



# **GLOBUS AND DYSPHAGIA – CLINICAL FEATURES AND DIAGNOSTICS**

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# **GLOBUS AND DYSPHAGIA – CLINICAL FEATURES AND DIAGNOSTICS**

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*Non scholæ  
sed vitæ discimus.*

# ABSTRACT

Globus is a non-painful sensation of a lump in the throat, which frequently improves with eating. Globus is a common symptom; however, little is known about the etiology, and the causes have remained controversial. Dysphagia, difficulty of swallowing, is also a common symptom affecting patients referred to otorhinolaryngological practice. Although globus patients lack swallowing difficulties, globus and dysphagia symptoms are often mixed together and are hard for patients and even clinicians to distinguish. Identifying the stage of the swallowing process at which the problem occurs directs us to possible further investigations in dysphagia diagnostics. The aim of this thesis was to investigate the etiology of globus, to clarify globus and dysphagia diagnostics, and to describe the natural course of these symptoms.

In the first study of this thesis, we examined the esophageal background of globus with transnasal esophagoscopy, high-resolution manometry, and 24-hour multichannel intraluminal impedance and pH monitoring. We had 30 globus patients and, as controls, 24 patients who were referred to the Department of Abdominal Surgery for evaluation of operative treatment because of difficult reflux symptoms. The study indicated that globus patients without reflux symptoms did not have acid or non-acid gastroesophageal reflux disease (GERD), the upper esophageal sphincter (UES) pressure was not elevated, and esophageal motor disorders diagnosed were mainly minor, a finding evident in healthy subjects, as well. However, globus patients had supragastric belching more often than controls with reflux, leading to a question of its possible role in some of the globus patients' symptoms.

In the second study, we examined how these 30 globus patients' symptoms evolved over a four-month follow-up measured by the Reflux Symptom Index (RSI), the Deglutition Handicap Index (DHI), and 15-Dimensional Measure of Health-Related Quality of Life (15-D). By analyzing patients' videolaryngoscopies using the Reflux Finding Score (RFS), we determined whether patients had findings of laryngopharyngeal reflux (LPR). A speech and language pathologist (SLP) interviewed and examined globus patients after four months to investigate if patients with persistent symptoms had problems with their voices. We observed that globus patients felt symptom relief in the RSI and DHI after a four-month follow-up without any treatment. None of the videolaryngoscopies revealed an LPR. The SLP found six patients with simultaneous functional voice problems, possibly associated with persistent globus.

In the third and fourth study, we searched from the hospital database all globus (n=76) and dysphagia (n=303) patients, respectively, who were referred to our clinic in 2009. From the medical records, we surveyed patients' symptoms, investigations, findings, and treatment. From the Finnish Cancer Registry (FCR) database, we recorded all of these patients' cancer diagnoses at the end of 2012. In the third study, the questionnaire concerning the globus patients' present symptoms was sent three and six years after their initial visit. Based on both questionnaires, half of the globus patients were asymptomatic or had fewer symptoms, whereas the rest suffered persistent symptoms. Videofluorography and neck ultrasound showed no benefit in globus diagnostics. The FCR data revealed no malignancies associated with globus during the follow-up to the end of 2012.

In the fourth study, dysphagia patients received a questionnaire about their current symptoms three years after their visit to our clinic. The questionnaires showed that almost half of the dysphagia patients were asymptomatic or had milder symptoms, implying that spontaneous recovery may occur. Based on the case records, most dysphagia diagnoses remained unspecific

dysphagia (55%) despite performing many investigations. All patients with a malignant disease either already had a positive finding at the ear, nose, and throat examination or suffered from alarming signs, such as progressive dysphagia symptoms, leading to gastroscopy, which revealed the diagnosis. The FCR data indicated no additional malignant cases during the three-year follow-up.

Our study clarifies the esophageal background of globus, but also offers some new insights into possible causes. The study updates globus and dysphagia diagnostics and presents the natural course of these symptoms. According to our study, many swallowing difficulties are mild and no specific cause can be identified. Our results emphasize the importance of a careful clinical evaluation to find possible malignancies and to determine whether further investigations in dysphagia diagnostics are necessary.

# TIIVISTELMÄ

Globuksella eli palantunteella tarkoitetaan kivutonta kurkussa tuntuva oiretta, joka yleensä helpottaa syödessä. Vaikka palantunne on yleinen vaiva, tiedetään sen aiheuttajista vain vähän. Dysfagia eli nielemisvaikeus on toinen yleinen oire korva-, nenä- ja kurkkutautien (KNK) poliklinikalla. Vaikka palantunnepotilailla ei määritelmällisesti ole nielemiseen liittyviä vaikeuksia, palantunne- ja nielemisvaikeusoireet menevät usein sekaisin, ja sekä potilaan että lääkärin saattaa olla hankala erottaa vaivoja toisistaan. Nielemisvaikeudesta kärsivää potilasta tutkittaessa on tärkeää selvittää, mihin nielemisen vaiheeseen ongelma liittyy, jotta mahdolliset tarvittavat jatkotutkimukset voidaan määrätä. Väitöskirjan tavoitteena oli tutkia palantunneen syitä, selvittää palantunneen ja nielemisvaikeuden diagnostiikkaa sekä kuvata näiden oireiden luonnollista kulkua.

Väitöskirjan ensimmäisessä osatyössä tutkittiin palantunneen ruokatorviperäisiä syitä nenän kautta tehtävällä ruokatorven ja mahalaukun tähystyksellä (transnasal esophagoscopy, TNE), tarkkuusmanometrialla (high-resolution manometry, HRM) sekä impedanssin ja pH:n pitkäaikaisrekisteröinnillä (24-hour multichannel intraluminal impedance and pH monitoring, 24-h MII-pH). Tutkimuksessa oli 30 HYKS:n Korvaklinikkaan lähetettyä palantunnepotilasta, ja kontrolliryhmänä toimi 24 hankalasta refluksista kärsivää potilasta, jotka oli lähetetty tämän vuoksi HYKS:n vatsaelinkirurgian klinikkaan leikkausarvioon. Tutkimuksessa todettiin, että niillä palantunnepotilailla, jotka eivät kärsineet närästysoireesta, ei ollut hapanta tai ei-hapanta refluksitautia, ruokatorven yläsulkijan paine ei ollut koholla ja diagnosoidut ruokatorven liikehäiriöt olivat pääosin lieviä, joiden kaltaisia voidaan löytää myös terveillä henkilöillä. Kuitenkin palantunnepotilailla oli ruokatorviröyhtäilyä yleisemmin kuin refluksista kärsivillä kontrollipotilailla, mikä herättää kysymyksen sen mahdollisesta yhteydestä palantunteeseen.

Toisessa osatyössä selvitettiin refluksin oirekyselyä (Reflux Symptom Index, RSI), nielemisen oirekyselyä (Deglutition Handicap Index, DHI) sekä 15-D elämänlaatukselyä (15-D) käyttäen, kuinka näiden 30 palantunnepotilaan oireet muuttuivat neljän kuukauden seurannassa. Selvittääksemme potilaiden mahdollisia kurkunpään refluksiin viittaavia löydöksiä arvioimme potilaiden videolaryngoskopia refluksin löydöspisteityksellä (Reflux Finding Score, RFS). Puheterapeutti haastatteli ja tutki palantunnepotilaat neljän kuukauden kuluttua ensikäynnistä selvittääksemme, oliko edelleen oireilevilla palantunnepotilailla ääneen liittyviä ongelmia. RSI:lla ja DHI:lla mitattuna palantunnepotilaiden oireet lievittyivät neljän kuukauden seurannassa ilman hoitoa. Kenenkään potilaan videolaryngoskopian löydös ei viitannut kurkunpään refluksiin. Puheterapeutti löysi kuudelta potilaalta ääneen liittyviä ongelmia, jotka voivat olla myötävaikuttava tekijä palantunneen jatkumiselle.

Kolmannessa ja neljännessä osatyössä haimme sairaalan tietokannasta kaikki 76 palantunne- ja 303 nielemisvaikeuspotilasta, jotka oli lähetetty HYKS:n Korvaklinikkaan vuonna 2009. Keräsimme tiedot potilaiden oireista, tutkimuksista, löydöksistä ja hoidosta. Kaikkien potilaiden vuoteen 2012 mennessä saamat syöpädiagnoosit pyydettiin Suomen Syöpärekisteristä. Kolmannessa osatyössä palantunnepotilaille lähetettiin kysely heidän senhetkisistä oireistaan kolmen ja kuuden vuoden kuluttua ensikäynnistä. Kummankin kyselyn perusteella puolet palantunnepotilaista olivat oireettomia tai heidän oireensa olivat lievittyneet, kun taas loput potilaista kärsivät edelleen palantunteesta. Videofluorografia ja kaulan ultraääni eivät olleet hyödyllisiä palantunnepotilaiden diagnostiikassa. Syöpärekisterin tiedot vahvistivat, ettei kenenkään palantunnepotilaan oire ollut kehittynyt syöväksi kolmen vuoden seurannassa.

Neljännessä osatyössä nielemisvaikeuspotilaille lähetettiin oirekysely kolme vuotta ensikäynnin jälkeen. Palautettujen oirekyselyiden mukaan puolet vastanneista nielemisvaikeuspotilaista olivat oireettomia tai heidän oireensa olivat lievittyneet, mikä osoittaa, että nielemisvaikeuksilla on myös spontaani toipumismahdollisuus. Potilastietojen perusteella yli puolessa tapauksista nielemisvaikeuspotilaan diagnoosi jäi epäselväksi, vaikka potilaita tutkittiin melko paljon. Kaikilla potilailla, joilla nielemisvaikeuden syy oli syöpä, löydös oli ollut nähtävissä jo KNK-tutkimuksessa tai potilaalla oli ollut hälyttäviä oireita, kuten etenevää nielemisvaikeutta, jonka vuoksi tehty gastroskopia paljasti syöpädiagnoosin. Syöpärekisterin tiedot vahvistivat, ettei kenellekään muulle nielemisvaikeudesta kärsivälle potilaalle kehittynyt tähän oireeseen liittyvää syöpää kolmen vuoden seurannassa.

Tutkimuksemme selvittää palantunteen ruokatorviperäistä taustaa mutta löytää myös uusia mahdollisia syitä oireelle. Tutkimus päivittää palantunteen ja nielemisvaikeuden diagnostiikkaa ja esittelee näiden oireiden luonnollista kulkua. Monet nielemisvaikeudet ovat lieviä, eikä oireelle löydy erityistä syytä. Tuloksemme painottavat kliinisen arvion tärkeyttä mahdollisen syövän löytämiseksi oireen taustalta ja arvioitaessa, tarvitseeko nielemisvaikeuspotilas jatkotutkimuksia.



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## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their roman numerals.

- I Nevalainen P, Walamies M, Kruuna O, Arkkila P, Aaltonen L-M.  
Supragastric belch may be related to globus symptom - a prospective clinical study. *Neurogastroenterol Motil.* 2016 May, 28(5): 680-6.
- II Järvenpää P, Laatikainen A, Roine RP, Sintonen H, Arkkila P, Aaltonen L-M.  
Symptom relief and health-related quality of life in globus patients: a prospective study. Submitted.
- III Järvenpää P, Ilmarinen T, Geneid A, Pietarinen P, Kinnari TJ, Rihkanen H, Ruohoalho J, Markkanen-Leppänen M, Bäck L, Arkkila P, Aaltonen L-M.  
Work-up of globus: Assessing the benefits of neck ultrasound and videofluorography. *Eur Arch Otorhinolaryngol.* In press\*
- IV Nevalainen P, Geneid A, Ilmarinen T, Pietarinen P, Kinnari TJ, Rihkanen H, Ruohoalho J, Markkanen-Leppänen M, Bäck L, Arkkila P, Aaltonen L-M.  
Dysphagia and malignancy: a three-year follow-up and survey of national cancer registry data. *Laryngoscope.* 2016 Sep, 126(9): 2073-8.

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\*This is the author's accepted manuscript of an article published as the version of record in *European Archives of Oto-Rhino-Laryngology*, published online 17 Sep 2016, <http://link.springer.com/article/10.1007/s00405-016-4307-8>

# ABBREVIATIONS

15-D	15-Dimensional Measure of Health-Related Quality of Life
CCI	Charlson Comorbidity Index
DHI	Deglutition Handicap Index
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
ENT	Ear, nose, and throat
FCR	Finnish Cancer Registry
FEES	Fiberoptic endoscopic evaluation of swallowing
FEEST	Fiberoptic endoscopic evaluation of swallowing with sensory testing
GERD	Gastroesophageal reflux disease
HRM	High-resolution manometry
HUH	Helsinki University Hospital
ICD-10	International Classification of Diseases, 10th edition
IQR	Interquartile range
LA	Los Angeles
LES	Lower esophageal sphincter
LPR	Laryngopharyngeal reflux
MII-pH	Multichannel intraluminal impedance and pH monitoring
MRI	Magnetic resonance imaging
PPI	Proton pump inhibitor
RFS	Reflux Finding Score
RSI	Reflux Symptom Index
SLP	Speech and language pathologist
SSRI	Selective serotonin reuptake inhibitor
TNE	Transnasal esophagoscopy
UES	Upper esophageal sphincter
VFG	Videofluorografia



# 1 INTRODUCTION

Globus (Latin *globus* = globe), the feeling of a lump in the throat, is a general symptom especially affecting women under 50 years. Among apparently healthy adults in a community, globus can affect up to 46% (Thompson & Heaton 1982). The etiology of globus is disputable, leading to disagreement regarding how these patients should be examined and treated. Historically, globus was considered a psychological problem (Merskey & Merskey 1993). Currently, it is obvious that the causes are rather multiform, although some patients' symptoms may have a psychological background. Gastroesophageal reflux disease (GERD), laryngopharyngeal reflux (LPR), esophageal motor disorders, and improper upper esophageal sphincter (UES) function are suggested to cause globus (Koufman 1991, Corso et al. 1998, Gooi et al. 2014). However, studies demonstrating the causal relationship between these disorders and globus are inadequate.

Currently, methods suitable for investigation of the esophageal etiology of globus are available. High-resolution manometry (HRM) provides more accurate diagnostics on UES pressure and in esophageal motor disorders (Peng et al. 2015). Combined esophageal multichannel intraluminal impedance and pH monitoring (MII-pH) distinguishes acid and non-acid reflux, as well as allows detection of possible proximal reflux, and has the ability to define whether refluxates are liquid, gas, or mixed (Zerbib et al. 2006). Moreover, a transnasal esophagoscopy (TNE) enables a well-tolerated endoscopy to be performed under local anesthesia (Postma 2006). However, only a limited number of studies have used some of these methods in globus diagnostics.

Common treatment for globus has been to explain the benign nature of the symptom to the patient (Galmiche et al. 2006). An outpatient examination has been suggested to be sufficient in patients with typical globus (Harar et al. 2004). However, many globus patients undergo further diagnostics such as radiographic swallowing examinations. It has been proposed that attention and reassurance alleviates globus symptoms, but contrary results also exist (Khalil et al. 2003, Millichap et al. 2005). Accordingly, some investigations may be performed to exclude a malignancy and to ensure both the patient and the clinician that the symptoms are harmless.

Dysphagia is a general symptom particularly affecting the elderly. Nearly 23% of patients in primary care experience swallowing difficulties (Wilkins et al. 2007). Patients with oropharyngeal dysphagia may have difficulties in starting to swallow, they may aspirate their food, or food may regurgitate into the nasopharynx. In esophageal dysphagia, a typical sign is food impaction in the esophagus. Many patients have a mild symptom, never talking to their physician (Wilkins et al. 2007). Since dysphagia is a common symptom, there is a need for a standardized diagnostic protocol to target possible further investigations properly. Despite investigations, some dysphagia patients never get a diagnosis (Hoy et al. 2013). Whether these symptoms may alleviate or progress into a malignancy in the long term is not known.

The aim of this study was to investigate the possible esophageal background of globus, to update globus and dysphagia diagnostics, and to evaluate the natural course of these symptoms.

## 2 REVIEW OF THE LITERATURE

### 2.1 GLOBUS

#### 2.1.1 DEFINITION AND PREVALENCE

Globus was already recognized in the time of Hippocrates. Historically, it was considered to be a hysterical symptom (Greek *hystericus* = related to uterus), globus hystericus, especially affecting anxious women (Merskey & Merskey 1993). In 1968, Malcomson observed that not all globus patients were hysterical or female and suggested use of the term globus pharyngeus (Malcomson 1968).

Overall, globus seems to be equally prevalent in healthy women and men (Batch 1988a). However, the symptom affects women age 50 and below three times more than men, and women are also more likely to seek medical advice regarding the symptom (Moloy & Charter 1982, Batch 1988a). Globus represents about 4% of new referrals to ear, nose, and throat (ENT) clinics (Deary et al. 1995). However, up to 78% of patients at other clinics have been found to suffer from globus-like symptoms, but had never sought health care for those symptoms (Ali & Wilson 2007).

#### 2.1.2 ETIOLOGY

##### 2.1.2.1 *Gastroesophageal reflux disease*

Gastroesophageal reflux disease (GERD) is defined as a condition in which the reflux of gastric contents causes difficult symptoms and/or complications (Vakil et al. 2006). The causative role of GERD in globus is disputable. Malcomson (1968) was the first to connect globus and GERD using barium swallow to show reflux in over 60% of globus patients. Thereafter, Cherry et al. (1970) demonstrated that 10 patients out of 12 reported globus after acid was supplied to the distal esophagus. Moreover, GERD was suggested to be a major cause of the symptom in up to 58% of globus patients with abnormal pH results (Koufman 1991). However, based on an ambulatory pH study, in a retrospective setting, findings of GERD were not more common in patients with globus than in controls (Corso et al. 1998).

In the past decade, the association of globus symptoms with GERD has been clarified. Globus is now considered to be a manifestation of a functional esophageal disorder, and when a patient has a globus symptom directly related to reflux the patient is considered to have GERD, even if other objective GERD findings are lacking (Galmiche et al. 2006). However, with use of new advanced investigation methods, it is expected that knowledge of the causative role of GERD as an etiological factor for globus will increase. Currently, large, prospective, and controlled studies are lacking.

##### 2.1.2.2 *Laryngopharyngeal reflux*

Laryngopharyngeal reflux (LPR) is considered to be an extraesophageal indication of reflux disease. In LPR, the retrograde flow of gastric contents comes in contact with the mucosa of the upper aerodigestive tract (Ford 2005). In contrast to esophageal mucosa, the larynx and pharynx are very sensitive to gastric reflux, so patients with LPR are more likely to have laryngeal symptoms, such as throat cleaning, but do not necessarily have symptoms of GERD, which requires frequent and prolonged exposure to reflux (Koufman 1991, Koufman et al. 1996, Phua

et al. 2005). Although hoarseness, cough, and throat clearing are usually considered to be LPR symptoms, these symptoms are nonspecific and may be caused by other disorders as well (Tauber et al. 2002). A study by Gooi et al. (2014) found that up to 48% of otolaryngologists considered LPR to be highly related to globus. However, the possible connection of globus and LPR has not been clarified.

The laryngeal findings indicating LPR are also nonspecific and prone to under- and overestimation (Kelchner et al. 2007, Musser et al. 2011). Moreover, the prevalence of these mucosal findings suggesting reflux is reported as high as 70% in normal volunteers (Hicks et al. 2002). Therefore, the diagnostic criteria for LPR have not met with universal consensus (Gooi et al. 2014).

### 2.1.2.3 *Abnormal upper esophageal sphincter function*

Several decades ago, Watson and Sullivan (1974) investigated globus patients and controls with manometry and found that cricopharyngeal sphincter pressure was statistically significantly higher in patients with globus. However, Cook et al. (1989) found in their study of 7 globus patients and 13 healthy controls that globus patients' resting upper esophageal sphincter (UES) pressure and its response to stress were normal. Moreover, in a study of 32 globus patients and 24 healthy volunteers, no statistical difference was found in UES resting pressure (Sun et al. 2002). Nonetheless, a strong association between hypertonicity of the UES and globus in conventional manometry was found in one retrospective study (Corso et al. 1998).

Currently, high-resolution manometry (HRM) is a more precise diagnostic method in the evaluation of the esophageal sphincter pressure (Peng et al. 2015). Kwiatek et al. (2009) used HRM to quantify the timing and magnitude of respiratory variation of the UES and discovered that in globus patients, respiration-related change in the resting UES pressure was significantly amplified compared to controls and GERD patients. In one retrospective study, UES basal and residual pressures between globus and dysphagia patients, as well as normal controls, were evaluated. The study showed that mean UES basal and residual pressures were normal in both globus patients and normal controls (Peng et al. 2015). Moreover, a study by Choi et al. (2013) showed that globus patients did not have elevated UES pressure upon HRM, compared to normal controls and patients with GERD.

### 2.1.2.4 *Esophageal motor disorders*

Only a limited number of studies have evaluated esophageal motor disorders as a possible cause or contributing factor in globus. Wilson et al. (1989) demonstrated that there were no differences between globus patients' and controls' esophageal body motility upon manometry. In another study, 67% of globus patients' esophageal manometry was abnormal, however, the most frequent finding (29%) was a nonspecific esophageal motility disorder (Färkkilä et al. 1994). In their prospective study, Knight et al. (2000) evaluated patients with suspected extraesophageal manifestations of GERD, such as globus. Upon esophageal manometry, 7 globus patients out of 12 had nonspecific esophageal disorders, while 2 had a hypertensive lower esophageal sphincter (LES) and 3 had normal results (Knight et al. 2000). Consequently, the esophageal motor disorders most often diagnosed in globus patients have been nonspecific. Nevertheless, it is expected that the use of a more accurate method, like HRM, may clarify the possible role of esophageal motor disorders in globus.



### **2.1.2.5 Psychological factors and stress**

Historically, the term globus hystericus was used to suggest a psychological origin to the symptom, and in fact, many studies have shown this. In a study by Deary et al. (1992), globus patients were significantly more depressed than controls. Globus patients had also more stress and severe life events throughout the year compared to controls in another study (Harris et al. 1996). Middle-aged women with globus were significantly more likely to experience neuroticism, to be less extroverted, and to have psychological distress, such as anxiety, low mood, and somatic concerns (Deary et al. 1995). Furthermore, up to 96% of globus patients felt more symptoms when a highly emotional state occurred (Thompson & Heaton 1982).

However, in one Finnish study, globus patients and the general population had a similar prevalence of psychiatric disorders (Färkkilä et al. 1994). Additionally, in a study by Moser et al. (1991) mean scores were similar for anxiety, depression, hysteria, and hypochondria in globus patients compared to general medical outpatients. Although the symptom's complex causes are accepted, it is still labelled as code F45.8, meaning somatoformic disorder, in the international classification of diseases, 10th edition, (ICD-10) (World Health Organization 2016).

### **2.1.2.6 Other causes**

Conditions causing irritation or inflammation in the pharynx and larynx, such as pharyngitis and postnasal drip, may increase local sensitivity and cause globus (Batch 1988b). Anatomical causes, including tongue base hypertrophy and a retroverted epiglottis touching the posterior pharyngeal wall, have been considered as local factors inducing globus (Mamede et al. 2004, Agada et al. 2007).

Some studies have investigated thyroid pathology and globus. One-third of patients with thyroidal mass experienced globus-like symptoms before thyroid surgery (Burns & Timon 2007). In one prospective study, thyroid nodules larger than 3 cm located anterior to the trachea were associated with globus (Nam et al. 2015). However, thyroidal findings, such as nodules, are common coincidence findings in healthy subjects, so their causative role in globus requires more investigation.

To exclude malignancy, many patients undergo further investigations. One retrospective study of 699 patients showed that typical globus symptoms were not hiding malignancy behind the symptom at the initial visit, whereas 5 patients with atypical symptoms revealed malignancies (Harar et al. 2004).

## **2.1.3 EXAMINATIONS USED IN GLOBUS DIAGNOSTICS**

Because the etiology of globus is unclear, uniform investigation strategy is lacking. Taking a careful clinical history is essential in order to determine whether a patient should be referred for further investigation, such as a radiological examination or direct esophagoscopy (Ardran 1982). However, globus patients without other symptoms are mainly diagnosed based on their history and a clinical examination, including neck palpation and nasolaryngoscopic examination (Galmiche et al. 2006). Pathological findings in globus patients can be detected by a clinical examination with fiber-optic nasoendoscope (Harar et al. 2004). Further investigations are not recommended when a patient has typical globus (Galmiche et al. 2006).

### 2.1.3.1 Neck ultrasound

Neck ultrasound is occasionally used in globus diagnostics. However, studies evaluating its usefulness are lacking. There are a few studies, which have assessed neck ultrasound findings in globus patients, but they have investigated only thyroid pathology (Burns & Timon 2007, Nam et al. 2015).

### 2.1.3.2 Videofluorography

Videofluorography is quite often used in globus diagnostics, although its benefit has not been proven (Webb et al. 2000). Ardran (1982) examined 300 globus patients with a cineradiographic examination: patients swallowed a fluid barium suspension showing that there was no visible lump in the throat. Also, a modified barium swallow study with esophagogram showed no benefit in globus diagnostics (Dworkin et al. 2015). Moreover, Luk et al. (2014) reviewed barium swallow pharyngoesophagographies of 908 globus patients and 86% had totally normal results. Authors concluded that the examination has limited diagnostic value and is therefore not recommended for globus patients; patients under 30 years old, in particular, had no findings.

### 2.1.3.3 Endoscopy

Rigid endoscopy has been the gold standard in otorhinolaryngologic practice when an endoscopic examination is needed. However, because it is an invasive investigation, it requires general anesthesia and the risk for esophagus perforation during the diagnostic endoscopic procedure has been reported to be up to 1.2% (Kubba et al. 2003). Rigid endoscopy has not been shown to be useful in globus diagnostics. Nonetheless, a survey concerning ENT consultants indicated that 61% of respondents used rigid endoscope in globus diagnostics (Webb et al. 2000). A retrospective study of 250 globus patients examined with rigid endoscopy showed no malignancies and the status of the larynx, pharynx, and upper esophagus was entirely normal in 87% (Takwoingi et al. 2006).

Transnasal esophagoscopy (TNE) allows examining the upper aerodigestive tract with a thin endoscope without sedation. Shaker, a gastroenterologist, published the initial report of TNE in 1994 (Shaker 1994). However, Aviv et al. (2001) were the first to publish a study of unsedated TNE in a laryngological practice. The procedure is performed on a sitting patient and, after a local anesthetic is applied to the nasal cavity, the thin endoscope is passed transnasally (Postma et al. 2005). TNE enables examination of the nasopharynx, hypopharynx, and larynx before the endoscope is passed into the esophagus, and a working channel provides an opportunity for taking biopsies (Postma et al. 2005).

TNE has been found to be safe and patients tolerate it well (Dean et al. 1996, Postma et al. 2005, Thota et al. 2005, Streckfuss et al. 2014). Patients prefer TNE to conventional esophagogastroduodenoscopy (EGD), and TNE is potentially more cost-effective (Dean et al. 1996, Thota et al. 2005). Globus is considered to be one of the indications for TNE (Postma et al. 2005, Amin et al. 2008).

### 2.1.3.4 Manometry

The possible connection between globus and esophageal motor disorders or elevated UES pressure has not been clarified. Previously, a conventional manometry with five to eight pressure sensors was a standard investigation method used upon suspicion of an esophageal bolus

transit pathology (Fox et al. 2004). However, patients' symptoms and manometric findings are considered to be poorly associated (Kahrilas et al. 1994).

Currently, HRM gives more precise information about an abnormal bolus transport, esophageal motility disorders, and UES pressure (Fox et al. 2004, Peng et al. 2015), and it has recently been studied in globus diagnostics (Kwiatk et al. 2009, Choi et al. 2013, Peng et al. 2015).

### **2.1.3.5 pH monitoring and 24-hour multichannel intraluminal impedance**

Previously, esophageal pH monitoring was a gold standard for investigating esophageal reflux events in GERD diagnostics (Zerbib et al. 2006). However, it was not able to detect weakly acidic or non-acidic reflux. Multichannel intraluminal impedance (MII) detects all reflux events: liquid, gas, or mixed (Sifrim et al. 1999, Zerbib et al. 2006). Moreover, when MII is combined with pH monitoring, it allows for detection of acid and non-acid reflux episodes and for analyzing associations between a patient's symptoms and MII-pH findings (Vela et al. 2001, Zerbib et al. 2006).

## **2.1.4 TREATMENT**

Because the etiology of globus is unclear, there is no strategy regarding how to treat globus patients. Proton pump inhibitor (PPI) medication is often prescribed because it has been suggested that globus may be related to GERD and LPR. Because exact GERD diagnostics require invasive and expensive examinations, empirical PPI therapy to diagnose and treat possible reflux is common. GERD responds well to PPI medication, but LPR's response to this medication varies and may require higher doses and longer treatment periods (Katz & Castell 2000, Park et al. 2005). One prospective, uncontrolled study demonstrated no changes in gene expression of cytokines related to inflammation when biopsies were taken from the posterior larynx tissue before and after a 10-week therapy of PPI (Thibeault et al. 2007). In addition, a meta-analysis concluded that using high-dose PPIs are no more effective than placebo in the treatment of laryngo-pharyngeal symptoms possibly connected to GERD (Gatta et al. 2007). Moreover, placebo has been as effective as PPIs in resolving globus symptoms (Noordzij et al. 2001, Vaezi et al. 2006).

When concomitant with disorders such as a major depression or panic disorder, antidepressants have been beneficial in resolving the globus symptoms as well, though study sample sizes were small (Brown et al. 1986, Cybulska 1997).

Globus patients with a thyroidal mass experienced improvement after thyroid surgery (Burns & Timon 2007). Moreover, globus patients with an epiglottis touching the posterior wall of the pharynx became asymptomatic after partial epiglottectomy (Agada et al. 2007). However, both of these studies lacked controls. Consequently, it is impossible to determine the operations' possible placebo effect.

Reducing laryngopharyngeal tension with neck and shoulder exercises, and relaxation techniques with voice hygiene and voice exercises improved 92% of globus patients' symptoms in one uncontrolled study (Wareing et al. 1997). In a sample of 36 globus patients, a speech and language pathologist (SLP) treated half of the globus patients with exercises to relieve laryngopharyngeal tension while controls were only given reassurance by a nurse. After three months, patients in the SLP group had significant improvement in their symptoms compared

to the control group (Khalil et al. 2003). However, whether globus patients only benefit from attention, rather than the SLP's therapy, remains ambiguous.

### **2.1.5 PROGNOSIS**

In globus patients, rapid symptom relief is often unlikely. During a follow-up period of an average of 7.6 years, 55% became asymptomatic and 45% had persistent symptoms (Rowley et al. 1995). In a study with a shorter follow-up, an average of 27 months, 50% of patients became asymptomatic or experienced symptom relief (Timon et al. 1991). Male gender, short duration of the globus symptom, and no other throat symptoms were associated with rapid resolution of symptoms (Timon et al. 1991).

## **2.2 DYSPHAGIA**

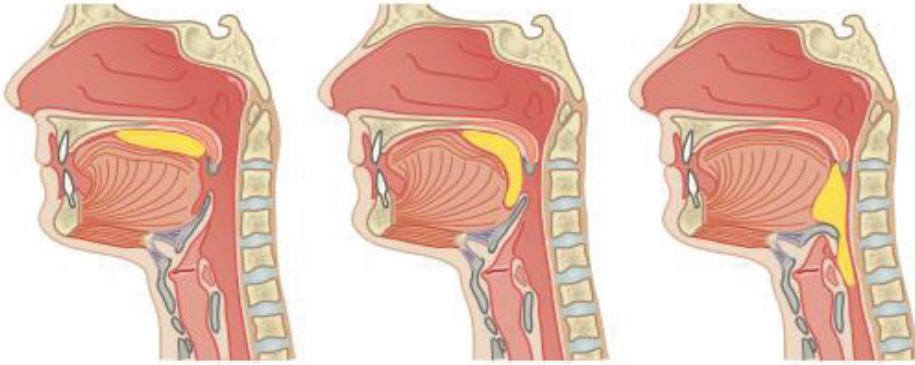
### **2.2.1 DEFINITION AND PREVALENCE**

Dysphagia affects the elderly in particular because the neurophysiology of normal swallowing alters with age (Jaradeh 1994). In a community, 5% to 8% of individuals over 50 report dysphagia (Lindgren & Janzon 1991). The prevalence increases to 16%, if considering patients over 80 (Bloem et al. 1990). Many age-related changes may contribute to an impaired pharyngeal swallow, such as diminished cooperation between the oral and pharyngeal phase of swallowing, and delayed anterior movement of the hyoid bone (Plant 1998). Problems in swallowing have a potential effect on nutrition, as well as a patient's quality of life.

### **2.2.2 PHYSIOLOGY OF DEGLUTITION**

Swallowing is a complex process. The brainstem receives input from the cerebral cortex and coordinates the motor and sensory activity of the swallowing process in the oral cavity, pharynx, and esophagus.

The oral phase in swallowing is voluntary and requires proper teeth to chew, a coordinated work of masticatory muscles and the tongue, and enough saliva to prepare the ingested material to be swallowed. At the end of the oral phase, the tongue pushes the bolus to the hard palate, which triggers the complex, reflex, involuntary pharyngeal phase of swallowing (Figure 1). Elevation of the soft palate and contraction of the posterior wall of the nasopharynx prevent nasal regurgitation (Ekberg 2012). The upward and forward movement of the larynx by suprahyoid muscles, the epiglottis bending backward, and the approximation of the vocal cords prevent food from being aspirated into the trachea. When the cricopharyngeus muscle, the physiological UES, relaxes while the larynx is moving up and forward, the striated pharyngeal muscles contract and the bolus is allowed to enter the esophagus. The involuntary upper esophageal muscles contractions drive the bolus forward into the middle and distal esophagus. As the LES relaxes, the involuntary esophageal phase of swallowing ends, when the bolus reaches the stomach.



**Oral phase**

(mainly voluntary)

- Lips closure (VII)
- Tongue movements / bolus formation (XII)
- Swallowing reflex / sensory of the palatoglossal arches (IX), and symmetry (X)

**Pharyngeal phase**

(involuntary)

- Palatal reflex (X, V)
- Elevation of the larynx (XII)
- Contraction of the tongue-base (V, XII)

**Esophageal phase**

(involuntary)

- Function of the upper and lower esophageal sphincter and peristaltic movements (X)

**Figure 1** The phases of swallowing and the cranial nerves related to the swallowing process. The figure is customized and translated from the article Aaltonen L-M et al. “Dysfagia – moniammatillinen haaste”, Duodecim 2009;125:1535-44, with permission of Duodecim.

**2.2.3 ETIOLOGY**

**2.2.3.1 Oropharyngeal dysphagia**

In oral dysphagia, the formation of the food bolus in the mouth is impaired or the patient is unable to pass the bolus into the pharynx. Patients with oral dysphagia have a prolonged masticatory and oral transit time, they require increased amount of swallows to pass the bolus to the pharynx and the food may regurgitate into the nasopharynx (Sebastian et al. 2015). Defects in teeth or dentures and xerostomia may impair the oral phase (Vainshtein et al. 2015). Moreover, Bell’s palsy, affecting the VII cranial nerve, may weaken the oral closure causing oral dysphagia. In pharyngeal dysphagia, the swallow reflex is absent or comes with a delay, so the patient may aspirate. Tumors in the oral cavity or in the oropharynx and larynx may cause oral and oropharyngeal dysphagia, respectively. Malignant tumors often also present other symptoms and signs, such as pain, bleeding, or unhealed mucosal lesions. In addition, operations, chemo- and radiation therapies of malignant oral, oropharyngeal, and laryngeal tumors may impair swallowing.

Stroke is the most common cause for oropharyngeal dysphagia, reportedly prevalent in up to 81% of stroke patients (Meng et al. 2000, Cook 2008). Cerebral, cerebellar, and brain stem strokes may lead to dysphagia (Martino et al. 2005). However, many other neurological disorders may cause dysphagia: Parkinson’s disease, myasthenia gravis, and motor neuron diseases, such as amyotrophic lateral sclerosis (Petit et al. 2012, Owolabi et al. 2014, Rajaei et al. 2015, Tabor et al. 2016). In degenerative diseases, like Alzheimer’s disease, swallowing is frequently impaired as the disease progresses (Secil et al. 2016). Pharmacological agents, such as benzodiazepines and neuroleptic drugs, may alter the neuromuscular function of the oropharynx (Ebadi et al. 1990).

Moreover, patients with disorders of the nervous system due to head injury or nerve damage after head and neck surgery may have swallowing difficulties.

Anatomically, the pharyngoesophageal segment consists of the inferior pharyngeal constrictor, the cricopharyngeus muscle and the proximal part of the cervical esophagus. The UES, also called the pharyngoesophageal segment, is a functional segment. The UES is a 2.5–4.5 cm high-pressure zone between the pharynx and the esophagus and may be visualized with manometry. The UES may open inadequately, causing pharyngeal dysphagia. The cricopharyngeus muscle, being 1-2 cm, is the only portion of the UES which actively participates in reflexive relaxation and tightening (Kuhn & Belafsky 2013). Cricopharyngeus muscle spasm was first described back in 1950 (Asherson 1950). However, cricopharyngeal dysfunction, as a cause for dysphagia, may be due to reduction of the maximal opening, as well as incoordination (Shaker et al. 2012).

There is no consensus regarding what leads to the Zenker's diverticulum formation, but a diminished upper esophageal sphincter opening, increased hypopharyngeal pressure, and diminished wall compliance during swallowing are possible causes (Cook et al. 1992). Zenker's diverticulum locates in the upper third of the esophagus where mucosa protrudes through the Killian's triangle, an area of relative muscular weakness. Patients with Zenker's diverticulum suffer from dysphagia, regurgitation, and halitosis. Zenker's diverticulum comprises 70% of diverticula of the esophagus, with an estimated prevalence of 0.01%-0.11% (Ferreira et al. 2008).

### 2.2.3.2 Esophageal dysphagia

The cause of esophageal dysphagia is either structural or functional. The most common cause for esophageal dysphagia is GERD, with swallowing difficulties affecting up to 11% of GERD patients (Watson & Lally 2009). In a systematic review, GERD's prevalence was 10-20% in the Western world and 5% in Asia (Dent et al. 2005). Untreated acid-GERD in particular may lead to development of a peptic stricture in the lower esophagus causing dysphagia (van Boeckel & Siersema 2015). Gastroesophageal reflux may damage the distal esophagus and cause intestinal metaplasia. This Barrett's mucosa, with the possible coexistence of other risk factors such as cigarette smoking, alcohol consumption and obesity, has an increased risk of progression to dysplasia and further to adenocarcinoma, one cause of esophageal dysphagia (Drahos et al. 2016). In addition, an extraesophageal process may also cause a mechanical obstacle in the esophagus. An enlarged goiter, an aortic aneurysm, and tumors in the mediastinum or in the bronchus may compress the esophagus, causing dysphagia.

Eosinophilic esophagitis is an increasing chronic inflammatory disease with eosinophilic infiltration in the esophageal epithelium (Attwood et al. 1993, Dellon et al. 2013). It is evident in 10% of dysphagia patients with endoscopically normal mucosa (Prasad et al. 2007). Also, the esophageal web, a thin membranous tissue protruding into the lumen of the cervical esophagus, and the Schatzki ring in the lower part of the esophagus may be structural causes for swallowing difficulties (Sreenivas et al. 2002). When a patient's symptoms arise rapidly, a foreign body should be considered. Infections, such as candida and herpes, in the esophagus are also possible causes, especially in immune-compromised patients.

After GERD, esophageal motor disorders are the next most common cause of functional esophageal dysphagia. A motor disorder may be spastic, with increased esophageal body contractions, or there may be esophageal hypomotility, characterized by an absence or reduction of esophageal contractions (Valdovinos et al. 2014). Achalasia is a primary esophageal motor



disorder involving insufficient LES relaxation and an aperistaltic esophagus which leads to esophageal dilatation, poor LES opening and esophageal emptying (Vaezi & Richter 1999). It is characterized by selective inhibitory neuron loss in the esophageal wall (Vaezi et al. 2013). Achalasia should be suspected if a patient has difficulties swallowing solids and liquids, has regurgitation of food and saliva, and suffers from chest pain (Vaezi & Richter 1999).

Distal esophageal spasm, previously called diffuse esophageal spasm, is a rare, primary esophageal motor disorder with simultaneous, rapid contractions causing dysphagia and chest pain (Pandolfino et al. 2011). Jackhammer's esophagus is a hypercontractile esophageal motor disorder in which a patient may feel the esophagus moves like a jackhammer (Kahrilas et al. 2015). Several reports have noted that GERD, distal esophageal spasm, and jackhammer's esophagus may progress to achalasia in some patients, suggesting that different motor disorders comprise a spectrum rather than unique, stable conditions (Smart et al. 1986, Anggiansah et al. 1990, Robson et al. 2000, Usai Satta et al. 2004).

## **2.2.4 DYSPHAGIA PATIENT'S EXAMINATIONS**

### *2.2.4.1 History and physical examination*

With careful patient history taking, it is possible to identify the cause of the dysphagia in 80-85% of cases (Spieker 2000). The main issue is to localize the dysphagia in either the oral, pharyngeal, or esophageal phase. Moreover, the onset, severity, and possible co-existing symptoms indicate the diagnosis. A patient's medication may have possible side effects, like xerostomia. ENT status including nasolaryngoscopy, neck palpation, and cranial nerve function testing concerning deglutition (Figure 1) are included in the examination of a patient with oropharyngeal dysphagia. The 100 mL water swallow test is an easy outpatient examination to perform for a patient if aspiration is suspected. The test is failed if the patient coughs, is unable to finish the task or the voice becomes wet after drinking (Brodsky et al. 2016).

### *2.2.4.2 Videofluorography*

Videofluorography has been the mainstay for evaluation of oropharyngeal dysphagia for decades. It has been adapted from the barium swallow, a radiographic examination of the pharynx and the esophagus. Logeman (1983) modified this examination with liquid and solid to identify the cause for swallowing difficulties. In videofluorography, esophageal structural abnormalities, such as Zenker's diverticulum and strictures, are well diagnosed (Figure 2). Moreover, it enables evaluation of the swallowing process, including cricopharyngeus muscle function, and reveals possible aspiration.

The movement of the contrast medium allows for detection of esophageal motor abnormalities in videofluorography. Aperistalsis, esophageal dilation, minimal LES opening, and poor esophageal emptying in videofluorography indicate achalasia (Vaezi & Richter 1999).

### *2.2.4.3 Fiberoptic endoscopic evaluation of swallowing*

After the fiberoptic laryngoscope became available, Langmore developed the fiberoptic endoscopic evaluation of swallowing (FEES) examination (Langmore et al. 1988). FEES includes a physical examination of the oropharynx and the larynx, including assessing structural movements, and evaluation of the deglutition process with different liquids and solids. In

addition, during the examination the patient is instructed to facilitate the deglutition with dietary and behavioral habits. In 1998, Aviv et al. (1998) introduced fiberoptic endoscopic evaluation of swallowing with sensory testing (FEESST), but this has not been widely used.

FEES has become another gold standard examination in the assessment of oropharyngeal dysphagia. Studies show that FEES is even better than videofluorography in evaluation of pharyngeal stasis, laryngeal penetration and aspiration, effective cough reflex, and velopharyngeal incompetence (Langmore et al. 1991, Wu et al. 1997). However, in FEES, esophageal structural and functional abnormalities are not evident, but since FEES is usually performed together with an ENT physician, or a phoniatrician and an SLP, it is more valuable for patient instruction.

#### 2.2.4.4 Endoscopy

Endoscopy, either EGD or TNE, is recommended as a first-line examination when a patient with esophageal dysphagia has alarming symptoms, such as weight loss and food impaction in the esophagus, to rule out malignancy (Katz et al. 2013). During a diagnostic EGD, it is also possible to manage the cause of dysphagia, such as a stricture, in the same procedure with a balloon dilatation. A dysphagia patient's endoscopy should also include biopsies from the middle of the esophagus to exclude eosinophilic esophagitis (Ferguson & Foxx-Orenstein 2007, Prasad et al. 2007).

#### 2.2.4.5 Manometry

Esophageal manometry is the gold standard to diagnose intraluminal esophageal pressures, peristalsis, and bolus transit. Previously, conventional manometry using 5 to 8 water-perfused channels with or without a measurement of continuous LES pressure was the diagnostic tool. In the 1990s, HRM was developed with up to 36 sensors, describing the bolus movement more accurately. HRM also identifies those esophageal motor dysfunctions which are not detectable in other investigations, including conventional manometry and videofluorography. HRM is performed in supine patients using a transnasally-placed solid-state catheter (Fox et al. 2004). In achalasia, HRM establishes the diagnosis, showing esophageal aperistalsis and insufficient LES relaxation. However, patients should also undergo endoscopy to exclude a tumor at the gastroesophageal junction causing pseudoachalasia (Vaezi & Richter 1999). To unify the diagnostics, the Chicago Classification is currently used to define major and minor esophageal motor disorders (Kahrilas et al. 2015).

#### 2.2.4.6 pH monitoring and 24-hour multichannel intraluminal impedance

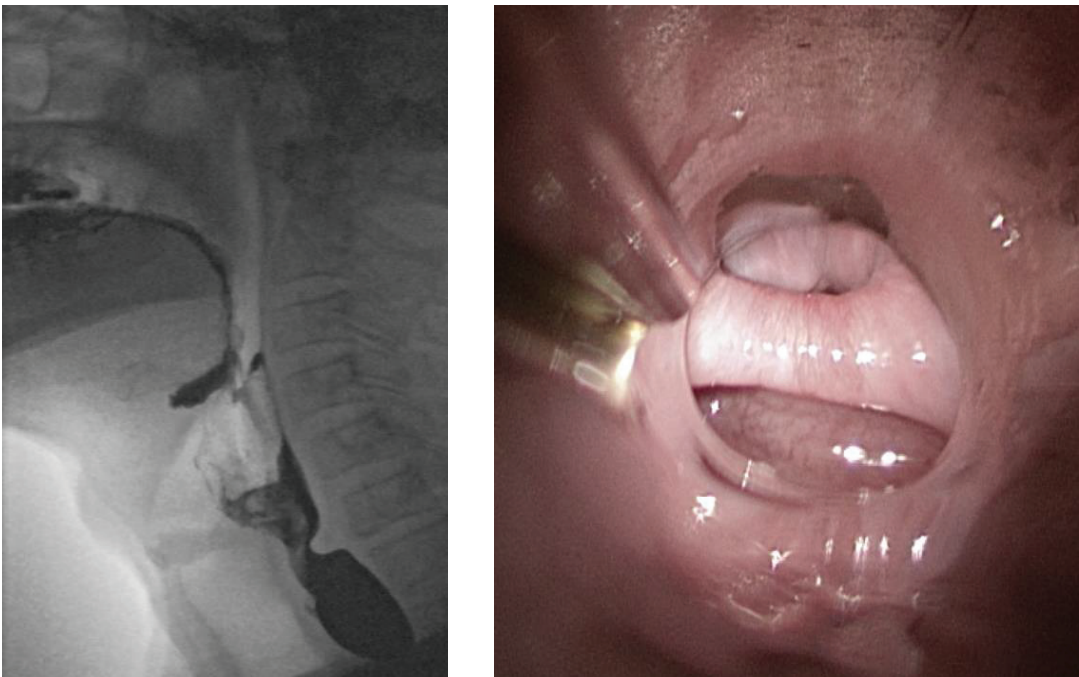
Esophageal pH monitoring has been the premier investigation in GERD diagnostics (Bollschweiler et al. 1993). Currently, combined pH monitoring with impedance allows for detection of acid, weakly acid, and non-acid reflux, as well as aerophagia and mixed-refluxates. The addition of impedance to the pH monitoring increases the identification of patients whose reflux symptoms are caused by reflux (Bredenoord et al. 2006). In a small case-control study, impedance also had the ability to measure the esophageal bolus transit time and stasis in dysphagia patients with an esophageal motor disorder (Bogte et al. 2015). Consequently, after patients with esophageal dysphagia have undergone endoscopy and manometry and after a tumor, eosinophilic esophagitis, and achalasia are excluded, pH monitoring with 24-hour MII may be helpful.



## 2.2.5 DYSPHAGIA PATIENT'S TREATMENT

Acute stroke patients' dysphagia symptoms often resolve during rehabilitation, but some patients remain with permanent deglutition difficulties (Mann et al. 1999). An SLP may instruct a patient with neurogenic dysphagia to eat safely and efficiently with the guidance of dietary modifications and behavioral strategies. However, in some patients, an oral diet is not safe enough and a feeding tube is required or a percutaneous gastrostomy, either temporarily or permanently.

Botulinum toxin injections to cricopharyngeus muscle are a safe and effective treatment for cricopharyngeus muscle spasm and hypertonicity (Blitzer & Brin 1997, Ahsan et al. 2000, Haapaniemi et al. 2001). Moreover, balloon catheter dilatation and laser myotomy are beneficial to enhance the cricopharyngeus muscle opening (Arenaz Bua et al. 2015). Esophageal strictures can be dilated with the balloon as well (van Boeckel & Siersema 2015). Additionally, balloon dilatation is considered a simple outpatient procedure having the least morbidity in the management of a cervical esophageal web (Sreenivas et al. 2002). For many years, the choice of treatment for Zenker's diverticulum was an open surgical diverticulectomy with cricopharyngeal myotomy. Nowadays, however, an endoscopic staple-assisted esophagodiverticulostomy (Figure 2) is often preferred since it is safe and effective, with a shorter operation time and hospital stay and leads to quicker oral intake (Richtsmeier 2003, Bonavina et al. 2012).



**Figure 2** Zenker's diverticulum visualized in videofluorography (left image), and in rigid endoscopy before the endoscopic staple-assisted esophagodiverticulostomy (right image). Pictures: Leena-Maija Aaltonen.

Empiric PPI therapy is recommended as a first-line trial to diagnose possible GERD in patients with typical symptoms: heartburn and regurgitation (Katz et al. 2013). Dysphagia resolves in patients with esophagitis during PPI medication (Vakil et al. 2004). For patients with a partial response to a once-daily dose, a twice-daily dose should be considered. Non-responders to PPI should be referred for further evaluation (Katz et al. 2013).

In achalasia, the two most effective treatment options are pneumatic dilation and surgical myotomy, the latter originally created by Heller (Heller 1913, Vaezi & Richter 1999, Wauters et al. 2014). However, for patients at high risk for complications due to the procedures, endoscopic injections of the LES with botulinum toxin or pharmacological treatment with nitrates or calcium channel blockers are alternatives (Vaezi & Richter 1999). Historically, distal esophageal spasm has been treated with these medications as well, with only a limited benefit, however. Also, endoscopic treatment with botulinum toxin injections and myotomy has been proposed, but further investigation is needed (Roman & Kahrilas 2015). Pharmacological treatments and pneumatic dilatation have been used in the treatment of jackhammer's esophagus, but further investigations are required (Jia et al. 2016). Surgical treatment is recommended for esophageal cancer, when possible. Based on a Cochrane database systematic review, in chemoradiotherapy, the short-term and long-term survival seems to be at least equivalent to surgery in patients with squamous cell esophageal carcinoma (Best et al. 2016). However, in adenocarcinoma, the comparison of significant benefits and harms between definitive chemoradiotherapy and surgical treatment has been unable to be assessed (Best et al. 2016).

### **3 AIMS OF THE STUDY**

The general objective of this thesis was to study the etiology of globus, to update the diagnostics of globus and dysphagia, and to clarify the natural course of these symptoms. The specific aims were to:

1. Investigate the possible esophageal background of globus with TNE, HRM, and 24-h MII-pH (I).
2. Evaluate whether globus patients' symptoms are relieved in the short term and if voice problems are associated with globus (II).
3. Determine whether radiographic examinations are useful in globus diagnostics (III).
4. Investigate how globus and dysphagia symptoms alter in the long term and whether these conditions are an early symptom of malignancy (III, IV).

## 4 SUBJECTS AND METHODS

### 4.1 PATIENTS AND CONTROLS

#### 4.1.1 STUDY I, II

We prospectively recruited 30 consecutive globus patients (67% female; median age 45, range 22-67) referred to the Helsinki University Hospital (HUU), Department of Otorhinolaryngology – Head and Neck Surgery between November 2011 and October 2013. Those who were previously examined in our clinic due to globus or were under 18 or over 75 years old were excluded. Referrals of globus patients with dysphagia, hoarseness, odynophagia, a diagnosis of rheumatoid arthritis, or head and neck malignancies were also excluded. Furthermore, two patients were excluded from the final analysis: one refused the study after her initial visit, the other also had throat pain and the ENT examination revealed a soft-palate tumor which was later diagnosed as a squamous cell carcinoma. Patients' general health was assessed using the Charlson Comorbidity Index (CCI) (Charlson et al. 1987). The CCI is a tool to evaluate a patient's possible comorbid conditions, such as diabetes and chronic pulmonary disease, which may alter the patient's risk of mortality. The CCI can be adjusted by age.

In study I, controls were prospectively recruited from 24 patients (67% female; median age 57, range 19-75) who were referred for an operative evaluation in the Department of Abdominal Surgery at HUU between May 2013 and May 2014 due to difficult reflux symptoms.

#### 4.1.2 STUDY III, IV

In these retrospective studies, we extracted from the hospital database all patients referred to our department in HUU in 2009 due to globus (III) and dysphagia (IV) using the International Statistical Classification of Diseases 10<sup>th</sup> edition (ICD-10) codes F45.8 and R13, respectively. The globus (III) and dysphagia (IV) diagnoses were confirmed by reviewing patients' clinical data. In study III, the CCI was used to determine the patients' general health.

## 4.2 METHODS

### 4.2.1 INVESTIGATIONS (I, II)

#### 4.2.1.1 *Clinical ear, nose, and throat examination and videolaryngoscopy (II)*

All 30 globus patients underwent a clinical ENT examination including neck palpation and videolaryngoscopy at their initial visit. Subsequently, each videolaryngoscopy was scored using the Reflux Finding Score (RFS) (Appendix 1), an eight-item clinical severity scale where seven points or more are considered to be suggestive for LPR (Belafsky et al. 2001).

#### 4.2.1.2 *Transnasal esophagoscopy and esophagogastroduodenoscopy (I)*

After informed consent, the patient underwent TNE (Olympus GIF-XP180N). Local anesthesia was used prior to the procedure, with two sprays of lidocaine (10%) to the nasal cavity and then with a 1% lidocaine cum adrenalin-moistened cotton swab placed in the nasal cavity for 10 minutes. No premedication was used. Lidocaine gel (2%) functioned as a lubricant on the endoscope when it was placed transnasally while the patient was sitting in front of the clinician. At first, the nasopharynx, hypopharynx, and larynx were investigated and then the endoscope

was passed into the esophagus. The TNE was performed by an otorhinolaryngologist and a gastroenterologist and included examination of the esophagus, stomach and the beginning of the duodenum. Biopsies were taken from the hypopharynx, the middle and lowest part of the esophagus, as well as from the antrum and corpus of the stomach.

All 24 controls underwent EGD either before the referral or at the Department of Abdominal Surgery. If biopsies were taken, they were from the lowest part of the esophagus and the antrum and corpus of the stomach.

In TNE and EGD, hiatal hernia and a loose lower esophageal sphincter were clinical diagnoses. Possible endoscopic esophagitis was classified according to the Los Angeles (LA) Classification system, which includes four grades (LA A-LA D) (Lundell et al. 1999). One (or more) mucosal breaks that did not extend between the tops of two mucosal folds and were no longer than 5 mm, or were more than 5 mm long, were classified as LA A and LA B esophagitis, respectively. According to LA Classification, one (or more) mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the circumference is considered to be LA C esophagitis. In LA D esophagitis, there are one (or more) mucosal breaks involving at least 75% of the esophageal circumference. In our study, however, there were no LA C or LA D esophagitis cases.

A histological diagnosis of esophagitis was made according to the generally recommended criteria (Genevay et al. 2010). The diagnosis of histological esophagitis included basal cell hyperplasia, papillae elongation, dilated intercellular spaces, and intraepithelial neutrophils, lymphocytes and possible eosinophils. However, the histological diagnosis of eosinophilic esophagitis would have required at least 15 eosinophils per high-power field (Furuta et al. 2007). The histological diagnosis of Barrett's esophagus required intestinal metaplasia with goblet cells and the same marks of inflammation as in esophagitis. The antral and corpus biopsies were assessed separately and the histological diagnosis of gastritis was made according to a modified Sydney classification (Price 1991) including the grading of acute and chronic inflammation, atrophy, intestinal metaplasia, dysplasia and *Helicobacter pylori*, of which the latter is evident in the Giemsa stain. The characteristics of all histologic specimens were graded from 0 to 3 (0=no changes, 1=mild changes, 2=moderate changes, 3=marked changes).

#### 4.2.1.3 High-resolution manometry (I)

After a fast of at least five hours, manometric studies were performed in supine patients. A 36-channel solid-state catheter (Manoscan 360, Given Imaging, Los Angeles, CA) was positioned transnasally. After a 5-min baseline recording, 10 x 5 mL water was given with a syringe. Using the Manoview ESO 3.01 program (Given Imaging, Duluth, CA), the swallow response was determined according to the Chicago classification (Bredenoord et al. 2012).

#### 4.2.1.4 24-hour multichannel intraluminal impedance and pH monitoring (I)

After manometry, combined MII-pH monitoring was performed with a ZepHr recorder (Sandhill Scientific Inc, Highlands Ranch, CO). The single-use catheter was placed transnasally: one pH electrode 5 cm above the proximal border of the LES and six impedance segments 3 to 17 cm above the LES. Patients were advised to keep records of their upright or recumbent position, meal times, and possible symptoms during ambulatory monitoring for the next 24 hours.

An acid-reflux episode was determined with a pH nadir <4, otherwise it was recorded as non-acid. In pH monitoring, the DeMeester score, indicating the overall pH score, was

calculated. The normal value of the DeMeester score was  $< 14.7$ . A supragastric belch was determined as a rapid antegrade movement of gas ( $\geq 1000 \Omega$ ) followed by a quick expulsion of gas in the retrograde direction, resulting in a return to baseline impedance level in the retrograde direction (Kessing et al. 2012). According to a previous study, 50% of healthy volunteers had a median of two (IQR 1-6) supragastric belches (Hemmink et al. 2009a). In this study, over six supragastric belches during a 24-hour measurement were considered to be a pathological amount. Air swallow was determined as a swallow with an impedance increase of  $1000 \Omega$  or more in the most distal recording segment (Hemmink et al. 2009b).

In the MII-pH monitoring, a catheter was fixed at the LES, however, a catheter with two fixation points was unavailable at the time the procedures were performed. Consequently, the proximal measuring point varied between patients. Because proximal reflux events are reported in approximately 50% of the distal reflux events, we considered a reference value for proximal reflux events as being more than 36 reflux episodes, which is half of the reference value of distal reflux events (73) (Shay et al. 2004).

#### 4.2.1.5 *A speech and language pathologist's examination (II)*

After a four-month follow-up, an SLP interviewed and examined the globus patients. Before the appointment, the patients filled in the Reflux Symptom Index (RSI) (Appendix 2), the Deglutition Handicap Index (DHI) (Appendix 3) and the 15-Dimensional Measure of Health-Related Quality of Life (15-D) (Appendix 4). The SLP's examination included an evaluation of vocal quality and the ability to control the pitch and loudness of the voice. The maximum phonation time was measured using /a/ and /s/. For women, the reference value of the maximum phonation time is 15-25 s and 25-35 s for men (Hirano 1981).

## 4.2.2 QUESTIONNAIRES (II, III, IV)

### 4.2.2.1 *The Reflux Symptom Index (II)*

The RSI is a nine-item questionnaire of symptoms possibly related to LPR (Belafsky et al. 2002). The point scale ranges from 0 to 5, and a total score over 13 is considered abnormal. In study II, the globus patients filled in the RSI at their initial visit at the ENT clinic and again at the four-month follow-up with the SLP.

### 4.2.2.2 *The Deglutition Handicap Index (II, III, IV)*

The DHI is a self-administered quality-of-life questionnaire related to deglutition (Woisard & Lepage 2010). It is divided into three subscales—physical, functional, and emotional—of 10 questions each. The point scale ranges from 0 to 4, maximum 120 points. A total score over 20 and/or 9 points or more in a single subscale is considered abnormal.

In study II, globus patients completed the DHI at the initial visit and at the four-month follow-up with the SLP.

In studies III and IV, the DHI was included in the follow-up questionnaires sent to the patients three (III, IV) and again six (III) years after the initial visit. The questionnaire also included a question asking whether the patient still had globus (III) or dysphagia (IV) symptoms. The questionnaire was only sent if the patient's native language was Finnish or Swedish and if the patient was alive based on the Population Registry. The three-year follow-up questionnaire was sent in December 2012 and, if needed, a reminder was sent in February 2013 (III, IV). The six-

year follow-up questionnaire was sent in October 2015 and with a reminder in November 2015, if the patient had not responded (III).

In studies II, III, and IV, we used the DHI translated into Finnish and Swedish (Aherto & Vilkmán 2008).

#### **4.2.2.3 *The 15-Dimensional Measure of Health-Related Quality of Life (II)***

The 15-D is a self-administered health-related quality of life instrument consisting of 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. In each dimension, the respondent chooses one of five levels to describe his or her present health status. The 15-D supplies a 15-dimensional profile and a single utility score between 0 (equivalent to being dead) and 1 (full health) (Sintonen 2001). In the 15-D score, the minimal clinically important change or difference is reported to be 0.015 (Alanne et al. 2015). The National Health 2011 Survey provided the representative population sample, which was standardized for age (Koskinen et al. 2012).

In study II, the 15-D was the third questionnaire that the globus patients filled in at the initial visit and at the four-month follow-up.

#### **4.2.3 MEDICAL RECORDS (III, IV)**

After identifying globus (III) and dysphagia (IV) patients from the hospital database, we surveyed patients' records and registered medical data: age, gender, symptoms and findings at clinical ENT examination and possible further examinations (neck ultrasound, videofluorography, FEES, TNE, EGD, HRM, 24-h MII-pH). Based on the data, the suspected cause of the globus (III) and dysphagia (IV) symptoms was reviewed.

#### **4.2.4 THE FINNISH CANCER REGISTRY DATA (III, IV)**

We surveyed the Finnish Cancer Registry (FCR) data, which clarified all the globus (III) and dysphagia (IV) patients' cancer diagnoses until the end of 2012. We recorded cancer diagnoses from the head and neck area and the aerodigestive track, of which globus or dysphagia could have been an early symptom.

### **4.3 STATISTICAL ANALYSIS**

In study I, the estimated prevalence of acid reflux determined the sample size: 25% in globus patients and 75% in controls. The sample size was calculated to be 16 patients. Subsequently, 20 patients were selected to both groups. The confidence interval was set at 95% ( $\alpha=0.05$  and  $\beta=0.1$ ). Either chi-square or Fisher's exact tests were used for comparisons of categorical variables between globus patients and controls, and the Mann-Whitney U test was used for comparisons of non-normally distributed continuous variables between globus patients and controls.

In study II, differences in globus patients' RSI and DHI between the initial visit and at the four-month follow-up were performed using the Wilcoxon signed-rank test. Differences in the 15-D, compared to those of the general population, were determined by the Mann-Whitney U test and differences between globus patients' 15-D baseline and four-month follow-up results were determined by the Wilcoxon signed-rank test.



In studies III and IV, differences in the age distributions between genders were determined with the independent samples *t* test, as were differences in age between respondents and non-respondents. Differences in gender distributions between respondents and non-respondents, however, were determined by the Pearson chi-square test. In study III, the globus patients' DHI differences and the self-ratings regarding present globus symptoms between the three and six year follow-ups were analyzed using the Wilcoxon signed-rank test. The globus self-ratings between those who had a specific cause for globus and those who did not were compared using the chi-square test. In study IV, the difference in the distributions of diagnoses between those returning and not returning the questionnaire was examined using the Mann-Whitney U test.

P-values were all two-tailed and the significance level was set at 0.05. All computations were performed using the Statistical Program for Social Sciences (SPSS for Windows, Version 22.0 statistical software; SPSS Inc, Chicago, IL, USA).

#### **4.4 ETHICAL CONSIDERATIONS**

The Ethics Committee of the Department of Surgery of the Helsinki and Uusimaa Hospital District approved all the study protocols. In studies I and II, the patients provided written informed consent before enrollment into the study. In studies III and IV, patients receiving the questionnaires were informed about the study protocol and that their confidential answers would be used in our research.



## 5 RESULTS

### 5.1 EXAMINATIONS (I, II)

#### 5.1.1 TRANSNASAL ESOPHAGOSCOPY (I)

TNE was performed on all 30 globus patients. However, we only had HRM and 24-h MII-pH monitoring results from 20 patients: 9 patients refused HRM and 10 patients refused 24-h MII-pH monitoring after the TNE. Age and gender distributions did not differ between those who underwent all investigations compared to those who did not. All 24 controls underwent EGD, HRM, and 24-h MII-pH monitoring. Globus patients were not on PPIs when participating in the study. Controls, on the other hand, did experience heartburn, despite their use of regular PPI medication but they did not have any globus symptoms.

TNE was macroscopically normal in globus patients more often than EGD in controls ( $P<0.001$ ) (Table 1). Moreover, hiatal hernia was evident more often in controls than in globus patients ( $P<0.001$ ) (Table 1). Some globus patients and controls had LA A or LA B esophagitis, but with regards to prevalence, no statistically significant differences were seen (Table 1). Biopsies revealed histologically mild esophagitis in the lowest and/or middle part of the esophagus in globus patients more often, but this difference did not reach statistical significance (Table 1).

**Table 1.** Endoscopic and histologic findings from transnasal esophagoscopy and esophagogastroduodenoscopy (study I).

	<b>Globus, n=30</b>	<b>Controls, n=24</b>	
<b>Findings from TNE / EGD</b>	<b>n (%)</b>	<b>n (%)</b>	<b>P value</b>
Esophagitis	3 (10.0)	6 (25.0)	0.165
- LA A esophagitis	1 (3.3)	3 (13.0)	0.312
- LA B esophagitis	2 (6.7)	3 (13.0)	0.646
Barrett's esophagus	1 (3.3)	1 (4.2)	1.000
Suspicion of gastritis	2 (6.7)	0	0.495
Hiatal hernia	0	23 (96.0)	<.001
Loose lower esophageal sphincter	1 (3.3)	2 (8.3)	0.585
No findings	14 (47.0)	0	<.001
	<b>Globus, n=29</b>	<b>Controls, n=18</b>	
<b>Histological findings</b>	<b>n (%)</b>	<b>n (%)</b>	<b>P value</b>
Mild esophagitis in lowest/middle part of esophagus	10 (34.0)	4 (22.0)*	0.516
<i>H.pylori</i> infection and mild active gastritis in corpus	1 (3.4)	0	1.000
Mild chronic gastritis in corpus	1 (3.4)	1 (5.6)	1.000
Mild/moderate gastric metaplasia in lowest part of esophagus	2 (6.9)	1 (5.6)	1.000
Mild intestinal hyperplasia in antrum	0	1 (5.6)	0.383
Barrett's esophagus (intestinal metaplasia)	1 (3.4)	0	1.000
Mild inflammation in hypopharynx	2 (6.9)		

\* ulcerative esophagitis in one patient

TNE=transnasal esophagoscopy, EGD=esophagogastroduodenoscopy, LA=the Los Angeles Classification system for endoscopic appearance for erosive esophagitis, *H.pylori*=*Helicobacter pylori*

### 5.1.2 HIGH-RESOLUTION MANOMETRY (I)

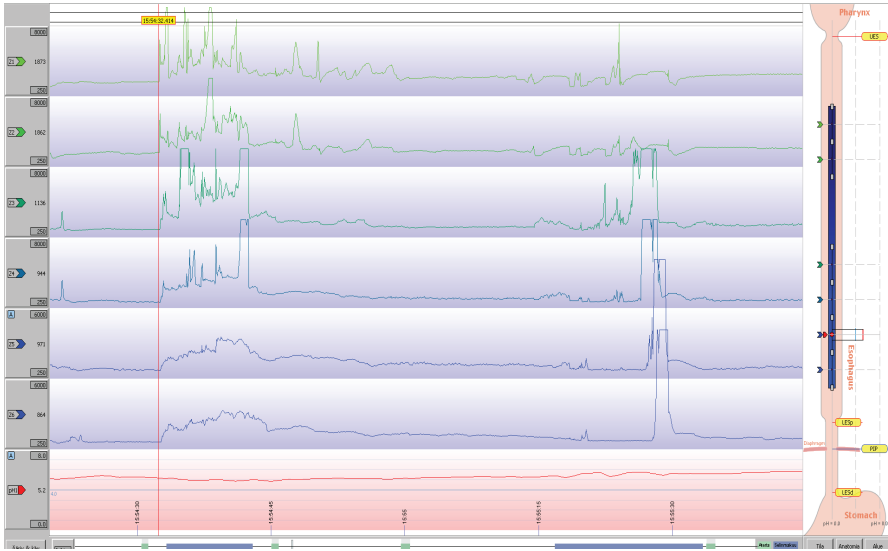
We had HRM results from 21 globus patients and 24 controls. In HRM, the UES basal and residual pressures were not elevated in globus patients, and no statistically significant difference was seen between globus patients and controls (Table 2).

Based on Chicago Classification version 2.0 criteria (Bredenoord et al. 2012), esophageal motility was normal in 8 globus patients (38.1%) and in 12 controls (50%). In both globus patients and controls, 11 individuals (52.4% and 45.8%, respectively) had minor motor disorders evident in HRM. Moreover, two globus patients (9.5%) and one control (4.2%) had a major motor disorder diagnosed. Globus patients' major motor disorders were absent peristalsis and esophago-gastric junction (EGJ) outflow obstruction. The major disorder for control was jackhammer's esophagus. Differences in findings between globus patients and controls regarding esophageal motility were statistically non-significant.

### 5.1.3 24-HOUR MULTICHANNEL INTRALUMINAL IMPEDANCE AND pH MONITORING (I)

All results from the 24-h MII-pH were available of 20 globus patients and 23 controls. One control's esophageal mucous membrane was in poor condition because of reflux and therefore his 24-h MII could not be analyzed. According to pH monitoring, the DeMeester scores and total time at pH < 4 were higher in controls ( $P < 0.001$ ). Also, the total reflux time for controls was longer ( $P = 0.004$ ) and they had more acid reflux ( $P = 0.002$ ) in MII. Controls had pathological total proximal reflux events more often (9/23, 39% vs. 1/20, 5%;  $P = 0.01$ ). The one globus patient who had a pathological amount of total proximal reflux events ( $n = 53$ ) also had a prolonged total reflux time (2.2%) in MII. Afterward, she reported that she had also suffered from heartburn. However, we did not exclude this patient from the final analysis. Regarding non-acid reflux, no statistically significant difference was evident between globus patients and controls. Detailed results from the 24-h MII-pH monitoring are presented in Table 2.

MII revealed that globus patients had supragastric belching more frequently than controls (6/20, 30% vs. 1/24, 4%;  $P = 0.038$ ). Moreover, aerophagia (Figure 3) was evident in globus patients more often than controls, although the difference was not statistically significant (5/20, 25% vs. 2/23, 9%).



**Figure 3** Aerophagia seen in multichannel intraluminal impedance monitoring.

**Table 2.** Results from high-resolution manometry and 24-hour multichannel intraluminal impedance and pH monitoring (study I).

	<b>Globus, n=21</b>	<b>Controls, n=24</b>	
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>P value</b>
<b>HRM</b>			
UES			
Mean basal pressure (mm Hg)	65.0 (56.5, 83.2)	66.0 (57.5, 74.0)	0.609
Residual pressure (mm Hg)	4.2 (0.2, 8.4)	6.3 (3.0, 10.1)	0.116
LES			
Mean pressure (mm Hg)	17.4 (10.6, 27.7)	14.8 (10.0, 20.0)	0.158
	<b>Globus, n=20*</b>	<b>Controls, n=24</b>	
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>P value</b>
<b>24-hour pH</b>			
DeMeester score	4.1 (1.0, 6.6)	14.4 (4.3, 27.9)	<.001
Total time pH < 4 (%)	0.8 (0.1, 1.6)	4.1 (1.0, 8.7)	<.001
	<b>Globus, n=20*</b>	<b>Controls, n=23**</b>	
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>P value</b>
<b>MII</b>			
Total reflux time (%)	0.8 (0.5, 1.3)	1.5 (1.1, 2.5)	0.004
Acid reflux events	15.5 (8.5, 26.5)	35.0 (25.0, 56.0)	0.002
Non-acid reflux events	20.5 (9.8, 26.8)	22.0 (9.0, 35.0)	0.443

\* one globus patient did not undergo 24-hour pH or MII after HRM

\*\* one control's MII was uninterpretable because of the poor condition of the esophageal mucous membrane

HRM=high-resolution manometry, UES=upper esophageal sphincter, LES=lower esophageal sphincter, MII=multichannel intraluminal impedance, IQR=interquartile range

### 5.1.4 PATIENT HISTORY, EAR, NOSE, AND THROAT EXAMINATION AND VIDEOLARYNGOSCOPY (II)

PPIs were prescribed to 18 (60%) globus patients before referral. However, most of them had used the medication only for a couple of weeks, without benefit. Seven patients (23%) reported voice problems, at least sometimes, at the initial visit. Seven patients (23%) suffered muscle tension in the head and neck. Three patients (10%) had stress. Two patients had depression and used selective serotonin reuptake inhibitor (SSRI) medication. One patient had a bipolar disorder. The median unadjusted and age-adjusted CCI were both 0 (ranges 0-2 and 0-3, respectively), with the CCI being 0 in 87% of patients.

The ENT examination revealed normal findings in 29 patients (97%). Because of lingual tonsil hypertrophy, one patient underwent magnetic resonance imaging (MRI) with normal findings. Neck palpation showed no pathological findings. We scored videolaryngoscopy in 28 patients (93%); in two cases, videos could not be interpreted. None of the patients had more than six points in the RFS.

### 5.1.5 SPEECH AND LANGUAGE PATHOLOGIST INTERVIEWS AND EXAMINATIONS (II)

The SLP interviewed and examined 23 (77%) patients (median age 44, range 22-67 years, and 15 (65%) female) four months (+/-14 days) after their initial visit. Three patients (10%) refused the interview and examination, another four patients answered and returned the follow-up questionnaires, but did not meet the SLP. Based on the SLP's interview and examination, six patients (26%) had functional problems with their voices. Problems were mainly associated with their voice quality (Table 3). They all suffered from persistent globus.

**Table 3.** Results of the speech and language pathologist's examination (study II).

	Normal n (%)	Abnormal n (%)
Vocal quality	17 (74)	6 (26)
Control of the vocal loudness	23 (100)	0 (0)
Control of the vocal pitch	23 (100)	0 (0)
Maximum phonation time	12 (52)	11 (48)
- /a/		
Measure of expiratory control	14 (61)	9 (39)
- /s/		

## 5.2 CHANGES IN GLOBUS AND DYSPHAGIA SYMPTOMS AT FOLLOW-UP (II, III, IV)

### 5.2.1 GLOBUS AT FOUR-MONTH FOLLOW-UP (II)

In study II, 30 globus patients filled in the RSI, DHI and 15-D questions at their initial visit. However, at the four-month follow-up we only received questionnaires from 27 (90%) patients (median age 44, range 22-67), of whom 17 (63%) were female. Globus patients' symptoms improved in the RSI ( $P=0.001$ ) and the DHI ( $P=0.003$ ) (Table 4). In the RSI, 17 (57%) patients

had more than 13 points at the initial visit, referring to an abnormal result. At follow-up, only five patients' (19%) RSI total score was elevated. In DHI, patients' symptoms were relieved on the physical ( $P=0.018$ ) and emotional subscales ( $P=0.004$ ), but not on the functional subscale (Table 4).

At the initial visit in the 15-D, globus patients had worse scores compared to an age-matched sample of the general population on 6 of the 15 dimensions: breathing, sleeping, eating, discomfort and symptoms, vitality, and speech. At the four-month follow-up, globus patients had improved in discomfort and symptoms ( $P=0.023$ ), but were more depressed ( $P=0.033$ ).

**Table 4.** Results from the Reflux Symptom Index and the Deglutition Handicap Index (study II).

	Initial visit n=30	4 month follow-up n=27	
	Median (range)	Median (range)	P value
<b>Reflux Symptom Index</b>	14.0 (3-27)	9.0 (1-22)	0.001
<b>Deglutition Handicap Index</b>	8.5 (0-60)	6.0 (0-45)	0.003
Physical subscale	5.5 (0-19)	4.0 (0-15)	0.018
Functional subscale	0 (0-18)	0 (0-15)	0.419
Emotional subscale	2.0 (0-23)	1.0 (0-15)	0.004

### 5.2.2 GLOBUS AT THE THREE- AND SIX-YEAR FOLLOW-UP (III)

In 2012, at the three-year follow-up, we sent the questionnaire concerning present pharyngeal symptoms to 70 patients who were alive based on the Population Registry, and whose native language was Finnish or Swedish. One patient had deceased, three patients' native language was other than Finnish or Swedish and two patients' contact information was lacking. We received three-year follow-up questionnaires from 37 globus patients (53%); median age was 57.0 (range 24-83) and 28 (76%) were female. In the DHI, the median score was 7.0 (range 0-71), with an elevated total DHI in six patients (17%). No globus symptoms were reported by 11 (38%) patients, 5 (17%) had fewer symptoms than at baseline, 11 (38%) had unchanged symptoms and 2 (7%) had more difficult symptoms. Eight patients' answers were not interpretable or they had not answered that question.

In 2015, a minimum of six years after the initial visit, we sent the same questionnaire again, and received it from 27 globus patients (39%); median age was 60 (range 35-86) and 23 were female (85%). The DHI median was 5.0 (range 0-51) and the total DHI was abnormal in four patients (15%). After six years, 12 (44%) patients had no globus symptoms anymore, two (7%) had less symptoms and 13 (48%) were still experiencing similar symptoms. None had worse symptoms.

In 2012 and 2015, age and gender distributions between responders and non-responders were similar. Follow-up questionnaires from both occasions were available for 22 patients. Between three and six years of follow-up, globus patients' DHI scores and self-ratings regarding present globus symptoms were similar. Moreover, globus self-ratings were similar between those having a suspected identifiable cause for globus at the initial visit and all others.

### 5.2.3 DYSPHAGIA AT THE THREE-YEAR FOLLOW-UP (IV)

Three years after the initial visit, we sent the follow-up questionnaire which included the DHI and a question on whether the patient had anymore dysphagia to 250 dysphagia patients. Based on the Population Registry, 44 patients were deceased and 9 patients' native language was other than Finnish or Swedish. We received questionnaires from 154 patients (62%): 30 (19%) reported no symptoms, 36 (23%) had fewer symptoms than baseline, 43 (28%) had unchanged symptoms, and 12 (8%) had worse symptoms. Patients' reported scores on the DHI are presented in Table 5.

**Table 5.** Patients reported DHI according to diagnostic groups three years after the clinical visit (study IV).

Diagnostic group (n=questionnaires sent)	DHI Median (IQR)	Responders n (%)
Descriptive diagnosis of dysphagia (n=143)	15.0 (8.0, 29.0)	78 (55)
GERD (n=50)	12.5 (4.0, 23.8)	28 (56)
Neurological cause (n=22)	53.0 (9.0, 62.5)	5 (23)
ZD / cricopharyngeus muscle dysfunction (n=16)	20.5 (7.8, 27.3)	10 (63)
Other cause (n=19)	17.0 (10.0, 35.3)	8 (42)

DHI=Deglutition Handicap Index, IQR=interquartile range, GERD=gastroesophageal reflux disease, ZD=Zenker's diverticulum

## 5.3 RESULTS FROM THE MEDICAL RECORDS (III, IV)

### 5.3.1 GLOBUS PATIENTS (III)

In 2009, a total of 76 patients were referred to our clinic because of globus. Their median age was 49.5 (range 20-88) and 59 (78%) were female; age distributions were similar by gender. Eleven patients (14%) had a psychiatric diagnosis and SSRI medication. Of those eleven, seven patients had depression, one had a panic disorder and one a bipolar disorder. Two patients' indication for SSRI medication was not evident. The median unadjusted and age-adjusted CCI were both 0 (ranges 0-5 and 0-7, respectively), and 79% of patients had no comorbidities.

An ENT examination including neck palpation was performed on all patients. Before referral, 23 patients underwent neck ultrasound; additionally, ultrasound was performed at our department on 14 patients. One patient had a palpable goiter, which the neck ultrasound confirmed. Otherwise, findings from the neck ultrasound revealed no additional information about the possible etiology of globus. Before referral, six patients underwent gastroscopy and one duodenal ulcer was diagnosed. Other gastroscopies were normal. At our department, one patient (1%) was examined using TNE with normal findings. After ENT examination, 22 patients (29%) underwent videofluorography. Two patients (9%) had slightly abnormal results, a minor residual of the contrast medium, all other examinations being otherwise normal.

Based on a retrospective analysis of medical records, a suspected cause for globus was evident in 44 (58%). Dry mucous membranes were the most common cause in 13 (17%). Other causes were muscle tension in the neck (12, 16%), psychological cause (6, 8%), problems with voice (5, 7%), lingual tonsil hypertrophy (3, 4%), epiglottis in contact with adjacent structures (3, 4%), goiter (1, 1%) and a sequela after acoustic neurinoma surgery (1, 1%).

During the outpatient visits, globus patients were mainly just advised about the symptom and they received support and reassurance. Patients with dry mucous membranes were instructed to drink enough water and humidify the inhaled air. A PPI was prescribed to 22 patients (29%) as a trial to diagnose possible silent reflux, even though patients had no heartburn. To support smoking cessation, one patient received a bupropion prescription. Three patients received a referral to an SLP and two other patients to a physiotherapist. The patient having a palpable goiter was referred to surgical evaluation and, after thyroid lobectomy, her globus symptom was relieved.

### 5.3.2 DYSPHAGIA PATIENTS (IV)

Based on the hospital database, 303 patients (62% female, median age 64, range 19-99) with dysphagia symptoms were referred to our clinic in 2009. Videofluorography was the investigation performed most frequently (173, 57%). Other performed investigations were FEES (55, 18%), neck ultrasound (36, 12%), EGD (39, 13%), manometry (9, 3%), pH measurement (4, 1%) and TNE (2, 1%). Most investigation findings were normal (Table 6).

According to retrospective analysis of medical records, most dysphagia patients investigated at our ENT clinic remained with a descriptive diagnosis of dysphagia, unspecific dysphagia (167, 55%). Specific causes for patients' dysphagia included suspected GERD in 52 (17%), neurological cause in 33 (11%), and Zenker's diverticulum or cricopharyngeus muscle dysfunction in 26 (9%) subjects. Dysphagia was related to sequelae of head and neck surgery or treated head and neck malignancies in 18 (6%) cases. Moreover, one patient had a palpable tumor in the neck that was later diagnosed as a goiter. A new malignant disease was diagnosed in five patients. In all cases, the status or suspicion of malignancy was evident at the initial visit. Three esophageal cancers were diagnosed in EGD; all of these patients had progressive dysphagia with food impaction in the esophagus. ENT examination revealed one laryngeal and one oropharyngeal cancer.

Most of the patients only received instructions during their clinical visit. A PPI was prescribed to 86 (28%) patients, 49 patients (16%) were referred to an SLP, and 7 (2%) to a physiotherapist. An endoscopic diverticulectomy with stapler was performed on four patients with Zenker's diverticulum. One patient with cricopharyngeal muscle dysfunction underwent cricopharyngeal myotomy and another underwent esophageal dilatation. Percutaneous endoscopic gastrostomy was performed on two patients.

**Table 6.** Examinations performed to dysphagia patients in 2009 (study IV).

Examination	Normal n (%)	Abnormal n (%)	Not done n (%)
Videofluorography	117* (38)	56 (18)	130 (43)
Neck ultrasound	26 (9)	10 (4)	267 (88)
FEES	25 (8)	30 (10)	248 (82)
Esophagogastrosopy	23 (8)	16 (5)	264 (87)
TNE	2 (1)	0 (0)	301 (99)
Manometry	6 (2)	3 (1)	294 (97)
pH measurement	3 (1)	1 (0)	299 (99)

\* Includes 44 patients with slight abnormalities.

FEES=fibroptic endoscopic evaluation of swallowing, TNE=transnasal esophagoscopy

## **5.4 THE FINNISH CANCER REGISTRY DATA (III, IV)**

In study III, the FCR data confirmed that during the three-year follow-up from 2009 to 2012, none of the globus patients developed malignancy in the head and neck area or in the aerodigestive track, of which globus could have been an early sign at the initial visit in 2009.

In study IV, based on the FCR data, none of the dysphagia patients had a new diagnosis of malignancy in the head and neck area or in the aerodigestive tract, which would not have already been identifiable in 2009.



## **6 DISCUSSION**

This thesis aimed to investigate the possible esophageal background of globus, to clarify globus and dysphagia diagnostics and to present the natural course of these symptoms and their potential as an early sign of malignancy. Our results indicate that globus patients without reflux symptoms did not have acid or non-acid GERD, their UES pressure was normal and major esophageal motor disorders were uncommon. However, supragastric belching was evident in globus patients more often than in controls with reflux symptoms. The three- and six-year follow-ups showed that some patients may suffer from persistent globus. However, the FCR data confirmed that globus was not an early sign of malignancy at the three-year follow-up. Many swallowing difficulties were mild and no specific diagnosis could be assessed. Dysphagia patients who did not suffer from alarming signs or whose ENT status was normal did not develop a malignancy at the three-year follow-up. This study emphasizes the need for careful clinical examination in determining whether further investigations are warranted in dysphagia diagnostics.

### **6.1 GLOBUS PATIENTS' CHARACTERISTICS**

In our prospective studies (I, II), the median age of the 30 globus patients was 45 (range 22-67) and 67% were female. In our retrospective study (III), women comprised 78% of the study population and the median age of all 76 globus patients was 49.5 (range 20-88). Consequently, the age and gender distribution was similar to what previous studies have reported (Moloy & Charter 1982, Batch 1988a). Although women may seek healthcare more often, globus probably affects women under 50 years of age in particular (Moloy & Charter 1982, Batch 1988a, Galmiche et al. 2006). In studies I, II and III, the CCI indicated that globus patients were in good health overall. This result is inline with the finding that globus is a common symptom in otherwise healthy subjects (Thompson & Heaton 1982).

### **6.2 THE ESOPHAGEAL BACKGROUND OF GLOBUS**

For decades, GERD has been considered one of the main causes for globus, although strong evidence is still lacking. The positive association between globus and GERD, however, has only been investigated with outdated and inaccurate methods in small samples (Malcomson 1968, Koufman 1991). It has also been unclear whether non-acid GERD may cause globus. In addition, globus has been connected to esophageal motor disorders and elevated UES pressure, but diagnoses are based on findings using conventional manometry (Watson & Sullivan 1974, Färkkilä et al. 1994). Currently, novel investigation methods, HRM and 24-h MII-pH are available for more precise diagnostics. In this study (I), we recruited 30 globus patients to investigate whether TNE, HRM, and 24-h MII-pH could clarify the esophageal background of globus.

We found that globus patients without reflux symptoms did not have acid GERD in 24-h MII-pH. Moreover, these patients' videolaryngoscopies revealed no LPR, as scored with the RFS, an eight-item severity scale developed to evaluate patient's laryngeal findings that are suggestive of LPR (Belafsky et al. 2001). The RFS has been criticized because laryngeal findings suggesting reflux may be present in 70% of healthy subjects as well (Hicks et al. 2002). However, our patients' findings in videolaryngoscopy were inline with those in 24-h MII-pH.

It has been speculated that globus patients may have non-acid GERD, which would explain why they do not benefit from PPIs. In our study, 24-h MII-pH also excluded non-acid GERD as a cause of globus patients' symptoms. Nevertheless, globus patients without heartburn often receive a PPI prescription, perhaps as a trial to diagnose silent reflux. In study I, 60% of globus patients had received a PPI prescription before referral to our clinic. Moreover, in study III one-third of globus patients were prescribed a PPI in our clinic. High-dose PPIs are, however, no more effective than placebo in the treatment of globus (Noordzij et al. 2001, Vaezi et al. 2006). Furthermore, PPIs may have long-term side effects, requiring justification for use of this medication (Ali et al. 2009). One globus patient in study I had a pathologic amount of proximal reflux and a prolonged total reflux time in 24-h MII-pH, but she reported afterward that she had recently been experiencing reflux symptoms. Currently, it is recommended that if globus is directly related to reflux, the diagnosis is GERD instead of globus (Galmiche et al. 2006).

In 24-h MII-pH, supragastric belching was diagnosed in globus patients more often than in controls. Belching is a physiological event to release the intragastric air that one has swallowed. However, a supragastric belch is generated when a rapid suction of air into the esophagus is expelled before it reaches the stomach. Some studies suggest a relationship between supragastric belching and GERD (Hemmink et al. 2009a). Nevertheless, supragastric belching in globus patients is a novel finding. Different mechanisms for how a supragastric belch is created have been described. A patient may contract pharyngeal muscles to draw air into the esophagus or breathe in through a closed glottis (Bredenoord 2010). Aerophagia, which indicates increased swallowing of air, was also diagnosed more often in globus patients than in controls. Speech therapy techniques have been demonstrated to alleviate symptoms in patients with supragastric belching (Hemmink et al. 2010). It is possible that some globus patients may contract their pharyngeal muscles inappropriately because of their lump sensation, which may lead to supragastric belching and aerophagia. In the future, increased use of 24-h MII-pH may clarify the connection between globus and supragastric belching or aerophagia. Because speech therapy may be helpful in supragastric belching, 24-h MII-pH may be considered for globus patients with prolonged and inconvenient symptoms.

HRM revealed an esophageal motor disorder in half of the globus patients diagnosed by the Chicago classification (Bredenoord et al. 2012). However, motor disorders were mainly minor and were similar to those that can also be detected in healthy subjects (Kahrilas et al. 2015). Two globus patients had a diagnosis of a major motor disorder: one with absent peristalsis and one with EGJ outflow obstruction, a subtype of achalasia. Patients with absent peristalsis may complain of dysphagia, odynophagia, heartburn, and regurgitation. However, manometric findings poorly correlate to a patient's symptoms and a patient with absent peristalsis may be asymptomatic as well (Smout & Fox 2012). In achalasia, a patient usually has difficulties in swallowing both solids and liquids and complains of chest pain (Vaezi & Richter 1999). One study of 21 globus patients presented a few patients with achalasia, decreased peristalsis and segmental aperistaltics measured by conventional manometry (Färkkilä et al. 1994). In that sample, motor disorders were mainly nonspecific which, at that time, referred to disorders other than achalasia, spasm, nutcracker esophagus, or LES dysfunction. A study by Moser et al. (1991) revealed that 7 globus patients out of 30 had achalasia and the authors discussed whether the globus sensation might precede further dysphagia. Because our patients with major motor disorders lacked dysphagia, they did not receive any treatment. Esophageal motor disorder as an etiologic cause for globus is an interesting possible explanatory mechanism, but requires further research with larger, prospective settings with the use of HRM.

In HRM, the globus patients' mean basal and residual UES pressures were within normal limits and the differences between globus patients and controls were statistically non-significant. Choi et al. (2013) compared globus patients, GERD patients, and normal controls and found a non-statistically significant difference in UES basal pressure. Moreover, a study of globus patients, dysphagia patients, and normal controls indicated that the mean UES basal pressure was normal in globus patients and controls (Peng et al. 2015). However, in their multivariate model, a measurable UES residual pressure independently predicted globus. Both of these studies were retrospective. The findings in our prospective study support the assumption that elevated UES pressure does not cause globus.

In TNE, 10% of globus patients had endoscopic esophagitis defined by the LA Classification system (Lundell et al. 1999). However, one study among a normal population without reflux symptoms showed that esophagitis was diagnosed in 9.5%, using gastroscopy (Ronkainen et al. 2006). One-third of the globus patients had a histological finding of esophagitis, which was more frequent than in control patients with reflux, however, that difference did not reach statistical significance. The controls' regular use of PPIs likely diminished their histological findings of esophagitis. However, different pathologists analyzed our specimens, which may have caused variation due to their subjective opinions. In addition, the histological diagnosis depends on how representative the specimen is.

TNE is considered a well-tolerated investigation method and our patients did not experience any complications. We also showed that taking a hypopharyngeal biopsy is possible during TNE. However, one-third of the patients refused HRM and 24-h MII-pH after TNE, which may indicate that the experience was unpleasant for some patients. On the other hand, the knowledge that there was not any lump causing the symptom may have reassured the patient enough and they found further investigations unnecessary.

In our study (I), TNE was performed by both an otorhinolaryngologist and a gastroenterologist together and also included investigation of the stomach and the beginning of the duodenum, but the examination showed no benefit in globus diagnostics. Moreover, the biopsies, including those from the hypopharynx, did not reveal any additional findings, such as eosinophilic esophagitis in globus patients, in this sample. In study III, TNE was performed on only one patient and the findings were normal. Six patients underwent EGD with five normal findings and one duodenal ulcer. Study III showed that endoscopy was not a common investigation method in our clinic and that there was no benefit to its use. Although, endoscopy has not been found useful in globus diagnostics, surveys to clinicians reveal that many have preferred to examine globus patients with the method (Webb et al. 2000).

### **6.3 OTHER ETIOLOGICAL FACTORS IN GLOBUS**

Globus patients typically have an ENT examination within normal limits, causing a diagnostic and therapeutic problem. Also, in our studies, globus patients' findings in ENT examination were minor and rare. In study II, none of the globus patients had any pathological neck palpation findings. In study III, one patient had a palpation finding of goiter. In study II, the ENT examination was normal in all cases except in one patient with a lingual tonsil hypertrophy. In study III, the clinicians considered lingual tonsil hypertrophy as a cause of globus in 4% of patients. However, causality of the findings is hard to determine, although some studies suggest that severe hypertrophy of the tongue base may cause globus (Mamede et al. 2004). Furthermore,

other local anatomical causes, such as the epiglottis touching the base of the tongue or the posterior pharyngeal wall, were suspected in single cases in study III. Partial epiglottectomy with CO<sub>2</sub> laser relieved symptoms in globus patients with the epiglottis touching the base of their tongue in a study by Agada et al. (2007). However, because controls were lacking, the procedure itself may have had a placebo effect.

In study III, the retrospective analysis of medical records showed that clinicians had determined the possible cause for a patient's globus in half of the cases. The most common cause was suspected to be dry mucous membranes in 17%. The side effects of a patient's medication or drinking too little water may cause xerostomia and lead to thick mucus in the throat, causing a globus sensation. However, only one study has investigated the relationship between globus and epipharyngeal stagnant mucus (Shiomi et al. 2002). After dry mucous membranes, muscle tension in the neck (16%) and voice disorders (7%) were the conditions second and the third most suspected for causing globus. In study II, the SLP interviewed and examined globus patients, and a functional voice problem was found in 26%. Other studies clarifying globus patients' possible voice disorders are lacking. However, a controlled study by Khalil et al. (2003) showed that globus patients felt significant improvement in their symptoms in the speech therapy group compared to the group receiving only reassurance. Also, Wareing et al. (1997) suggested that laryngeal and pharyngeal tension may be partly associated with the globus symptom, finding in their non-controlled study that 92% of globus patients felt improvement in their symptoms after speech therapy. However, it has been shown that when treating patients with non-organic dysphonia, speech therapy also has statistical benefit in decreasing patients' autonomic symptoms that are unrelated to voice (Demmink-Geertman & Dejonckere 2008). Therefore, whether the globus patient benefits from a specific speech therapy or the attention itself remains ambiguous.

Historically, globus was considered solely a psychological problem. Although the understanding has changed, the psychological background is considered to be one etiologic cause. In study II, 10% of globus patients declared stress to be a factor in their lives. In study III, a concomitant psychological cause was evident in 8%. Those patients had simultaneously reported a stressful period of life with the occurrence of the globus. One case-control study observed that before the globus appeared, the patients had experienced a significant event in their lives (Deary et al. 1992). Moreover, another study found that, throughout the year before the globus onset, globus patients confronted severe life events more often than controls (Harris et al. 1996). These findings are inline with ours in studies II and III.

In study II, only a few patients had a diagnosis of depression (7%) or a bipolar disorder (3%). In study III, based on medical records, 14% had an SSRI medication and a psychiatric diagnosis, depression being the most prevalent (9%). Currently, about 6% of the Finnish population has the diagnosis of depression (Ferrari et al. 2013). Accordingly, in studies II and III, the distribution of depression is quite similar compared to the Finnish general population. A Finnish study by Färkkilä et al. (1994) concluded that psychiatric diagnoses among globus patients did not differ from that of the general population. In contrast to their study, in both of our samples the psychiatric diagnoses were assessed before the patients were referred to the ENT clinic, while their study included a psychiatrist who evaluated the patients. In study II, the globus patients filled in the 15-D, which includes a question about depression. At baseline, globus patients were not more depressed than age-matched general population subjects, but at the four-month follow-up globus patients were more depressed. However, it is possible that in our small sample, a single patient's outcome may have skewed the results.

## 6.4 RADIOLOGICAL EXAMINATIONS IN GLOBUS DIAGNOSTICS

Currently, studies concerning neck ultrasound and globus focus on thyroid pathology only. In study III, our review of the medical records revealed that neck ultrasound was performed on half of the globus patients. However, it was only useful in one patient who already had a palpable finding of an enlarged thyroid, which the ultrasound confirmed to be a goiter. Other neck ultrasounds were within normal limits. An enlarged thyroid may cause compression symptoms and may also induce globus. In one prospective study, one third of patients with a thyroid mass complained of globus-like symptoms (Burns & Timon 2007). Our patient underwent thyroid lobectomy and became asymptomatic. Also, in the study by Burns & Timon (2007) 80% of patients felt that their globus was relieved after surgery. However, all surgical procedures may, themselves, have a curative effect and spontaneous recovery cannot be excluded completely.

Some studies have suggested that thyroid nodules could also cause globus. One study showed that thyroid nodules larger than 3 cm, when locating anterior to the trachea, had an association with globus (Nam et al. 2015). In study III, one patient had a finding of a small, under 1 cm, thyroid nodule in neck ultrasound. She also had pain in palpation and therefore was referred for an MRI. The examination was unsuccessful, however, because she suffered a panic attack. After four years, she felt a palpable tumor in her neck, which was revealed to be thyroid cancer. As Nam et al. (2015) concluded, an association of small thyroid nodules with globus is improbable. Furthermore, our study showed that neck ultrasound did not provide any benefit in globus diagnostics if there were no pathological palpation findings in the neck. Consequently, neck ultrasound should be considered for globus patients only when palpable findings exist.

Videofluorography was performed on almost one-third of globus patients in study III, but showed no benefit in diagnostics. Our result is inline with other studies that have used radiographic swallow examinations in globus diagnostics (Luk et al. 2014, Dworkin et al. 2015). Videofluorography is one of the gold standards in otorhinolaryngological practice for dysphagia diagnostics. However, globus patients without swallowing difficulties should not be examined with these procedures because they unnecessarily expose patients to a radiation load.

Indeed, one reason to perform examinations, such as videofluorography or neck ultrasound, is the need to convince the patient, and sometimes the clinician, that the globus is harmless. However, these examinations are not beneficial in globus diagnostics and should be avoided. In addition, it is assumed that a patient will be satisfied if the clinician explains why further examinations are not necessary.

## 6.5 GLOBUS – PROGNOSIS AND THE FINNISH CANCER REGISTRY DATA

In study II, we had the baseline and four-month follow-up questionnaires from 27 (90%) globus patients. During this four-month period, most patients underwent TNE, HRM, and 24-h MII-pH, but they received no special treatment. The four-month follow-up ended, when globus patients met the SLP. During this visit, three patients disclosed that because they underwent the ENT examination and TNE with normal findings they were convinced that their globus was harmless.

Based on the baseline and follow-up questionnaires in study II, globus patients felt improvement in their symptoms, as measured by the RSI and DHI. Although these questionnaires



are not specifically targeted to globus patients, they are frequently used in our clinic, which is why they were chosen. In study II, globus patients' symptoms had a median duration of six months at the initial visit. However, the exact duration of the symptoms was difficult to estimate for many patients. A study by Timon et al. (1991) ascertained that globus symptoms experienced for only a short duration predicted faster recovery. This is inline with our finding in study II that most of the patients' symptoms had lasted a quite short time at their initial visit and that symptoms also significantly recovered during our short four-month follow-up.

The RSI is used to evaluate possible laryngeal symptoms relating to LPR. Belafsky et al. (2002) showed the usefulness of the RSI in a study where they used it before and after treatment and found that symptoms for LPR patients alleviated after PPI medication. In our study, GERD and LPR were excluded in globus patients with normal results from 24-h MII-pH and, furthermore, although they did not receive any treatment, they felt that their symptoms were relieved, as measured by the RSI. At the initial visit, over half of the patients had elevated scores suggesting LPR, but after the follow-up only 19% had elevated scores. Therefore, the RSI was useful in evaluating the recovery of globus patients' symptoms because the results were similar in the RSI and DHI. However, the RSI was not useful for diagnosing LPR.

The DHI is a quality-of-life questionnaire directed for use in dysphagia patients (Woisard et al. 2006). Overall, globus patients had low scores in the DHI in studies II and III, as was suspected. We thought that the emotional subscale of the DHI would have been particularly useful for surveying globus patients' symptoms and for better understanding how globus concerns them as well. During the follow-up of study II, total DHI scores, as well as the physical and emotional subscales, improved, but the functional subscale did not change, suggesting that those symptoms are experienced more permanently.

In the 15-D, globus patients had worse scores in six dimensions compared with age-matched general population subjects at the initial visit. However, at the follow-up, globus patients did improve, though in only one subscale, but also felt more depressed. Consequently, the scores from the 15-D did not improve as the scores in the RSI and DHI did at follow-up. However, the RSI and DHI are concentrated on pharyngeal symptoms while the 15-D focuses on different parts of a patient's life. Accordingly, our study suggests that globus symptoms may alleviate quite fast, but whether the alleviation is caused by spontaneous recovery, fluctuating symptoms or patients benefiting from evidence that their symptoms are harmless remains unanswered.

In study III, globus patients initially examined in our clinic in 2009 received a questionnaire concerning their present symptoms three and six years later. At both follow-ups, approximately half of the patients reported that they were asymptomatic or that they had fewer symptoms than at the initial visit. However, almost half of the patients felt that their symptoms were the same at follow-ups. Whether the patient had a suspected cause for his or her globus did not influence these globus self-ratings. Our follow-up time was at least six years from the initial visit; consequently, our results regarding the persistence of globus are inline with other studies with average follow-ups of 27 months and 7.6 years (Timon et al. 1991, Rowley et al. 1995).

In study III, the FCR data confirmed that during the three-year follow-up none of the 76 globus patients developed a malignancy in the upper aerodigestive tract or in the head and neck area, of which globus could have been an early symptom. In a study by Rowley et al. (1995) none of the 74 globus patients developed an upper aerodigestive track malignancy during the seven-year follow-up. However, that study was based on a questionnaire, and if a patient noted they were symptomatic, re-examination was performed. In our study (III), the data were collected from the FCR, thus, no cases of cancer were missed. Moreover, in studies I and III, TNE and EGD

revealed no tumors, which is inline with other studies (Takwoingi et al. 2006). Consequently, a malignancy should not be suspected in a patient with typical globus.

## 6.6 DYSPHAGIA – CAUSES AND OUTCOME

In study IV, we had 303 dysphagia patients who were referred to our clinic in 2009. Some patients' symptoms were mild and occurred only occasionally. Consequently, the clinicians prescribed no further examinations to those patients and patients received only instructions. Over half of the patients underwent videofluorography. A suspicion of structural abnormalities, for example Zenker's diverticulum, is an indication for videofluorography. Videofluorography also enables evaluation of the swallowing process, cricopharyngeus muscle dysfunction and can reveal possible aspiration. However, Zenker's diverticulum and cricopharyngeus muscle dysfunction were evident in only 9%. In most cases, the videofluorography result was normal. Accordingly, many of the investigations could have been avoided by taking a more careful patient history. Spieker (2000) concluded that a careful patient history might reveal the cause of dysphagia in up to 85% of cases.

FEES was the second most often performed examination. It is both a diagnostic and therapeutic procedure and enables clinicians to properly instruct patients with a swallowing difficulty. FEES is recommended to be performed on patients with oropharyngeal dysphagia of a neurological origin if there is a need to evaluate the safety of swallowing; it also serves as a rehabilitation procedure. In our study, patients with neurogenic dysphagia had usually already had their neurological diagnosis and had come for consultation. However, a few patients, whose oropharyngeal dysphagia was later diagnosed as neurogenic, were referred to our clinic first. The ENT examination, which included testing of the neurological background of swallowing, aroused the suspicion of a neurological cause and directed these patients to further consultation. Accordingly, an ENT examination should always include neurological testing when examining patients with oropharyngeal dysphagia (Figure 1).

Neck ultrasound was performed in 12% of dysphagia patients. The reason for ultrasound was probably to diagnose a possible goiter causing a patient's swallowing difficulty. However, based on medical records, only one patient had a goiter and it was already evident in neck palpation. She underwent thyroidectomy and felt her dysphagia was relieved. Patients with goiter who complain of swallowing difficulties preoperatively experience significant improvement in their symptoms after thyroidectomy (Greenblatt et al. 2009). Although it is possible that an enlarged thyroid may cause compression and impair swallowing, such an enlargement seen in a neck ultrasound would most likely have been palpable as well. Consequently, compression symptoms concomitant with an enlarged thyroid are usually related to the size of the thyroid (Banks et al. 2012). However, retrosternal goiter, which may cause dysphagia, usually requires computed tomography, or MRI, for the diagnosis (Shaha 1990).

EGD, TNE, manometry and pH measurement were performed only on a limited amount of patients in our clinic, since these are investigations used in esophageal dysphagia. A substantial amount of patients whose dysphagia symptoms affect the esophageal phase of swallowing are usually referred to gastroenterological units for EGD. However, based on the medical records, a suspicion of GERD (17%) was the most often identifiable cause for patients' symptoms in our sample. GERD is known to be the most common cause for esophageal dysphagia (Watson & Lally 2009). In our study, the diagnosis was usually based on patients' alleviation of symptoms with

PPI. To diagnose possible GERD, empiric PPI therapy is permitted, but those whose symptoms do not resolve should be examined further with EGD (Katz et al. 2013).

There were only a few dysphagia patients with malignancy, and in all cases the suspicion was already evident. The diagnoses were revealed in either the ENT examination or an EGD was performed because of the patient's progressive dysphagia and food impaction in the esophagus. Alarming signs and findings, such as weight loss, progressive dysphagia symptoms with food impaction in the throat or esophagus require immediate evaluation to exclude a malignancy. In our study, the FCR data confirmed that if the patient lacked these alarming signs and the ENT examination was normal, the patient's symptom did not develop into a malignancy during the three-year follow-up. This emphasizes the importance of taking a careful patient history along with the ENT examination.

The survey of medical records revealed that the cause of the dysphagia patient's symptoms remained unclear in 55%. Some dysphagia symptoms may occur only occasionally, may be related to hasty eating habits or have a psychological background. Hoy et al. (2013) retrospectively investigated 100 dysphagia patients' diagnoses at their tertiary-care voice and swallowing center and the cause of dysphagia remained unspecific in 20%. They speculated that mucosal hypersensitivity and a psychological background, including malingering, were possible causes for those patients' symptoms.

The questionnaire concerning patients' current symptoms at the three-year follow-up revealed that almost half of the dysphagia patients felt that their symptoms had alleviated or disappeared. As seen in the patients' DHI scores, those with neurogenic dysphagia had the worst scores, indicating that neurogenic dysphagia is more often permanent and progressive. However, patients whose dysphagia remained unspecific indicated a low median score in the DHI, suggesting that their symptoms were mild and likely did not worsen remarkably during the follow-up.

Dysphagia is a multifaceted symptom. With a careful patient history, a clinician must first distinguish at what phase of swallowing the problem is located: oral, pharyngeal, or esophageal phase. Possible neurological symptoms and signs should be noted and patients with alarming signs suggesting a malignancy require immediate examination. Based on our study and experience, we created algorithms to guide how best to examine patients with oropharyngeal (Figure 4) and esophageal dysphagia (Figure 5). Evaluation of dysphagia patients in the right place, at the right time safeguards against both wasted resources and delays in investigating the patients' symptoms.

## 6.7 LIMITATIONS OF THE STUDY

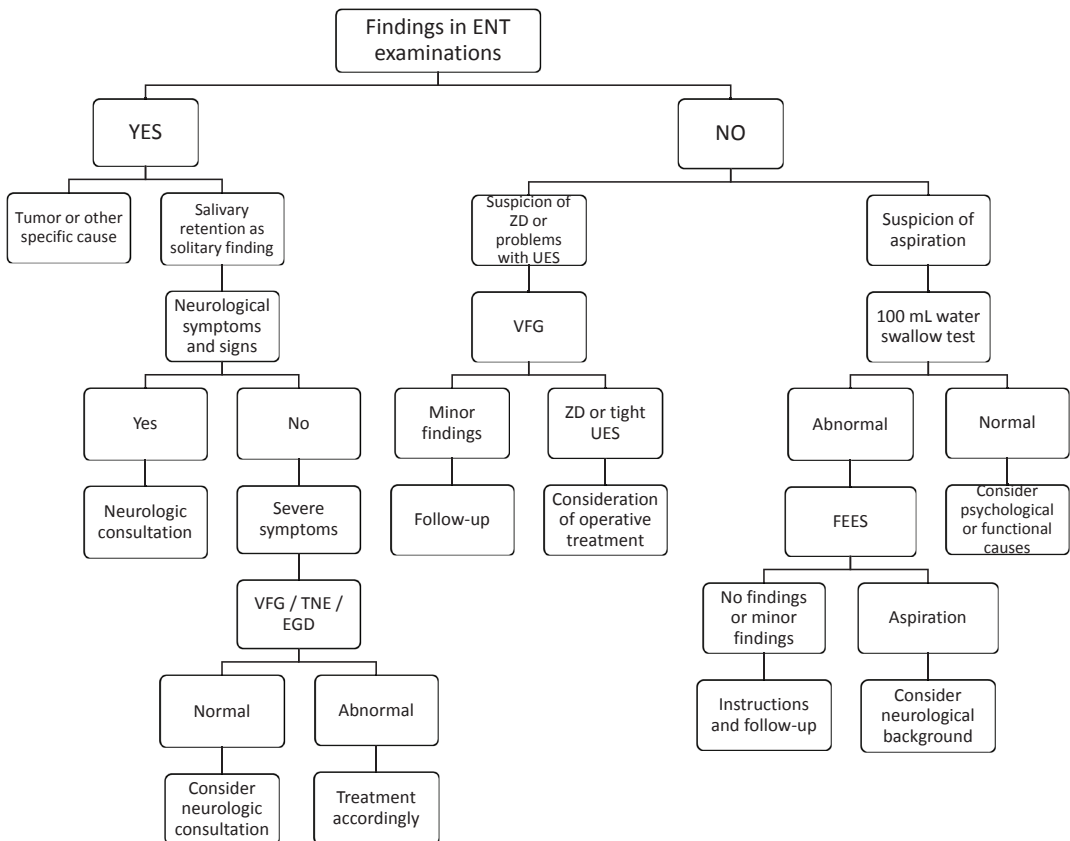
In study I, we were only able to recruit a limited number of patients due to the study's resource-demanding setting. The invasive investigations may be the reason that one-third of globus patients refused HRM and 24-h MII-pH after TNE, which reduced the available data. The relatively low number of globus patients and controls may cause false positive results (type I error), but based on our power calculation, this seems unlikely. In study II, we did not have a psychiatrist who could have evaluated the psychological state of patients, however, it is possible that some patients would have felt uncomfortable in that setting and may have refused. Furthermore, we did not use a depression questionnaire, but the 15-D did contain one question regarding depression. The fact that we had no normal controls with an SLP interview and examination is a limitation. Moreover,



patients' voice evaluations could have been more precisely documented. Since studies III and IV were retrospective, some medical records were deficient and lacked the clinician's opinion of the reason causing the patient's symptom. Additionally, since the FCR data are published with a delay, we only had data through the end of 2012. In studies III and IV, there may be a small chance of a false negative result (type II error) because the follow-up time was only three years and malignancy is supposed to be rare in these patient groups. In patient surveys, response rates are often low, indeed, in studies III and IV, we only received answers from 39-62% of patients, which may reduce the reliability of the study.

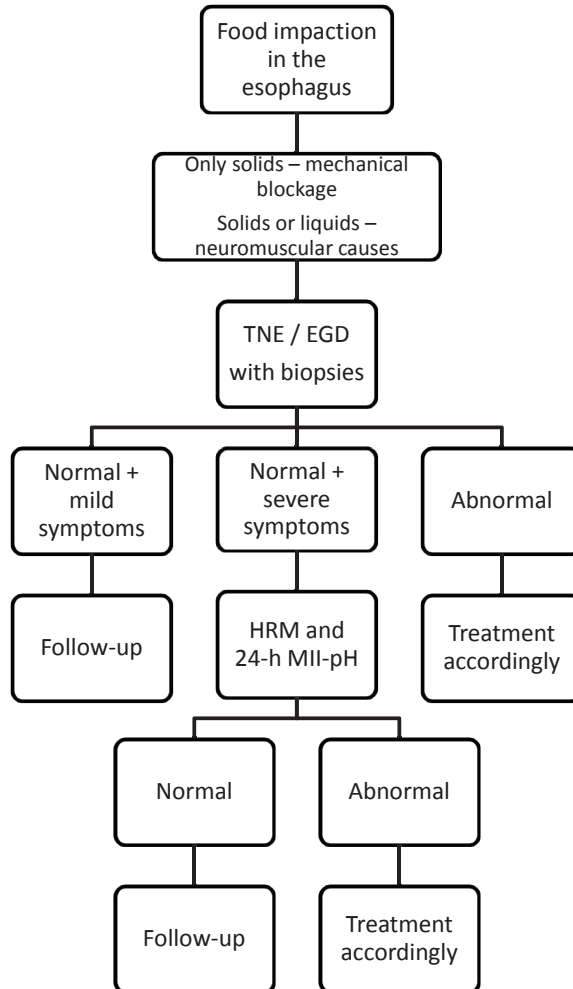
## 6.8 FUTURE PERSPECTIVES

Currently, new investigation methods, such as HRM and 24-h MII-pH, enable more accurate diagnostics and further studies will clarify if our findings of supragastric belching, aerophagia and major esophageal motor disorders are overrepresented in globus patients. This knowledge would also enhance the available treatment options since treatment has mainly been to give reassurance to the patients. Some globus patients seem to have a coexisting voice problem, which may increase the SLP's role in globus diagnostics and treatment.



**Figure 4** Algorithm for oropharyngeal dysphagia diagnostics. ENT=ear, nose, and throat; VFG=videofluorography; TNE= transnasal esophagoscopy; EGD=esophagogastroduodenoscopy; ZD=Zenker's diverticulum; UES=upper esophageal sphincter; FEES=fiberoptic endoscopic evaluation of swallowing.

In our study, dysphagia patients underwent many investigations with mainly normal findings. Accordingly, many investigations were performed unnecessarily. The use of an algorithm would allow for diagnosing dysphagia patients in a more systematic way. Multidisciplinary cooperation in the diagnostics and treatment are also warranted in order to use resources sensibly and for the best care of the patient. It would be beneficial to consider whether dysphagia clinics in tertiary care units could improve patient care in the future.



**Figure 5** Algorithm for esophageal dysphagia diagnostics.

TNE=transnasal esophagoscopy; EGD=esophagogastroduodenoscopy;

HRM=high-resolution manometry; 24-h MII-pH=24-hour multichannel intraluminal impedance and pH monitoring

## 7 CONCLUSIONS

1. Globus patients without reflux symptoms did not have acid or non-acid gastroesophageal reflux disease in 24-hour multichannel intraluminal impedance (MII) and pH monitoring. However, in MII, globus patients had supragastric belching more often than controls with reflux symptoms, suggesting its role in some globus patients' symptoms. The upper esophageal sphincter pressure was not elevated in globus patients in high-resolution manometry (HRM). If an esophageal motor disorder was diagnosed in HRM, it was usually a minor disorder, often also detected in healthy subjects. Moreover, transnasal esophagoscopy with biopsies, including examination of the stomach and the beginning of the duodenum, showed no benefit in globus diagnostics.
2. Globus patients showed significant symptom relief at the four-month follow-up, as measured by the Deglutition Handicap Index and the Reflux Symptom Index. The speech and language pathologist's interview and examination revealed 6 (26%) globus patients with functional voice problems, possibly associated with persistent globus.
3. Neck ultrasound was not beneficial in patients whose neck palpation was normal. Moreover, videofluorography did not add any clinically relevant information in globus diagnostics.
4. After a three- and six-year follow-up, almost half of the globus patients experienced persistent symptoms, indicating that globus may cause long-term discomfort. The Finnish Cancer Registry (FCR) data verified that none of the globus patients developed a malignancy over the three-year follow-up. Dysphagia patients without alarming signs or findings in the ear, nose, and throat examination revealed no malignancies during a three-year follow-up, confirmed by the FCR. Almost half of the dysphagia patients became asymptomatic or had fewer symptoms after three years, indicating the possible spontaneous recovery of the condition.

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## APPENDICES

### APPENDIX 1. THE REFLUX FINDING SCORE (RFS)<sup>1</sup>

Pseudosulcus (infraglottic edema)	0=Absent, 2=Present
Ventricular obliteration	2=Partial, 4=Complete
Erythema and hyperemia	2=Arytenoids, 4=Diffuse
Vocal fold edema	1=Mild, 2=Moderate, 3=Severe, 4=Polypoid
Diffuse laryngeal edema	1=Mild, 2=Moderate, 3=Severe, 4=Obstructing
Posterior commissure hypertrophy	0=Absent, 2=Present
Granuloma/granulation tissue	0=Absent, 2=Present
Thick endolaryngeal mucus	0=Absent, 2=Present

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<sup>1</sup> A total score over six is considered suggestive of laryngopharyngeal reflux.

## APPENDIX 2. THE REFLUX SYMPTOM INDEX (RSI)<sup>2</sup>

Within the last month, how much did the following problems affect you? Circle the appropriate response	0=No Problem						5=Severe problem					
	1. Hoarseness or a problem with your voice	0	1	2	3	4	5	0	1	2	3	4
2. Clearing your throat	0	1	2	3	4	5	0	1	2	3	4	5
3. Excess throat mucus or postnasal drip	0	1	2	3	4	5	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5	0	1	2	3	4	5
5. Coughing after you eat or after lying down	0	1	2	3	4	5	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5	0	1	2	3	4	5
8. Sensation of something sticking to your throat or a lump in your throat	0	1	2	3	4	5	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5	0	1	2	3	4	5
	Total											

<sup>2</sup> A total score over 13 is considered abnormal, suggesting laryngopharyngeal reflux.



### APPENDIX 3. THE DEGLUTITION HANDICAP INDEX (DHI)<sup>3</sup>

<b>Physical subscale</b>	N	AN	S	AA	A
I feel discomfort when I swallow	0	1	2	3	4
Food sticks or stays blocked in my throat	0	1	2	3	4
I have difficulty swallowing liquids	0	1	2	3	4
I cough or clear my throat during or after a meal	0	1	2	3	4
I suffocate when eating or drinking	0	1	2	3	4
I feel food or liquid coming up after a meal	0	1	2	3	4
I have difficulty chewing	0	1	2	3	4
Food comes up to my nose when I eat or drink	0	1	2	3	4
I dribble when I eat	0	1	2	3	4
My throat hurts when I swallow	0	1	2	3	4
<b>Functional subscale</b>					
I am unable to eat certain foods because of my swallowing difficulties	0	1	2	3	4
I have to modify the consistency of my food in order to swallow	0	1	2	3	4
It takes longer to eat a meal because of my swallowing difficulties	0	1	2	3	4
I eat less because of my swallowing problems	0	1	2	3	4
I am still hungry or thirsty after a meal	0	1	2	3	4
I am tired because of my swallowing problems	0	1	2	3	4
I have lost weight because of my swallowing difficulties	0	1	2	3	4
I am afraid of eating	0	1	2	3	4
I have had bronchitis or pulmonary infections more often since my swallowing problems	0	1	2	3	4
I have more trouble breathing since my swallowing problems	0	1	2	3	4
<b>Emotional subscale</b>					
I avoid eating with others because of my swallowing difficulties	0	1	2	3	4
My swallowing problem limits my personal or social life	0	1	2	3	4
I am bothered by the way I eat during meals	0	1	2	3	4
Eating has become a disagreeable time because of my swallowing problems	0	1	2	3	4
I find that others do not understand my swallowing problems	0	1	2	3	4
Others seem to be irritated by my swallowing problems	0	1	2	3	4
I am tense when I eat with others because of my swallowing problems	0	1	2	3	4
I am ashamed of my swallowing problem	0	1	2	3	4
I feel handicapped because of my swallowing difficulties	0	1	2	3	4
<b>Total</b>					

N=never, AN=almost never, S=sometimes, AA=almost always, A=always

<sup>3</sup> A total score over 20 and/or 9 points or more in a subscale is considered abnormal.

## **APPENDIX 4. THE 15-DIMENSIONAL MEASURE OF HEALTH-RELATED QUALITY OF LIFE (15-D)**

Please read through all of the alternative responses to each question before placing a cross (x) for the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

### **QUESTION 1. MOBILITY**

- 1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
- 2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
- 3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
- 4 ( ) I am able to walk indoors only with help from others.
- 5 ( ) I am completely bed-ridden and unable to move about.

### **QUESTION 2. VISION**

- 1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
- 2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
- 3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
- 4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
- 5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

### **QUESTION 3. HEARING**

- 1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
- 2 ( ) I hear normal speech with a little difficulty.
- 3 ( ) I hear normal speech with considerable difficulty; in conversation, I need voices to be louder than normal.
- 4 ( ) I hear even loud voices poorly; I am almost deaf.
- 5 ( ) I am completely deaf.

### **QUESTION 4. BREATHING**

- 1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
- 2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
- 3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
- 4 ( ) I have shortness of breath even after light activity, e.g. washing or dressing myself.
- 5 ( ) I have breathing difficulties almost all the time, even when resting.

### **QUESTION 5. SLEEPING**

- 1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
- 2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
- 3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
- 4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
- 5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

**QUESTION 6. EATING**

- 1 ( ) I am able to eat normally, i.e. with no help from others.
- 2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
- 3 ( ) I need some help from another person to eat.
- 4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
- 5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

**QUESTION 7. SPEECH**

- 1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
- 2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
- 3 ( ) I can make myself understood, but my speech is, for example, disjointed, faltering, stuttering or stammering.
- 4 ( ) Most people have great difficulty understanding my speech.
- 5 ( ) I can only make myself understood by gestures.

**QUESTION 8. ELIMINATION**

- 1 ( ) My bladder and bowel work normally and without problems.
- 2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
- 3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
- 4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
- 5 ( ) I have no control over my bladder and/or bowel function.

**QUESTION 9. USUAL ACTIVITIES**

- 1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
- 2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
- 3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
- 4 ( ) I can only manage a small proportion of my previous usual activities.
- 5 ( ) I am unable to manage any of my previous usual activities.

**QUESTION 10. MENTAL FUNCTION**

- 1 ( ) I am able to think clearly and logically, and my memory functions well
- 2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
- 3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
- 4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
- 5 ( ) I am permanently confused and disoriented in place and time.

**QUESTION 11. DISCOMFORT AND SYMPTOMS**

- 1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
- 2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
- 3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
- 4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.
- 5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching, etc.

**QUESTION 12. DEPRESSION**

- 1 ( ) I do not feel at all sad, melancholic or depressed.
- 2 ( ) I feel slightly sad, melancholic or depressed.
- 3 ( ) I feel moderately sad, melancholic or depressed.
- 4 ( ) I feel very sad, melancholic or depressed.
- 5 ( ) I feel extremely sad, melancholic or depressed.

**QUESTION 13. DISTRESS**

- 1 ( ) I do not feel at all anxious, stressed or nervous.
- 2 ( ) I feel slightly anxious, stressed or nervous.
- 3 ( ) I feel moderately anxious, stressed or nervous.
- 4 ( ) I feel very anxious, stressed or nervous.
- 5 ( ) I feel extremely anxious, stressed or nervous.

**QUESTION 14. VITALITY**

- 1 ( ) I feel healthy and energetic.
- 2 ( ) I feel slightly weary, tired or feeble.
- 3 ( ) I feel moderately weary, tired or feeble.
- 4 ( ) I feel very weary, tired or feeble, almost exhausted.
- 5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

**QUESTION 15. SEXUAL ACTIVITY**

- 1 ( ) My state of health has no adverse effect on my sexual activity.
- 2 ( ) My state of health has a slight effect on my sexual activity.
- 3 ( ) My state of health has a considerable effect on my sexual activity.
- 4 ( ) My state of health makes sexual activity almost impossible.
- 5 ( ) My state of health makes sexual activity impossible.

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