probleme mit der Stimme:

0 1 2 3 4 5

Vermehrtes Räuspern:

0 1 2 3 4 5

Vermehrte Schleimbildung im Rachenbereich:

0 1 2 3 4 5

Probleme beim Schlucken von Essen, Flüssigkeiten und/oder Tabletten:

0 1 2 3 4 5

Vermehrtes Husten nach dem Essen / Hinlegen:

0 1 2 3 4 5

Atembeschwerden nach Hustenattacken:

0 1 2 3 4 5

Vermehrter, störender Husten:

0 1 2 3 4 5

Gefühl eines Fremdkörpers im Hals / irritierendes Gefühl im Hals:

0 1 2 3 4 5

Brennen hinter dem Brustbein, Aufstoßen, Oberbauchschmerzen:

0 1 2 3 4 5

Figure 34: Symptom Check List (SCL)

Name: _____

Geb. Datum: _____

präoperativ O

postoperativ: bei Entlassung: O 3 Monate: O .....Jahr(e) O

nach Korrektureingriff bei Entlassung: O 3 Monate: O .....Jahr(e) O

SYMPTOME

wie schwer?
0: nicht vorhanden
1: leicht
2: mittel
3: schwer
4: sehr schwer

wie häufig?
0: nie
1: bis 1x wöchentlich
2: mehrmals in der Woche
3: täglich
4: dauernd

Bitte beides ankreuzen! **UND**

	wie schwer?					wie häufig?						
Sodbrennen	0	1	2	3	4	0	1	2	3	4		
Aufstossen von Mageninhalt	0	1	2	3	4	0	1	2	3	4		
Aufstossen von Luft (Rülpsen)	0	1	2	3	4	0	1	2	3	4		
Blähungen	0	1	2	3	4	0	1	2	3	4		
Winde	0	1	2	3	4	0	1	2	3	4		
Völlegefühl	0	1	2	3	4	0	1	2	3	4		
Verstopfung	0	1	2	3	4	0	1	2	3	4		
Durchfälle	0	1	2	3	4	0	1	2	3	4		
Oberbauchschmerz	0	1	2	3	4	0	1	2	3	4		
Schluckstörungen	0	1	2	3	4	0	1	2	3	4		
Geschmacksstörungen	0	1	2	3	4	0	1	2	3	4		
Asthma	0	1	2	3	4	0	1	2	3	4		
Heiserkeit	0	1	2	3	4	0	1	2	3	4		
Husten	0	1	2	3	4	0	1	2	3	4		

Hauptzeit(en) der Beschwerden:

Tagsüber O Nachts O Morgens O tageszeitunabhängig O nach Mahlzeiten O

Ansprechen auf Säure-blockierende Medikamente:

kein Anprechen: O teilweises Ansprechen: O vollständiges Ansprechen: O

Nehmen Sie derzeit regelmäßig oder bei Bedarf Säure-blockierende Medikamente (Protonenpumpenhemmer) ein?

Nein: O Ja: O

Täglich: O bei Bedarf: O

Welches Präparat? .....Dosierung?.....mg tgl.

VIELEN DANK FÜR IHRE MITARBEIT!!!

Vote of the ethics committee

Figure 35: Vote of the ethics committee, page 1

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SCHWESTERN
Linz

Ethik-Kommission
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Herrn
Dr. Michael Weitzendorfer
Allgemeine Chirurgie und Viszeralchirurgie
Krankenhaus d. Barmh. Schwestern
Betriebs-GmbH
Seilerstätte 4
4010 Linz

Linz, 2016-04-21

Blatt Nr. 1
des Protokolls

Auszug aus dem Protokoll über die Sitzung der Ethik-Kommission am Allgemeinen öffentlichen Krankenhaus der Barmherzigen Schwestern in Linz am 11.4.2016

Anwesende Mitglieder laut Liste

Antragsteller: Dr. Michael Weitzendorfer

Prüfungsleiter: Dr. Michael Weitzendorfer

Es besteht gegen die Durchführung der Studie Nr. EK 10/16 (hausinterne Studiennummer):

Studientitel
Reflux-Hormonstatus-Studie (RH-Studie): Evaluierung der Auswirkungen des Hormonstatus auf die Motilität der Speiseröhre, sowie gastro- intestinale Symptomatik, bei Patienten mit reflux- assoziiertem Erkrankungsbild.

kein Einwand.

Zur Beurteilung für eingereichte Dokumente:
- Antrag A + B vom 8.2.2016
- Projektplan 1. Version
- CRF Hormonstudie
- Patienteninformation und Einwilligung vom 11.4.2016

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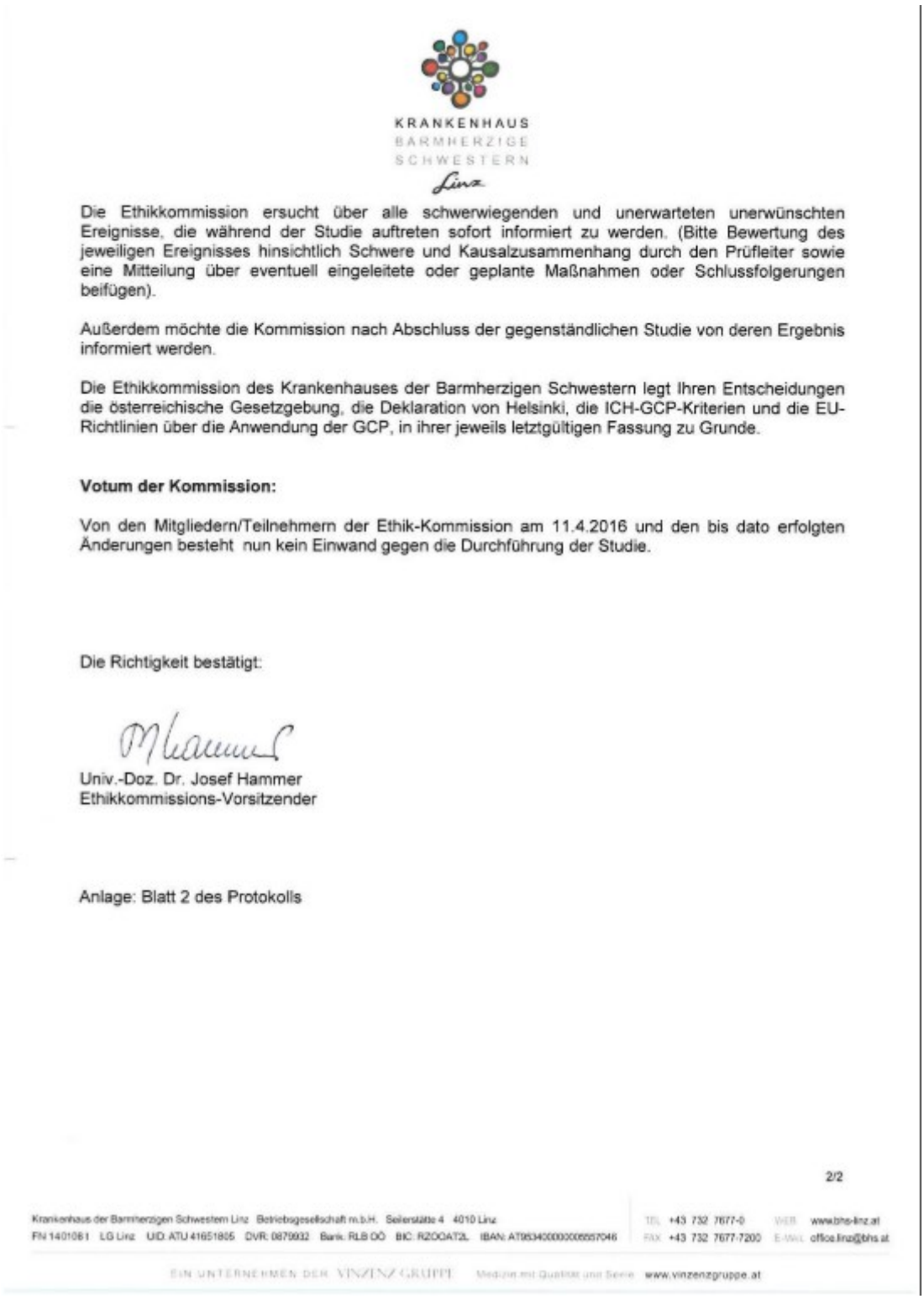
Figure 36: Vote of the ethics committee, page 2



KRANKENHAUS
BARMHERZIGE
SCHWESTERN
Linz

Die Ethikkommission ersucht über alle schwerwiegenden und unerwarteten unerwünschten Ereignisse, die während der Studie auftreten sofort informiert zu werden. (Bitte Bewertung des jeweiligen Ereignisses hinsichtlich Schwere und Kausalzusammenhang durch den Prüfleiter sowie eine Mitteilung über eventuell eingeleitete oder geplante Maßnahmen oder Schlussfolgerungen beifügen).

Außerdem möchte die Kommission nach Abschluss der gegenständlichen Studie von deren Ergebnis informiert werden.

Die Ethikkommission des Krankenhauses der Barmherzigen Schwestern legt Ihren Entscheidungen die österreichische Gesetzgebung, die Deklaration von Helsinki, die ICH-GCP-Kriterien und die EU-Richtlinien über die Anwendung der GCP, in ihrer jeweils letztgültigen Fassung zu Grunde.

Votum der Kommission:

Von den Mitgliedern/Teilnehmern der Ethik-Kommission am 11.4.2016 und den bis dato erfolgten Änderungen besteht nun kein Einwand gegen die Durchführung der Studie.

Die Richtigkeit bestätigt:

Univ.-Doz. Dr. Josef Hammer
Ethikkommissions-Vorsitzender

Anlage: Blatt 2 des Protokolls

2/2

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