DISSERTATIONES
MEDICINAE
UNIVERSITATIS
TARTUENSIS
**342**

LINDA SÕBER

# Impact of thyroid disease and surgery on patient's quality of voice and swallowing

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
**342**

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
**342**

**LINDA SÕBER**

# Impact of thyroid disease and surgery on patient's quality of voice and swallowing

UNIVERSITY OF TARTU
Press
1632

Department of Surgery, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

Department of Oto-Rhino-Laryngology, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Philosophy (Medicine) on 21st December 2022 by the Council of the Faculty of Medicine, University of Tartu, Tartu, Estonia

Supervisors: Professor Urmas Lepner, MD, PhD
Vice Dean, Institute of Clinical Medicine, Faculty of Medicine, University of Tartu, Estonia
Head of Surgery Clinic, Tartu University Hospital, Estonia

Priit Kasenõmm, MD, PhD
Otorhinolaryngologist, Tartu University Hospital, Ear Clinic, Tartu, Estonia

Reviewers: Professor Pille Taba, MD, PhD
Head of Institute of Clinical Medicine, Faculty of Medicine, University of Tartu, Estonia
Head of Neurology Clinic, Tartu University Hospital, Estonia

Professor Aare Märtson, MD, PhD
Department of Traumatology and Orthopedics, Institute of Clinical Medicine, Faculty of Medicine, University of Tartu, Estonia
Head of I Clinical Area, Tartu University Hospital, Estonia

Opponent: Adj. Professor Ahmed Geneid, MD, PhD
Consultant of Otorhinolaryngology and Phoniatrics
Head of Phoniatrics Department, Helsinki University Hospital and University of Helsinki, Finland

Commencement: 31st of March 2023

ISSN 1024-395X (print) ISSN 2806-240X (pdf)
ISBN 978-9916-27-131-5 (print) ISBN 978-9916-27-132-2 (pdf)



University of Tartu Press
www.tyk.ee

# TABLE OF CONTENT

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Effect of endotracheal intubation versus laryngeal mask airway on patient's quality of voice and swallowing. Int J Otorhinolaryngol Head Neck Surg 2019 Jul 5(4)820–825. doi: 10.18203/issn.2454-5929.ijohns20192699

II Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Prethyroidectomy voice and swallowing disorders and the possible role of laryngopharyngeal reflux disease. Logoped Phoniatr Vocol. 2021 Dec 23:1–6. doi: 10.1080/14015439.2021.2020894.

III Sõber L, Lepner U, Kirsimägi Ü, Puksa L, Kasenõmm P. Voice and Swallowing Disorders After Thyroid Surgery. J Voice. 2022 Apr 8: S0892–1997(22)00077–7. doi: 10.1016/j.jvoice.2022.03.013.

**Contribution of Linda Sõber to original publications:**
Study design, patient recruitment, clinical evaluation of patients, participation in data analysis, writing the paper

# ABBREVIATIONS

| | |
|---|---|
| AVA | acoustic voice analysis |
| EBSLN | external branch of the superior laryngeal nerve |
| EMG | electromyography |
| ETI | endotracheal intubation tube |
| $F_0$ | fundamental frequency |
| GERD | gastroesophageal reflux disease |
| GRBAS | Grade Roughness Breathiness Asthenia Strain |
| IBSLN | internal branch of the superior laryngeal nerve |
| IONM | intraoperative nerve monitoring |
| Jitt | jitter |
| LMA | laryngeal mask airway |
| LPR | laryngopharyngeal reflux |
| MDVP | Multidimensional Voice Program |
| MPT | maximum phonation time |
| NHR | noise to harmonics ratio |
| PCA | posterior cricoarytenoid muscle |
| RFS | Reflux Finding Score |
| RLN | recurrent laryngeal nerve |
| RSI | Reflux Symptom Index |
| Shim | shimmer |
| SIS | Swallowing Impairment Score |
| SLN | superior laryngeal nerve |
| SPI | soft phonation index |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TA | thyroarytenoid muscle |
| TSH | thyroid stimulating hormone |
| UES | upper esophageal sphincter |
| VHI | Voice Handicap Index |
| VLS | videolaryngostroboscopy |
| VTI | voice turbulence index |

# 1. INTRODUCTION

The thyroid gland is located in the anterior part of the lower neck. The thyroid lobes are in close proximity to two cervical branches of the vagus nerve on each side – the recurrent laryngeal nerve and the superior laryngeal nerve, as well as the pharyngeal and laryngeal vasculature and the esophageal inlet. This anatomical relationship has important implications for laryngeal function in the setting of thyroid disorders and following thyroid surgery (Pfaff *et al.,* 2017).

Postoperative voice and swallowing problems are frequent complaints following thyroid surgery. A temporary decrease in voice quality after thyroidectomy may occur in up to 38–87% of patients. Permanent changes have been described in 13–35% of cases (Soylu *et al*., 2007; Henry *et al.*, 2010; Lombardi *et al.*, 2009; Sinagra *et al.*, 2004). Furthermore, transitory swallowing difficulties may occur in up to 80% and persistent in one-fifth of patients (Lombardi *et al.*, 2009; Krekeler *et al.*, 2018; Martins *et al.*, 2020). Both altered voice quality, as well as deterioration of swallowing function can have major influence on the patients' quality of life, as well as a serious socio-economic impact.

However, early postoperative voice and swallowing problems can also be associated with general anesthesia itself. Up to 69% of patients complain short-term voice disorders following endotracheal intubation (Brodsky *et al*., 2021; Mendels *et al*., 2012) and 73% of patients show alterations in the laryngeal mucosa (Pröschel *et al.*, 1993). The incidence of dysphagia after short-term general anesthesia varies from 10–43% (Rieger *et al*., 1997; Brodsky *et al*., 2021). Previous studies have described alterations in voice and swallowing quality already in preoperative thyroid patients in up to 76% of cases (Fiorentino *et al.*, 2011; Mclvor *et al*., 2000; Viana Baptista *et al*., 2020). In most patients, these symptoms are associated with compression by the enlarged thyroid gland, which can lead to compression of the laryngeal nerves and esophagus, or affect laryngeal elevation during swallowing (Alfonso *et al*., 1981; Sorensen *et al*., 2018). Additionally, hypo- and hyperthyroid status may account for some of these complaints. Coexisting laryngopharyngeal reflux (LPR) has also been associated with voice and swallowing dysfunction in thyroid patients, but the latter results have been inconclusive (Fiorentino *et al.*, 2011; Holler and Anderson, 2014).

Therefore, despite the fact that thyroid surgery is one of the most common surgical procedures worldwide, many questions still remain unclear regarding the causes and duration of the thyroid related dysphonia and dysphagia. The etiology of voice and swallowing problems in thyroid patients is complex, influenced by both pre-and postoperative factors.

The goal of the present PhD thesis was to evaluate pre- and postoperative voice and swallowing disorders in thyroid patients, the clinical significance of symptoms' impact on patient's quality of everyday life, to identify dynamic changes during a follow-up period of 12–18 months and to find possible

indicative signs of permanent or temporary vocal fold palsy. In addition, we aimed to explore the possible role of thyroid enlargement, LPR disease and general anesthesia in the etiology of these alterations.

# 2. REVIEW OF THE LITERATURE

## 2.1 Anatomy of the thyroid gland

The thyroid gland, one of the largest endocrine glands in the body, is a butterfly-shaped gland, lying in the anterior neck at the level of the second to fourth tracheal rings. The gland is composed of two lateral lobes, joined by a central isthmus, with each lobe measuring approximately 4 cm cranial-caudal, 1.5 cm transverse, and 2 cm anterior-posterior. These dimensions can be drastically altered by disease. Each of the elongated lateral lobes consists of a superior and an inferior pole. Occasionally, a pyramidal lobe is present cranially, representing the remnant pathway as the thyroid gland descended from the foramen caecum near the base of the tongue to its final place in the lower neck (Lee *et al.,* 2012). The gland is covered by a thin fibrous capsule without true lobulations. Posteriorly, the condensation of the deep cervical fascia forms the suspensory ligament of Berry, which firmly attaches the thyroid to the trachea and larynx (Sasou *et al*., 1998).

Attached to the posterolateral surface of the thyroid gland are the superior and inferior parathyroid glands. Their function is to produce parathyroid hormone, which regulates the circulating level of calcium through intestinal and renal absorption, and bone remodeling. There are typically four parathyroid glands; however, supernumerary glands and less than four glands have been reported (Mohebati *et al*., 2011).

The main arterial supply to the thyroid gland is derived from the superior thyroid artery, which is a branch of the external carotid artery, and the inferior thyroid artery, which is a branch of the thyrocervical trunk. A third vessel, the thyroidea ima artery, in some cases may replace the inferior thyroid artery and become one of the principal arteries supplying the gland (Hoyes and Kershaw, 1985). Venous drainage of the thyroid includes the superior, middle, and inferior thyroid veins. The superior thyroid artery and vein travel in close association within the superior pole vascular pedicle, while the middle and inferior thyroid veins travel without arteries and drain into the internal jugular vein and the internal jugular or brachiocephalic vein, respectively (Lee *et al.,* 2012). The lymphatic drainage of the thyroid gland parallels venous drainage. The lymphatic channels that accompany the superior and the middle veins drain into the upper deep nodes of the cervical chain (Mohebati *et al*., 2011).

The principal innervation of the thyroid itself occurs via the autonomic nervous system, including parasympathetic fibers from the vagus nerve and sympathetic fibers from the superior sympathetic chain.

The thyroid lobes are in close proximity to two cervical branches of the vagus nerve on each side that innervate the larynx – the recurrent laryngeal nerve (RLN) and the superior laryngeal nerve (SLN). This anatomical relationship has important implications for laryngeal function in the setting of thyroid disorders and following thyroid surgery (Pfaff *et al*., 2017). The embryologic origin of the RLN gives it a unique anatomical course. On the right, the RLN

branches from the vagus nerve and loops around the subclavian artery at the level of the innominate artery. It then ascends in the neck traveling from lateral to medial in an oblique course, crossing the inferior thyroid artery and eventually approaching the tracheoesophageal groove behind the common carotid artery. On the left, the RLN arises from the vagus nerve just below the aortic arch and loops medially under the aorta. It then emerges from underneath the aortic arch and enters the thoracic inlet in a paratracheal position, coursing upward along the tracheoesophageal groove, ultimately crossing the distal branches of the inferior thyroid artery (Lee *et al.,* 2012). The approximate length of the left RLN from the aorta to the cricothyroid joint is about 12 cm, whereas the length of the right RLN from the subclavian to the cricothyroid joint is about 5–6 cm (Weisberg *et al*., 1997). Eventually, each recurrent laryngeal nerve enters the larynx between the inferior cornu of the thyroid cartilage and the arch of the cricoid, branching after laryngeal penetration in two-thirds of cases. In the remaining one-third of cases, the RLN branches prior to its laryngeal entry point (Lee *et al.,* 2012). In rare cases, there exists a rare anatomic variant – non-recurrent laryngeal nerve with a reported incidence of 0.3–0.8% on the right and 0.004% on the left side (Mahmodlou *et al*., 2013). In that case, the nerve enters the larynx directly after its origin from the cervical vagus. The RLN provides motor innervation to all intrinsic laryngeal muscles except the cricothyroid muscle, which receives motor innervation from the external branch of the SLN (EBSLN). The RLN supplies sensation to the vocal folds and subglottic larynx, upper esophagus, and trachea as well parasympathetic innervation to the lower pharynx, larynx, trachea, and upper esophagus (Pfaff *et al*., 2017).

The SLN is one of the first branches of vagus separating at the nodose ganglion about four cm from the carotid bifurcation and descending posteriorly and medial to the carotid sheath. In about 1.5 cm inferiorly, the SLN divides into the internal and external branches (Randolph, 2003). The EBSLN sends motor fibers to the cricothyroid muscle and innervates parts of the intralaryngeal mucous membrane (Moran and Castro, 1951). The internal branch of the SLN (IBSLN) supplies sensation to the lower pharynx, supraglottic larynx and base of the tongue, and supplies special visceral afferents to epiglottic taste receptors (Pfaff *et al.,* 2017).

## 2.2 Thyroid physiology

The thyroid gland is responsible for the production of two major metabolic hormones – thyroxine (T4) and triiodothyronine (T3), which play a critical role in the regulation of the body's basal metabolic rate. The thyroid gland is composed of follicles consisting of a colloid matrix that contain the protein thyroglobulin. The colloid contains various amino acids and molecules of iodine involved in the production of thyroid hormones. Formation of thyroid hormones requires the enzyme peroxidase, which is responsible for the oxidation of

iodine. The oxidized iodine is then combined with the amino acids to form thyroid hormone, which is stored in the follicles until its release. Thyroid hormones are released from the gland in response to thyroid-stimulating hormone (TSH) from the pituitary. Ninety-seven percent of thyroid hormone released from the gland is in the form of thyroxine (T4), which is later converted to its active form, triiodothyronine (T3) in the tissues. When the level of circulating thyroid hormone is sufficient, it inhibits the pituitary from releasing more TSH (Guyton *et al.*, 2006).

## 2.3 Epidemiology of thyroid dysfunction

Globally, approximately 200 million people have thyroid disorders of various types, with a clear female preponderance of 4:1. Because of its often indolent initial signs and symptoms, more than 50% of these disorders remain undiagnosed (Moini *et al*., 2019).

Population differences in iodine nutrition have a major role in the global prevalence of thyroid dysfunction. Nodular thyroid disorders are more prevalent in areas where iodine deficiency is more common, while autoimmune thyroid disorders, including Hashimoto thyroiditis and Graves disease, occur more frequently in iodine-replete populations (Taylor *et al*., 2018). However, there exist several other risk factors including genetic, gender, smoking status, alcohol consumption, presence of other autoimmune conditions etc. About 33% of the global population lives in an iodine-deficient area. Iodine deficiency causes low blood iodine levels, which leads to a reduction in $T_4$ levels and increased secretion of thyroid stimulating hormone to restore $T_4$ concentration. The increased TSH secretion stimulates thyroid follicular cell hyperplasia and hypertrophia leading to a diffuse enlargement of the thyroid gland (Krohn *et al*., 2000). Estonia is considered a mildly iodine deficient country (50–99 μg/l) (deBenoist *et al*., 2004). Thyroid nodules are extremely common, with up to 50% of all individuals having at least one nodule by the age of 60 years. About 5% of the global population have hypothyroidism, and about 2% have hyperthyroidism. Thyroiditis has been seen in as many as 12.5% of populations in various countries and Graves' disease affects up to 5% of females and 0.7% of males globally.

The incidence of thyroid cancer has increased dramatically during the past three decades and it is now the fastest growing cancer in women (Wiltshire *et al*. 2016). There are more than 560,000 new cases of thyroid cancer reported every year around the world (Moini *et al*., 2019).

## 2.4 Thyroid dysfunction and the effect on voice and swallowing

Signs and symptoms of hyperthyroidism include excessive sweating, heat intolerance, tachycardia and other heart arrhythmias, weight loss despite increased appetite, diarrhea, anxiety, insomnia, palmar hyperhidrosis, tremors, skin thickening (especially in the pretibial region), hyperreflexia, irritability, and occasionally exophthalmos. Hypothyroidism can lead to excessive fatigue, depression, weight gain, constipation, menorrhagia and other menstrual abnormalities, impaired fertility, cold intolerance, hyporeflexia, bradycardia, periorbital puffiness, nonpitting edema, and thinning of the hair and nails (Pfaff *et al.*, 2017).

In addition to the systemic signs and symptoms, voice disorders are among the most frequent presenting complaints in patients with thyroid disease. Previous studies have described voice and swallowing disturbances in preoperative thyroid patients in up to 76% of cases (Fiorentino *et al*., 2011; McIvor *et al*. 2000; Viana Baptista *et al.*, 2020). In most patients, these symptoms are caused by the enlarged thyroid gland, which leads to compression of the surrounding tissues and nerves (Alfonso *et al*., 1981; Sorensen *et al*., 2018). According to Heman-Ackah *et al*., 47.4% of patients who presented to their laryngology practice with vocal fold paresis were found to have underlying undiagnosed thyroid disease. The diagnoses included benign growths (29.9%), thyroiditis (7.8%), hyperthyroidism (4.5%), hypothyroidism (3.6%), and thyroid malignancy (1.6%) (Heman-Ackah *et al*., 2011).

Additionally, the hypo- and hyperthyroid status may account for some of these complaints. The presence of thyroid hormone receptors TR-α and TR-β among the fibrous lamina propria, cartilage, and glandular elements of the human larynx, has led to the suggestion that thyroid hormones play an important role in normal laryngeal physiology. Hypothyroidism leads to increased levels of acid mucopolysaccharides in the lamina propria, which is likely to result in an osmotic increase in fluid content, leading to edema and decreased vocal fold vibration (Altman *et al*., 2003). With thyroid hormone replacement therapy, improvement can be achieved in voice quality (Birkent *et al*., 2008). In hyperthyroidism, voice changes are believed to result from tremor and decreased subglottic pressure caused by the weakness of the breathing and laryngeal muscles (Kovacic, 2018).

Dysphagia in thyroid dysfunction is explained by the compression of the enlarged thyroid gland on the laryngeal, pharyngeal and esophageal structures, and nerves. Reduced laryngeal elevation, upper esophageal sphincter (UES) relaxation and gastrointestinal tract motility lead to impaired bolus transport and sensation of globus (Alfonso *et al*., 1981; İlhan *et al*., 2014; Sorensen *et al*., 2018; Scerrino *et al*., 2013). Dysphagia due to thyrotoxic myopathy is a rare primary manifestation of hyperthyroidism (Chiu *et al*., 2004).

Previous research has shown that some of the symptoms regarded as compressive have not resolved after thyroid surgery, leading to the suggestion of a

different cause of origin. The potential role of coexisting or aggravated LPR as the reason for voice and swallowing dysfunction has been considered, but the results have been rather conflicting (Fiorentino *et al*., 2011; Holler and Anderson, 2014). LPR is defined as an inflammatory condition of the upper aerodigestive tract tissues related to the direct and indirect effect of gastric or duodenal content reflux, inducing morphological changes in the upper aerodigestive tract (Lechien *et al*., 2019). The symptoms of LPR include globus sensation, pharyngeal irritation, and voice disorders, which are very similar to the complaints, caused by thyroid gland compression and may easily be confused with one another. LPR presents in about 50% of patients with voice or throat disorders (Koufman *et al*., 2000). An enlarged thyroid decreases UES pressure and provides a basis for LPR. UES is innervated by branches of the vagal nerves, pharyngoesophageal, superior laryngeal (SLN) and recurrent laryngeal (RLN), glossopharyngeal nerve and cervical sympathetic nerves. Motor fibers are provided by pharyngoesophageal nerve and SLN, sensory by glossopharyngeal nerve. Sympathetic nerves are regarded to innervate the mucosa, blood vessels and glands (Lang *et al.*, 1997). The posterior branches of the RLN are anastomosed with fibers of the EBSLN and hence participate in the innervation of the cricopharyngeal muscle, a definitive component of the UES (Chandrasekhar *et al.*, 2013). Compression of these nerves might affect the normal functioning of the sphincter.

## 2.5 Conventional thyroidectomy

Thyroidectomy is one of the most common interventions in endocrine surgery. Indications for thyroidectomy include a number of benign and malignant conditions such as thyroid nodules, hyperthyroidism, obstructive or substernal goiter, differentiated (papillary or follicular) thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer, and metastases to the thyroid from extrathyroidal primary cancer (most commonly renal cell cancer and lung cancer).

An incision through the skin, subcutaneous tissue, fat, and platysma is made in or parallel to a horizontal skin crease for an optimal cosmetic result, ideally 1 cm inferior to the cricoid cartilage, overlying the thyroid isthmus. Subplatysmal flaps are raised superiorly and inferiorly, leaving the anterior jugular veins down (Roman *et al*., 2019). The strap muscles (sternohyoid and sternothyroid) are lateralized by incising the median raphe until the thyroid capsule is identified. During the removal of a large multi-nodular goiter, the strap muscles may rarely require horizontal division to improve exposure. If the division of these muscles is necessary, it should take place as high as possible to preserve the strap muscles' innervation by the ansa cervicalis (Henry *et al.*, 2008). The thyroid lobe can be pulled and rotated medially, revealing the middle thyroid vein on the anterior lateral surface of the gland, which can be ligated safely. The next step varies based on the surgeon’s preference. Some address the inferior pole and lower parathyroid, whereas some address the superior pole, SLN, and

upper parathyroid gland. Others mobilize the gland partially at both the inferior and superior poles before retracting the gland medially to identify the RLN. Regardless of the approach, these next steps should identify and preserve both the superior and inferior parathyroid glands, the SLN, and the RLN (Roman *et al*., 2019). The SLN can be preserved by meticulous dissection of the upper pole. Displacement of the RLN by a large goiter, presence of extralaryngeal RLN branching, and a nonrecurrent RLN can make identification of the RLN difficult. Once these structures have been identified and preserved, the gland can be elevated off the trachea, and Berry's ligament can be divided or cauterized using bipolar cautery to free the gland. The ligament of Berry should be divided as close to the trachea as possible, with care not to enter the trachea. In hemithyroidectomy, the isthmus can be tied off with a surgical tie or divided with a harmonic scalpel. In total thyroidectomy, the initially dissected lobe can be removed to increase the working space in the neck or left *in situ* so that the entire thyroid can be removed *en bloc* (Bliss *et al*., 2000).

Prior to closure, the divided strap muscles and platysma are re-approximated with sutures, followed by a re-approximation of the skin. If necessary, a drain is placed to monitor the output.

## 2.6 Complications after thyroidectomy

Possible complications after thyroidectomy include hemorrhage, respiratory obstruction, hypocalcemia, hypothyroidism, thyroid storm, dysphonia, dysphagia, and wound infection. The most severe voice and swallowing problems are considered to be caused by injury to the RLN. Prior studies demonstrate high variability in RLN injury rates with temporary nerve damage occurring in 1.4–38.4% and permanent nerve damage in 0–18.6% of cases (Rosato *et al*., 2004; Bergenfelz *et al*., 2008; Jeannon *et al*., 2009). Risk factors for RLN injury are secondary or re-operative thyroid operation, surgery for advanced disease, especially thyroid malignancy, and extended resection (Choi *et al*., 2018; Banks *et al*., 2012). Caroline *et al*. suggested a thyroid size greater than 5 cm to be a predictor of increased nerve injury postoperatively (Caroline *et al*., 2012).

### 2.6.1 Voice disorders following thyroid surgery

The RLN innervates four intrinsic muscles of the larynx: the thyroarytenoid, posterior cricoarytenoid (PCA), lateral cricoarytenoid, and interarytenoid muscles. Muscle innervation is unilateral except for the interarytenoid muscle, which receives contributions from both RLNs. The thyroarytenoid and lateral cricoarytenoid muscles are vocal fold adductors. Unilateral denervation of these muscles results in an inability to close the glottis, leading often to a breathy voice and reduced airway protection during swallowing. After a few weeks, the contralateral vocal fold may provide some compensation by adducting further over the midline. Better glottic closure improves vocal quality and the risk of

aspiration. The PCA is the main vocal fold abductor. Paralysis of this muscle results in the inability to abduct during inspiration. Denervation of the PCA may cause the arytenoid cartilage to subluxate anteromedially in unilateral vocal fold paralysis, as PCA no longer counters the anterior pull on the arytenoid cartilage by the vocal ligament. If both PCA muscles are denervated, airway obstruction may occur (Crumley *et al.*, 1994).

Typically, 4–6 month after injury some degree of detectable reinnervation might be expected. The RLN regenerates, but this does not always ensure the useful motion of the vocal fold. The precise clinical picture will depend on the degree of reinnervation and synkinesis. Laryngeal synkinesis describes a random distribution of regenerated axons to opposing vocal fold muscles, both adductor and abductor. As a result, there occurs physiological co-activation of the laryngeal muscles during antagonistic maneuvers, resulting in the immobility or hypomobility of the vocal fold (Flint *et al*., 1991). The incidence of synkinesis is up to 85%. As these new axons tend to have a small diameter and a low-quality myelin sheath, muscular contractions are of poor quality or absent. Although synkinesis worsens the prognosis for motion recovery, it protects the muscle fibers from degeneration (Müller, 2020). Recent studies show that in RLN paralysis, the PCA muscle is always affected, either by atrophy or synkinesis, or a combination of both, while TA is affected only in two third of cases. This explains also the maintenance of vocal fold muscle bulk irrespective of motion deficit (Förster *et al*. 2021).

More subtle and non-specific are the signs and symptoms of EBSLN injury. Previous research has shown that the EBSLN is at a high risk of injury during dissection of the superior thyroid pole in approximately one-third of the patients (Barczyński *et al*., 2013). The EBSLN innervates the cricothyroid muscle, which controls longitudinal tension, stiffening and thinning of the vocal folds and plays an important role in controlling vocal fundamental frequency. (Sanders *et al*., 1993). The clinical findings described in previous studies are contradictory and range in a very large scale from barely noticeable changes to sluggish motion, shortening of the vocal fold, height difference in the vertical plane, especially in the region of the vocal process, laryngeal tilt to the weaker side etc. Classic symptoms of EBSLN injury include vocal fatigue, hoarseness, breathiness, loss of projection, volume disturbance, and loss of range, which results in a low-pitched, monotonous, and sometimes weaker voice that fatigues easily (Dursun *et al*., 1996; Aluffi *et al.*, 2001). This impairment in the production of higher pitches and alteration of speaking fundamental frequency is especially troublesome for singers and other professional voice users (Soylu *et al*., 2007).

Analysis of patients with untreated iatrogenic vocal fold paralysis by Husain *et al*. revealed that the recovery time of voice quality may extend to more than 1 year. Of the patients 30% recovered vocal fold motion. However, mean time until vocal recovery did not differ between patients with return of motion versus no return of motion (Husain *et al.*, 2018).

### 2.6.2 Dysphagia following thyroid surgery

In addition to vocal fold motion disorders, injury to laryngeal nerves can result in dysphagia. Swallowing impairment of various degrees can follow either RLN or EBSLN or a combination of both.

During normal deglutition, the mechanical closure of the glottis and supraglottis acts as a physical barrier between the hypopharynx and the trachea. The larynx elevates anterosuperiorly in conjunction with the relaxation and opening of the UES. The reflex relaxation of the pharyngoesophageal junction during laryngeal elevation results in post-cricoid negative pressure. Complete and sustained glottal closure allows a rise in subglottic air pressure, which compensates for the rise in pharyngeal pressure during swallowing. The maintenance of the closed glottis is essential for raising subglottic pressure for an efficient swallow. The suction sump increases bolus flow and causes rapid elimination of the pharyngeal content into the cervical esophagus before the laryngeal opening (Carrau *et al*., 1999). Injury to these nerves can result in penetration and/or aspiration due to multiple abnormalities of the laryngopharyngeal function – delayed onset of the swallowing reflex, decreased laryngeal elevation and epiglottic closure, impaired residue clearance in the valleculae and pyriform sinus, as well as incomplete glottic closure, impeding negative hypopharyngeal sump pressure for propelling bolus through the pharynx (Bhattacharyya et al., 2002; Jang *et al*., 2012).

### 2.6.3 Nonneural complications after thyroid surgery

Other possible causes of voice and swallowing disturbances after thyroid surgery in the absence of nerve injury involve localized neck pain, surgical trauma induced muscle dysfunction (both intrinsic and extrinsic laryngeal muscles), soft tissue edema, hematoma or infection, change in vascularization and venous drainage of the larynx, laryngotracheal fixation with vertical movement impairment, and psychological reaction to surgery (Sinagra *et al*., 2004; Stojadinovic *et al.*, 2008; Dursun *et al*. 1996).

Additionally, postoperative laryngeal injury from intubation can affect voice and swallowing quality following surgery in general anesthesia. Injury may be caused either by direct intubation trauma (including hematoma, mucosal edema and dislocation or subluxation of the arytenoids) or by compression of the intubation tube cuff, which might lead to edema, inflammation and impaired laryngeal motility. When pressure from the unyielding walls of the tube exceeds capillary pressure in the mucosa of the larynx, mucosal ischemia causes irritation, inflammation, congestion and edema already within the first few hours (Gaynor *et al*., 1985). Several risk factors may contribute to this laryngeal injury, such as difficult airway, tube type and size, cuff design and pressure, duration of anesthesia, as well as demographic factors such as sex, weight, history of smoking and LPR (Maktabi *et al*., 2003; Kitahara *et al*., 2005; Mencke *et al*., 2003). In general, these complaints resolve in a few days or even

shorter time; however, some studies have reported changes in voice and swallowing function even 6 months later (Friedrich *et al*., 2000). According to a meta-analysis by Brodsky et al., edema is the most frequently reported mild injury, with a prevalence of 9–84%. Severe injuries that include subluxation of the arytenoids and vocal fold paralysis are rare (<1%). The most prevalent patient complaints post-extubation are dysphagia (43%), pain (38%), coughing (32%), sore throat (27%), and hoarseness (27%) (Brodsky *et al*., 2021). Laryngeal mask airway (LMA) has proven to have some advantages over endotracheal intubation (ETI) when comparing postoperative laryngopharyngeal symptoms and voice quality (Van Esch *et al*., 2016). Use of the LMA decreases patients' subjective and objective laryngopharyngeal complaints and reduces the duration of symptoms (Chun *et al.*, 2015; Gong *et al.*, 2020).

### 2.6.4 Laryngopharyngeal reflux after thyroid surgery

Although several studies have described improvement in local neck symptoms after thyroid surgery, in a remarkable number of patients these complaints remain postoperatively unchanged or even worsen in the case of the intact laryngeal nerves (Lombardi *et al*., 2006; Lombardi *et al*., 2009; Sabaretnam *et al*., 2012). Aggravated LPR has been suggested as a possible cause of exacerbated post-thyroidectomy voice and swallowing complaints. Thyroidectomy is thought to worsen the anti-reflux defence mechanisms, although the exact etiology and pathogenesis are still unclear.

Cusimano *et al*. proposed that the unrecognized injury of the EBSLN could lead to pharyngeal inferior constrictor muscle dysfunction, an essential component of the UES, as approximately 20% of EBSLN run through the fibers of the pharyngeal inferior constrictor muscle (Cusimano *et al.*, 2016). UES is considered to be the most important barrier against the pharyngeal reflux of gastric or duodenal contents. Scerrino *et al*. reported a postoperatively reduced UES pressure of approximately 25% after thyroidectomy, although it remained within the normal range (Scerrino *et al.*, 2013). Another theory, suggested by Cusimano *et al.,* is that injury to the sternohyoid and the sternothyroid muscle during thyroid surgery compromises elevation and anteriorization of the hyolaryngeal complex, keeping the subepiglottic space open and worsening LPR. Additionally, this downward pull leads to shortening of the cricothyroid distance and lengthening of the vocal folds, resulting in persistent and aggravated local neck symptoms (Cusimano *et al.*, 2016).

## 2.7 Summary of the literature review

Thyroid disorders are one of the most common endocrine disorders requiring surgical treatment. Voice and swallowing disturbances are well-known complications of both thyroid disease and surgery. However, the true causes of these complaints remain often unclear.

An enlarged thyroid gland can lead to compressive symptoms as globus sensation, dysphagia, odynophagia, and dyspnea. LPR is a condition with very similar complaints and can easily be mistaken for thyroid induced compression. As the data about LPR as a cofactor or the underlying reason for these complaints is limited, further investigation is needed to prevent unnecessary surgical interventions.

In addition, there is still much confusion regarding voice and swallowing disorders following thyroid surgery. Close proximity of the laryngeal nerves can lead to hasty generalization and hence to misinterpretation of true etiopathogenetic factors. Our hypothesis was that a substantial amount of voice and swallowing disturbances are induced by factors other than direct nerve injury.

Early correctly targeted interventions have proven to improve long-term outcomes. Therefore, it is necessary to identify the dynamic changes during the possible nerve regeneration period and to find indicative signs of permanent or temporary vocal fold palsy. Our hypothesis was that the majority of the vocal fold palsies are temporary and affect voice and swallowing quality in short term.

# 3. AIMS OF THE STUDY

I To evaluate voice and swallowing disorders before thyroid surgery and the impact of symptoms on patient's quality of everyday life, as well as to explore the possible etiologic factors.

II To evaluate voice and swallowing disorders following thyroid surgery and the impact of symptoms on patient's quality of everyday life, as well as to explore the possible etiologic factors.

III To identify dynamic changes in postoperative voice and swallowing function during a follow-up period of 12–18 months and to find possible indicative signs of permanent or temporary vocal fold palsy.

IV To evaluate the possible role of general anesthesia in the development of post-thyroidectomy voice and swallowing disorders.

# 4. MATERIALS AND METHODS

## 4.1 Inclusion and exclusion criteria

The present research included 118 patients of the study group who underwent either hemi- or total thyroidectomy. The control group consisted of 110 patients who underwent laparoscopic cholecystectomy with endotracheal intubation (ETI) anesthesia and 100 patients who underwent open hernioplasty or lower extremity varicectomy with laryngeal mask airway (LMA). All investigations were conducted as prospective studies. All study participants were recruited from among the preoperative patients of the Surgery Clinic of Tartu University Hospital between September 2013 and December 2016. Participation in the studies was voluntary.

Patients were excluded if they were under 18 years of age, presented a videostroboscopic finding of a preexisting vocal fold mucosal lesion (polyp, cyst, granuloma etc.), previous vocal fold paralysis, or if they failed to complete pre- and postoperative evaluations. All patients of the thyroidectomy group had a euthyroid status prior to surgery. All cholecystectomy, hernioplasty and varicectomy group's patients were interviewed about their medical history to rule out underlying thyroid disease.

## 4.2 Preoperative data and follow-up visits

All patients were examined preoperatively and in the 1$^{st}$ postoperative week at the Ear Clinic of Tartu University Hospital. In the case of a clinical finding of laryngeal injury, 1$^{st}$, 6-month and 12–18-months follow-up visits were conducted. For all patients of the thyroidectomy group, irrespective of laryngeal injury, a 12–18-month follow-up visit was conducted.

The pre- and postoperative data were documented using standardized forms. The data included demographic data, weight, smoking status, occupational voice use, anesthesia method, duration of intubation, intubation tube size, cuff inflation pressure, number of intubation attempts. For thyroidectomy patients additionally thyroid specimen's weight, histologic diagnosis and extent of surgery were recorded.

At all visits, patients filled in forms of subjective evaluation of voice and swallowing and reflux complaints. In addition, laryngeal imaging by video-laryngostroboscopy (VLS), acoustic voice analysis (AVA), measurement of maximum phonation time (MPT) and perceptual voice evaluation were performed. VLS was performed during sustained vowel /e/ phonation, using either a 90-degree rigid laryngoscope (Karl Storz model 8707 DA) or a flexible fiberoptic nasopharyngolaryngoscope (Kay Pentax model VNL 8- J10) depending on the availability of the instrument and the patient's ability to cooperate with the rigid endoscope. VLS recordings were viewed and evaluated according to the Reflux Finding Score (RFS) by a blinded evaluator. To minimize any bias

due to the limited field of view in the case of the rigid endoscope, we used circular movements to get a broader overview of the laryngopharynx and the esophageal inlet.

The RFS is a clinical rating scale developed to evaluate LPR induced laryngopharyngeal changes. The score varies from 0 (normal anatomy) to 26 (serious anatomical changes). Score values above 7 have been shown to be suggestive of LPR (Belafsky *et al*., 2001).

Patients, in whom we suspected laryngeal nerve injury based on clinical findings, underwent laryngeal electromyography (EMG) 4 weeks after operation.

### 4.2.1 Subjective evaluation forms

Subjective evaluations of voice, swallowing and reflux complaints were assessed by using Voice Handicap Index (VHI), Swallowing Impairment Score (SIS) and Reflux Symptom Index (RSI), respectively.

The VHI is a standardized 30-point questionnaire developed by Jacobson *et al*. in 1997, to evaluate the impact of voice disorder on the patient's quality of life. Each answer is graded 0 (never) to 4 (always) depending on the severity of the voice problem and the sum ranges from a minimum of 0 to a maximum of 120. The score is divided into three subscales – physical, functional and emotional (Jacobson *et al*., 1997).

The SIS is a series of six questions related to the frequency of swallowing abnormality. It ranges from a minimum score of 0 (no swallowing alteration) to a maximum of 24 (most severe swallowing impairment) (Lombardi *et al.*, 2006).

The RSI is a subjective questionnaire published by Belafsky *et al*. in 2002. It consists of 9 questions regarding the patient's self-evaluation of LPR symptoms. It is highly reproducible and exhibits excellent construct and criterion-based validity. Values above 13 are regarded as pathologic (Belafsky *et al.*, 2002).

### 4.2.2 Acoustic Voice Analysis

Objective acoustic voice analysis (AVA) was performed by using the Multi-Dimensional Voice Program (MDVP) (Model 5105, version 3.1.7; KayPENTAX), measuring average fundamental frequency ($F_0$, Hz), mean percentage vocal jitter (Jitt) and shimmer (Shim), voice turbulence index (VTI), noise-to-harmonic ratio (NHR) and soft phonation index (SPI). The microphone was positioned at a distance of approximately 20 cm from the patient’s mouth. The level of environmental noise was < 30 dB. Three voice tokens of sustained vowel /a/ at habitual pitch and loudness from the mid-portion were recorded for 4 seconds each. The most stable performance of the three trials was used for data analysis. To evaluate glottic efficiency, maximum phonation time (MPT) was collected by having the patient sustain vowel /a/ for as long as possible on a single breath, following a maximum inhalation. Three trials were obtained and the longest of the three attempts was used for further data analysis.

### 4.2.3 Perceptual Voice Analysis

Perceptual voice analysis was performed by an experienced phoniatrician using the Grade, Roughness, Breathiness, Asthenia and Strain (GRBAS) rating scale. The scale was developed by The Committee of Phonatory Function Tests of the Japan Society of Logopedics and Phoniatrics. Each of the above-mentioned voice aspects is rated on a four-point scale ranging from 0 (normal) to 3 (severely abnormal). The scale is recommended for both clinical and research purposes by the European Laryngeal Research Group and has proven inter- and intra-rater reliability (Hirano, 1981).

## 4.3 Surgical and anesthetic management

All participants underwent short-term anesthesia lasting less than 150 minutes. We did not interfere with the daily routine of anesthetic management, i.e. the medical conditions remained unchanged. In the group of thyroidectomy and laparoscopic cholecystectomy a single-use polyvinylchloride ETI was used and in the group of hernioplasty and varicectomy a LMA of appropriate size was used. The cuff was inflated up to a point of air-leakage stop and pressure was measured and recorded. Postoperative analgesic management followed the hospital's protocol.

In patients of the thyroidectomy group conventional transcervical thyroidectomy was performed. Strap muscles were retracted. Recurrent laryngeal nerves were identified in the majority of cases and efforts were made to preserve the nerves' anatomic integrity and function. EBSLN preservation was attempted by meticulous preparation of the superior poles of the thyroid gland. No intraoperative nerve monitoring (IONM) was applied.

## 4.4 Statistical analysis

Statistical analysis was performed using the TIBCO Statistica™ version 10.0 software package and R software (R Core Team, 2019). Data was expressed as mean with standard deviation (±SD) or median with the interquartile range (IQR). Normally distributed paired data was analyzed using a paired t-test, non-normally distributed data was analyzed using the Wilcoxon signed rank test. For independent samples, t-test or the Mann-Whitney U test was employed. Significant differences in categorical data between the groups were tested by Chi-Square test or Fisher's exact test. Spearman rank order correlation and odds ratio were used to determine relationship between variables. Reliability analyses were expressed using weighted Cohen's kappa. Statistical significance was defined as a $p$ value less than 0.05 for all parameters.

## 4.5 Ethical Considerations

Participation in the studies was voluntary. All subjects were informed about the nature of the studies and, after signing the informed consent form approved by the ethics committee, they were enrolled in the study. Approval was obtained from the Research Ethics Committee of the University of Tartu, license no. 212/T-7.

# 5. RESULTS

## 5.1 Preoperative voice and swallowing function in thyroid patients (II)

Table 1 presents the clinicopathologic characteristics of the study and control groups. The study group consisted of 118 preoperative thyroid patients, ranging in age from 18 to 83 years. The control group consisted of 110 preoperative cholecystectomy patients, ranging in age from 23 to 82 years. Both groups were matched in terms of gender and age distribution. Smoking as a vocal risk factor did not differ between groups. The choice of cholecystectomy patients for the control group was based on the similar predominance of female gender among the thyroid and cholelithiasis patients.

**Table 1.** Clinicopathologic characteristics of the thyroidectomy and cholecystectomy (control) groups.

| Characteristic | Thyroid patients (N=118) | Controls (N=110) | *p* value |
|---|---|---|---|
| Age (yr) | 57.63±16.28 | 55.1±16.96 | 0.252 |
| Gender | | | |
| male, n (%) | 19 (16.1) | 27 (24.55) | 0.112 |
| female, n (%) | 99 (83.9) | 83 (75.46) | |
| Current smoking, n (%) | 16 (13.56) | 19 (17.27) | 0.437 |
| Histological diagnosis, n (%) | | | |
| nodular | 81 (68.64) | | |
| autoimmune | 15 (12.71) | | |
| malignant | 21 (17.8) | | |
| normal tissue | 1 (0.85) | | |
| Thyroid weight (g) | 42 (29–101) | | |

Values are expressed as means (±SD), prevalence (%) and medians (IQR).

We found no statistical difference in the subjective evaluation of voice (VHI) between the study and control groups, either in the total score, or in any of the subscales (Table 2). The most notable difference was detected in the emotional subscale of the VHI score, but it was statistically insignificant ($p$=0.074).

The overall distribution of voice disturbances was also homogenous in both groups. In the thyroid patients' group 4 patients felt severe handicap (3.4%), 12 patients felt moderate handicap (10.2%) and 102 patients felt mild handicap (86.4%) of whom 20 scored 0 (17%). In the cholecystectomy patients' group 3 patients reported severe handicap (2.7%), 8 patients (7.3%) reported moderate handicap and 99 patients (90%) reported mild handicap of whom 20 scored 0 (18.2%). Moreover, perceptual evaluation of voice quality too, showed no detectable difference in the voices of the patients of the study and control group in any of the GRBAS subscales (Table 2).

**Table 2.** Comparison of preoperative subjective evaluation of voice, swallowing, reflux complaints, clinical findings of reflux and perceptual evaluation of voice.

| Variables | Thyroid patients (N=118) | Controls (N=110) | *p* value |
|---|---|---|---|
| VHI functional | 2.00 (0.00–7.00) | 2.00 (0.00–6.00) | 0.811 |
| VHI physical | 4.00 (0.00–11.00) | 2.00 (0.00–7.00) | 0.198 |
| VHI emotional | 0.00 (0.00–3.00) | 0.00 (0.00–2.00) | 0.074 |
| VHI total | 7.00 (1.00–20.00) | 6.00 (2.00–13.00) | 0.328 |
| SIS | 4.00 (1.00–7.00) | 1.00 (0.00–5.00) | **0.001** |
| RSI | 8.50 (3.00–17.00) | 5.00 (3.00–11.00) | **0.006** |
| RFS | 7.00 (4.00–10.00) | 8.50 (5.00–11.00) | 0.220 |
| G | 1.00 (0.00–1.00) | 1.00 (0.00–1.00) | 0.538 |
| R | 1.00 (0.00–1.00) | 1.00 (0.00–1.00) | 0.343 |
| B | 0.00 (0.00–1.00) | 0.00 (0.00–1.00) | 0.202 |
| A | 0.00 (0.00–1.00) | 0.00 (0.00–1.00) | 0.095 |
| S | 0.00 (0.00–0.00) | 0.00 (0.00–0.00) | 0.824 |

Values are expressed as medians (IQR).
VHI − Voice Handicap Index, SIS − Swallowing Impairment Score, RSI − Reflux Symptom Index, RFS − Reflux Finding Score, G – grade, R – roughness, B – breathiness, A – asthenia, S – strain

We found further confirmation that there were no remarkable differences in the voice quality of the preoperative thyroid patients, using AVA and MPT (Table 3). However, we did note higher values in the thyroid group patients' jitter and NHR values, but statistically significant differences were not found between any of the investigated parameters of the MDVP.

**Table 3.** Comparison of preoperative acoustic analysis of voice and phonatory efficiency

| Variables | Thyroid patients (N=85) | Controls (N=78) | *p* value |
|---|---|---|---|
| Fo (Hz) | 162.91 (118.95–201.77) | 159.12 (116.42–206.02) | 0.736 |
| Jitter (%) | 1.29 (0.61–2.18) | 0.88 (0.53–1.61) | 0.066 |
| Shimmer (%) | 5.68 (3.32–9.13) | 5.15 (3.84–6.87) | 0.420 |
| NHR | 0.15 (0.13–0.18) | 0.14 (0.13–0.16) | 0.094 |
| SPI | 14.40 (9.77–20.87) | 15.27 (10.24–22.33) | 0.585 |
| MPT (sec) | 15.1 (12.05–18.45) | 14.35 (11.90–17.90) | 0.694 |

Values are expressed as medians (IQR).
Fo – Fundamental frequency, NHR – Noise to harmonics ratio, SPI – Soft phonation index, MPT − maximum phonation time

To identify if any specific aspect of voice quality disturbs thyroid patients the most, we used Spearman's correlation coefficient to determine the relationship between VHI total score and MDVP parameters. However, we found no correlation between the studied variables. Moreover, there was no correlation between VHI scores and weight of the thyroid gland postoperative histologic specimen.

The SIS revealed significantly worse swallowing function in the group of thyroid patients ($p$=0.006; Table 2). Ninety patients (73.3%) reported swallowing symptoms at least some of the time based on SIS score in thyroid patients versus 63 patients (57.3%) in the control group.

We also searched for a relationship between swallowing impairment and weight of the thyroid gland but found no correlation ($\rho$=-0.082). Comparison of the subjective evaluation of reflux complaints (RSI) showed that the patients of the thyroid group have significantly higher values compared to the control group. Of thyroid patients 31% had RSI scores above the normative value (>13) versus 19% for cholecystectomy patients. Nevertheless, the clinical LPR signs evaluated by RFS obtained equal scores in both groups.

To clarify if any specific LPR symptom of the RSI led to an increase in the overall score for thyroid patients, we compared the scores of each single question between the study group and the control group (Table 4). The results revealed that all questions about local neck symptoms (nos. 2 to 8) obtained significantly higher scores for the patients of the thyroid group, whereas, question no. 9, which was specifically directed to reflux complaints (heartburn, chest pain, indigestion or stomach acid coming up), showed higher scores for the patients of the control group. Question no. 1 about voice disorders showed no difference between the two groups, which is in accordance with our previous analysis.

**Table 4.** Comparison of Reflux Symptom Index questions

| Question no. | Thyroid patients (N=118) | Controls (N=110) | *p* value |
|---|---|---|---|
| 1. Hoarseness or a problem with your voice | 0.00 (0.00–2.00) | 0.00 (0.00–1.00) | 0.088 |
| 2. Clearing your throat | 1.00 (1.00–3.00) | 1.00 (0.00–2.00) | **<0.001** |
| 3. Excess throat mucus or postnasal drip | 1.00 (0.00–3.00) | 0.00 (0.00–1.50) | **0.011** |
| 4. Difficulty swallowing food, liquids or pills | 0.00 (0.00–1.00) | 0.00 (0.00–0.50) | **0.032** |
| 5. Coughing after you ate or lying down | 1.00 (0.00–2.00) | 0.00 (0.00–1.00) | **0.001** |
| 6. Breathing difficulties or chocking episodes | 0.00 (0.00–2.00) | 0.00 (0.00–0.00) | **0.001** |
| 7. Troublesome or annoying cough | 1.00 (0.00–2.00) | 0.00 (0.00–1.00) | **0.002** |
| 8. Sensation of sth. sticking in your throat or a lump in your throat | 1.00 (0.00–3.00) | 0.00 (0.00–1.00) | **0.001** |
| 9. Heartburn, chest pain, indigestion or stomach acid coming up | 1.00 (0.00–2.00) | 1.00 (0.00–2.50) | 0.071 |

Values are expressed as medians (with 25% and 75% percentiles).

Furthermore, we investigated the correlation between RSI and SIS, as well as between RFS and SIS, in the group of thyroid patients and found strong positive correlation between RSI and SIS ($\rho$=0.641), but no correlation between RFS and SIS ($\rho$=-0.002).

When searching for correlation between thyroid specimen's weight and reflux scores, we found a weak positive correlation between thyroid weight and RFS ($\rho$=0.379), but no correlation between thyroid weight and RSI ($\rho$=-0.085).

## 5.2 Voice and swallowing disorders after thyroid surgery (III)

The study flowchart is presented in Figure 1. The patient and operative data are presented in Table 5.

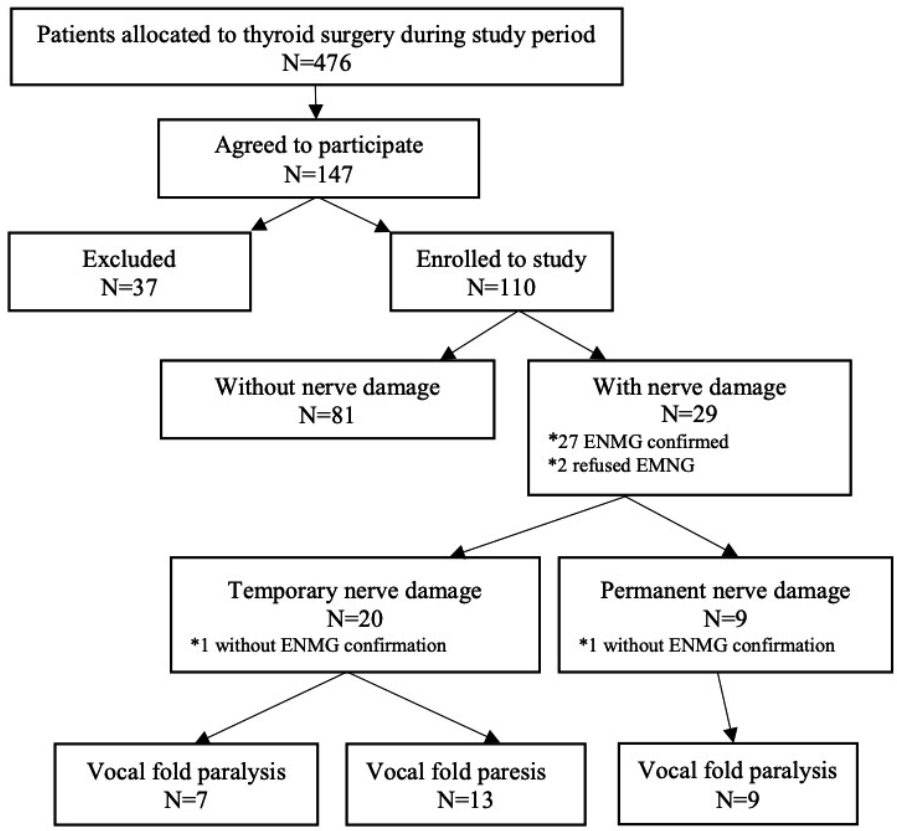


**Figure 1.** Study flowchart (Voice and swallowing changes after thyroid surgery III)

**Table 5.** Baseline characteristics of thyroidectomy patients

| Characteristic | Thyroid patients (N=110) |
|---|---|
| Age (yr) | 57.3±16.5 |
| Gender, n (%) | |
| male | 18 (16.4) |
| female | 92 (83.6) |
| Current smoking, n (%) | 15 (13.6) |
| Histological diagnosis, n (%) | |
| benign goiter | 77 (70.0) |
| autoimmune | 15 (13.6) |
| malignant | 18 (16.4) |
| Type of surgery, n (%) | |
| total thyroidectomy | 79 (71.8) |
| lobectomy | 31 (28.2) |
| Thyroid weight (g) | 71.2 (±61.8) |
| Duration of intubation (min) | 93.0 (±28.1) |

Values are expressed as means (±SD) and prevalence (%).

In the first postoperative week videostroboscopic evaluation, we suspected laryngeal nerve injury in 31 patients. Of these, 29 agreed to undergo laryngeal EMG, which revealed some degree of nerve injury in 27 patients. Two patients refused to pass the procedure (one with paralysis and one with paresis) and in two patients EMG confirmed normal function of the laryngeal nerves. Out of these 27 patients, one had bilateral vocal fold paralysis (3.7%), 14 patients had unilateral paralysis (51.9%), 7 right-sided and 7 left-sided, and 12 patients showed signs of vocal fold paresis (44.4%).

Based on the dynamic evaluation of laryngeal anatomy within the 12–18-month period after surgery, we concluded that 19 cases (70.4%) of the EMG-confirmed nerve injury turned out to be temporary, which usually resolved by the 6th month. In addition, one patient with clinical signs of paresis, who refused to undergo the EMG procedure, showed clinical recovery within 6 months. Minimal deficiencies were noted after the 12–18-month monitoring period in 4 patients (slight shortening of the vocal fold, mild motion deficiency). Seven out of these transitory injuries manifested as vocal fold paralysis. Permanent paralysis was observed in 8 patients (29.6%), plus one patient who refused to undergo the EMG procedure but showed distinct persistent clinical signs. One patient suffered from bilateral vocal fold paralysis, five left-sided and three right-sided.

When analyzing the videostroboscopic findings of patients with the clinical signs of vocal fold paralysis, we detected arytenoid prolapse in seven patients with permanent paralysis; two patients had a normal position of the arytenoid cartilage. In five patients the position of the arytenoid had not altered over time, whereas in two patients it had normalized by the 6th month follow-up visit. All patients with temporary paralysis had a anteromedial position of the arytenoid cartilage, in four patients we observed improvement in vocal fold motion and

arytenoid position by the first month and in three patients by the 6th month. Furthermore, we could not detect any consistency in the vocal fold contour: in both groups, either with permanent or temporary paralysis, we identified both straight (7 vs 4) and bowing vocal folds (2 vs 3).

Due to the relatively high drop-out rate in our study, we could not identify the precise incidence of postoperative vocal fold palsy. The failure to attend the postoperative follow up visits by our patients was almost exclusively explained by the lack of subjective complaints. Taking the above-mentioned fact into consideration, the incidence of permanent paralysis in our study could vary between 6.1–8.2% and temporary nerve injury (including paralysis, paresis as motion deficits and loss of tonicity) between 12.2–18.2%.

In a considerable number of patients (N14), we detected postoperative motion deficits and bilateral loss of tonicity, which resulted in evident subjective and objective voice disturbances. In all of these patients, except for one, EMG confirmed either a bi- or unilateral RLN injury and in seven patients an additional EBSLN injury. In the majority of the cases, this distinct clinical finding resolved by the $6^{th}$ month follow-up visit, with two exceptions that persisted longer with remission observed at the last follow-up visit. All these patients had undergone total thyroidectomy.

To analyze the influence of laryngeal nerve injury on postoperative voice and swallowing function we divided the patients into two groups – with or without postoperative nerve injury. The patients of both groups had similar baseline characteristics regarding age, sex, duration of intubation, size of the intubation tube, pressure of the intubation tube cuff, preoperative values of VHI, SIS, RSI, RFS, $F_0$, Jitt, Shim, NHR, MPT, smoking status and daily voice use.

Our study confirmed the association between large thyroid weight and increased risk of laryngeal nerve injury, as we found a significant difference in the thyroid gland histologic specimen's weight ($p$=0.02). Median thyroid weight in patients without nerve injury was 40.0g (27.0–75.3), compared to 79.0g (37.5–128.0) in patients without nerve injury. We found no correlation between older age, smoking status, thyroid disease or the extent of surgery and increased risk of nerve injury.

Analysis of changes regarding the subjective and objective voice characteristics at the first postoperative week revealed that patients with intact laryngeal nerves postoperatively had no objective voice changes. Subjective evaluation showed a slight decline in the VHI physical domain and increased strain in voice. In contrast, patients with nerve injury showed a drastic decline both in subjective voice quality (all VHI subscales and total score) and jitter parameter in acoustic voice analysis. Furthermore, perceptual voice analysis showed disturbances in all rated scales – overall voice quality, roughness, breathiness, asthenia and strain. The decline in maximum phonation time was indicative of increased glottic insufficiency ($p$=0.005) (Table 6).

**Table 6.** Voice changes in patients at 1st postoperative week with and without laryngeal nerve injury.

| Variables | Without laryngeal nerve injury (N=81) | *p* value vs pre-op | With laryngeal nerve injury (N=29) | *p* value vs pre-op |
|---|---|---|---|---|
| VHI functional | | | | |
| pre-op | 3 (0–7) | | 2 (0–5) | |
| 1 week | 4 (0–9) | 0.295 | 16 (5–21) | **<0.001** |
| VHI physical | | | | |
| pre-op | 4 (0–11) | | 3 (0–10) | |
| 1 week | 5 (1–12) | **0.048** | 18 (11–30) | **<0.001** |
| VHI emotional | | | | |
| pre-op | 1 (0–3) | | 0 (0–2) | |
| 1 week | 0 (0–5) | 0.390 | 9 (1–14) | **<0.001** |
| VHI total | | | | |
| pre-op | 9 (2–20) | | 7 (0–15) | |
| 1 week | 9 (3–25) | 0.119 | 38 (21–74) | **<0.001** |
| SIS | | | | |
| pre-op | 5.6 (±5.3) | | 4.7 (±5.2) | |
| 1 week | 7.1 (±6.7) | **0.014** | 8.0 (±5.8) | **0.001** |
| Fo (Hz) | | | | |
| pre-op | 158.9 (±50.9) | | 178.8 (±45.5) | |
| 1 week | 161.1 (±46.7) | 0.726 | 153.7 (±50.0) | 0.056 |
| Jitter (%) | | | | |
| pre-op | 1.40 (0.61–2.02) | | 0.93 (0.75–2.29) | |
| 1 week | 0.96 (0.58–1.64) | 0.05 | 1.94 (1.14–3.34) | **0.024** |
| Shimmer (%) | | | | |
| pre-op | 5.69 (3.30–9.07) | | 5.42 (3.53–8.59) | |
| 1 week | 5.53 (4.10–8.85) | 0.704 | 8.29 (6.15–10.51) | 0.141 |
| NHR | | | | |
| pre-op | 0.14 (0.13–0.18) | | 0.16 (0.13–0.20) | |
| 1 week | 0.15 (0.13–0.17) | 0.877 | 0.16 (0.14–0.23) | 0.432 |
| MPT (sec) | | | | |
| pre-op | 16.7 (±6.7) | | 14.3 (±4.6) | |
| 1 week | 15.7 (±6.2) | 0.116 | 11.2 (±5.7) | **0.005** |
| G | | | | |
| pre-op | 1 (0–1) | | 1 (0.5–1) | |
| 1 week | 1 (0–2) | 0.228 | 1 (0.5–1) | **<0.001** |
| R | | | | |
| pre-op | 1 (0–1) | | 0 (0–1) | |
| 1 week | 1 (0–1) | 0.107 | 1 (0–2) | **0.007** |
| B | | | | |
| pre-op | 0 (0–1) | | 1 (0–1) | |
| 1 week | 0 (0–1) | 0.88 | 2 (1–2) | **0.006** |
| A | | | | |
| pre-op | 0 (0–1) | | 1 (0–1) | |
| 1 week | 0 (0–1) | 0.858 | 1 (1–2) | **<0.001** |
| S | | | | |
| pre-op | 0 (0–0) | | 0 (0–0) | |
| 1 week | 0 (0–0) | **0.049** | 1 (0–1.5) | **0.003** |

Values are expressed as medians (IQR) or means (±SD).
VHI − Voice Handicap Index, SIS − Swallowing Impairment Score, NHR – Noise to Harmonics Ratio, MPT – Maximum Phonation Time, G – grade, R – roughness, B – breathiness, A – asthenia, S – strain

The analysis of first postoperative week subjective swallowing function revealed remarkable disturbances in all postoperative patients regardless of the presence of the nerve injury ($p$=0.014, $p$=0.001 resp). However, patients with postoperatively intact laryngeal nerves showed quick resolution of complaints already by the 1st month follow-up visit. Furthermore, at the end of the follow-up period, we detected a significantly improved swallowing function compared to the pre-operative status ($p$=0.008). In contrast, for patients with nerve injury, the increased values of SIS score were evident during the whole follow-up period, although statistically not significant from the 6th month visit (Table 7).

**Table 7.** Dynamic changes of Swallowing Impairment Score in patients with or without laryngeal nerve injury.

| SIS | Without laryngeal nerve injury (group A) n mean±SD | *p* value vs. pre-op | With laryngeal nerve injury (group B) n mean±SD | *p* value vs. pre-op | *p* value group A vs group B |
|---|---|---|---|---|---|
| Pre-op | 5.6±5.3 | | 4.7±5.2 | | 0.368 |
| 1 week | 81 7.1±6.7 | **0.014** | 29 8.0±5.8 | **0.001** | 0.246 |
| 1 month | 27 5.0±5.0 | 0.299 | 29 6.9±6.0 | **0.017** | 0.211 |
| 6 month | 11 5.0±5.9 | 0.450 | 28 6.2±6.4 | 0.149 | 0.556 |
| >12 month | 75 4.2±4.5 | **0.008** | 28 5.4±5.4 | 0.438 | 0.412 |

SIS Swallowing Impairment Score

Depending on clinical recovery during the follow-up period, we divided the patients with vocal fold palsy into two groups – patients either with temporary (N20) or with persistent vocal fold palsy (N9). These groups also included two patients who refused to pass EMG evaluation but showed clinical signs of palsy. Further on, we analyzed the postoperative dynamic changes in voice and swallowing quality for these two groups. The most remarkable changes during the follow-up period in both groups were observed in the values of VHI scores, jitter and perceptual voice quality (Table 8). When analyzing the VHI subscales, the most drastic decline became evident in the physical domain (pVHI). Swallowing impairment was evident in both groups but was statistically significant only in patients with temporary palsy, whereas reduced phonatory efficiency was only seen in patients with permanent nerve injury.

**Table 8.** Dynamic changes of voice and swallowing quality during the follow-up period in patients with temporary and permanent vocal fold palsy.

| | Temporary palsy (n=20, group A) | *p* value vs. pre-op | Permanent palsy (N= 9, group B) | *p* value vs. pre-op | *p* value group A vs group B |
|---|---|---|---|---|---|
| VHIf | | | | | |
| Pre-op | 1 (0–5) | | 3 (1–7) | | 0.346 |
| 1 week | 10 (3–20) | **<0.001** | 20 (17–28) | **0.009** | 0.056 |
| 1 month | 12 (6–22) | **<0.001** | 24 (18–27) | **0.004** | 0.056 |
| 6 months | 4 (0–11) | 0.115 | 8 (4–19) | 0.142 | 0.263 |
| >12 months | 2 (0–10) | 0.241 | 8 (0–19) | 0.205 | 0.593 |
| VHIp | | | | | |
| Pre-op | 3.5 (0–11) | | 3 (1–14) | | 0.777 |
| 1 week | 16 (7–21) | **<0.001** | 27 (18–34) | **0.009** | **0.028** |
| 1 month | 17 (9–28) | **<0.001** | 26 (18–34) | **0.004** | 0.099 |
| 6 months | 7 (0–16) | 0.054 | 20 (6–26) | 0.142 | 0.088 |
| >12 months | 5 (0–12) | 0.084 | 11 (3–22) | 0.205 | 0.347 |
| VHIe | | | | | |
| Pre-op | 0 (0–2) | | 0 (0–4) | | 0.982 |
| 1 week | 7 (0–13) | **0.004** | 10 (6–23) | **0.009** | 0.172 |
| 1 month | 9 (2–18) | **<0.001** | 17 (5–25) | **0.014** | 0.540 |
| 6 months | 0 (0–9) | **0.032** | 9 (1–13) | 0.074 | 0.253 |
| >12 months | 0 (0–6) | 0.125 | 3 (0–18) | 0.106 | 0.461 |
| VHItotal | | | | | |
| Pre-op | 8 (0–15) | | 6 (2–24) | | 0.604 |
| 1 week | 28 (17–53) | **<0.001** | 57 (39–84) | **0.004** | **0.040** |
| 1 month | 39 (17–67) | **<0.001** | 57 (39–82) | **0.004** | 0.151 |
| 6 months | 10 (0–32) | 0.050 | 43 (10–51) | 0.151 | 0.195 |
| >12 months | 8 (0–26) | 0.142 | 22 (3–57) | 0.142 | 0.401 |
| SIS | | | | | |
| Pre-op | 4.0±4.0 | | 6.3±7.1 | | 0.525 |
| 1 week | 6.9±4.9 | **0.004** | 10.6±7.0 | 0.109 | 0.258 |
| 1 month | 5.7±4.8 | **0.036** | 9.6±7.6 | 0.192 | 0.268 |
| 6 months | 5.2±6.0 | 0.271 | 8.9±7.1 | 0.393 | 0.155 |
| >12 months | 4.6±4.9 | 0.428 | 7.3±6.5 | 0.828 | 0.321 |
| G | | | | | |
| Pre-op | 1 (0.5–1) | | 1 (0.5–1.5) | | 0.525 |
| 1 week | 2 (1.5–2.5) | **0.001** | 2 (2–3) | **0.012** | 0.278 |
| 1 month | 1 (1–2) | **0.014** | 2 (2–3) | **0.012** | **0.039** |
| 6 months | 1 (1–2) | **0.015** | 2 (1.5–2) | **0.019** | 0.084 |
| >12 months | 1 (1–1.5) | **0.042*** | 1 (1–2.5) | 0.203 | 0.321 |
| R | | | | | |
| Pre-op | 0.5 (0–1) | | 0 (0–1) | | 0.869 |
| 1 week | 2 (0–2) | **0.011** | 0 (0–2.5) | 0.395 | 0.509 |
| 1 month | 1 (0–2) | **0.029** | 1 (0–1.5) | 0.408 | 0.491 |
| 6 months | 1 (0–1.5) | 0.080 | 1 (0–1) | 0.999 | 0.576 |
| >12 months | 1 (1–2) | **0.006** | 1 (0.5–2.5) | 0.072 | 0.978 |
| B | | | | | |
| Pre-op | 0 (0–1) | | 1 (0–1) | | 0.169 |
| 1 week | 1 (1–2) | **0.014** | 2 (1.5–3) | **0.019** | 0.085 |
| 1 month | 1 (0–1) | 0.318 | 2 (1–3) | **0.010** | **0.009** |
| 6 months | 1 (0–1) | 0.627 | 1 (0.5–1.5) | 0.424 | 0.222 |
| >12 months | 0.5 (0–1) | 0.608 | 1 (0–1) | 0.999 | 0.593 |

| | Temporary palsy (n=20, group A) | p value vs. pre-op | Permanent palsy (N= 9, group B) | p value vs. pre-op | p value group A vs group B |
|---|---|---|---|---|---|
| A | | | | | |
| Pre-op | 1 (0–1) | | 0 (0–1) | | 0.795 |
| 1 week | 1 (1–2) | **0.003** | 2 (0.5–3) | **0.019** | 0.480 |
| 1 month | 1 (1–2) | **0.029** | 2 (0–2) | **0.027** | 0.572 |
| 6 months | 1 (0–1) | 0.105 | 2 (1–2) | **0.031** | 0.063 |
| >12 months | 1 (0–1.5) | 0.105 | 1 (0.5–2) | 0.089 | 0.593 |
| S | | | | | |
| Pre-op | 0 (0–0) | | 0 (0–0.5) | | 0.621 |
| 1 week | 0.5 (0–1.5) | **0.013** | 1 (0–1.5) | 0.168 | 0.982 |
| 1 month | 0 (0–1) | **0.031** | 1 (0–1) | 0.203 | 0.572 |
| 6 months | 0 (0–1) | **0.048** | 0 (0–1) | 0.423 | 0.859 |
| >12 months | 0 (0–1) | **0.048** | 0 (0–1) | 0.586 | 0.980 |
| $F_0$ | | | | | |
| Pre-op | 185.7±43.5 | | 164.1±49.0 | | 0.336 |
| 1 week | 159.4±39.1 | 0.073 | 141.6±69.5 | 0.439 | 0.749 |
| 1 month | 163.7±49.4 | 0.195 | 138.9±44.5 | 0.207 | 0.178 |
| 6 months | 182.3±46.0 | 0.822 | 184.3±63.4 | 0.227 | 0.741 |
| >12 months | 198.8±45.6 | 0.361 | 200.2±95.3 | 0.292 | 0.461 |
| Jitt | | | | | |
| Pre-op | 0.93 (0.68–2.45) | | 1.07 (0.73–2.06) | | 0.816 |
| 1 week | 1.78 (1.11–2.23) | 0.353 | 3.4 (2.04–5.63) | **0.008** | **0.045** |
| 1 month | 3.15 (1.71–5.00) | **0.011** | 3.65 (2.38–4.22) | **0.016** | 0.957 |
| 6 months | 0.75 (0.54–0.96) | **0.045** | 2.19 (0.78–3.85) | 0.156 | **0.039** |
| >12 months | 0.99 (0.51–1.31) | 0.089 | 1.15 (0.78–2.95) | 0.938 | 0.274 |
| Shim | | | | | |
| Pre-op | 4.94 (3.42–8.78) | | 6.62 (3.74–11.87) | | 0.662 |
| 1 week | 7.11 (6.10–8.90) | 0.353 | 12.12 (6.75–23.79) | 0.313 | 0.154 |
| 1 month | 11.29 (6.54–15.68) | 0.064 | 9.96 (7.20–15.63) | 0.25 | 0.999 |
| 6 months | 5.18 (4.00–6.63) | 0.782 | 7.93 (5.62–15.41) | 0.375 | 0.05 |
| >12 months | 4.94 (3.14–8.03) | 0.459 | 5.58 (3.75–6.12) | 0.297 | 0.98 |
| NHR | | | | | |
| Pre-op | 0.16 (0.13–0.22) | | 0.17 (0.13–0.19) | | 0.977 |
| 1 week | 0.16 (0.14–0.21) | 0.938 | 0.24 (0.13–0.49) | 0.195 | 0.522 |
| 1 month | 0.2 (0.15–0.33) | 0.169 | 0.18 (0.15–0.25) | 0.945 | 0.518 |
| 6 months | 0.13 (0.12–0.15) | 0.115 | 0.17 (0.13–0.24) | 0.297 | **0.037** |
| >12 months | 0.13 (0.12–0.16) | **0.015** | 0.14 (0.12–0.22) | 0.297 | 0.309 |
| MPT | | | | | |
| Pre-op | 14.5±5.3 | | 13.9±3.3 | | 0.977 |
| 1 week | 13.2±5.8 | 0.274 | 7.0±2.6 | **0.001** | **0.005** |
| 1 month | 12.8±5.4 | 0.120 | 6.1±2.6 | **<0.001** | **<0.001** |
| 6 months | 14.5±5.8 | 0.976 | 9.2±4.5 | **0.045** | 0.109 |
| >12 months | 14.2±5.2 | 0.754 | 10.3±5.3 | 0.167 | 0.079 |

Values are expressed as medians (IQR) or means (±SD).

VHI − Voice Handicap Index, SIS − Swallowing Impairment Score, NHR – Noise to Harmonics Ratio, MPT – Maximum Phonation Time, G – grade, R – roughness, B – breathiness, A – asthenia, S – strain

To identify any possible prognostic factors for recovery of laryngeal nerve palsy, we additionally analyzed differences between the two groups in different time points of the follow-up period (Table 8). We did note visible differences at the 1st week and 1st month visits between the two groups in several parameters. The most strongly affected variables were VHI total score and physical domain, maximum phonation time, overall perceptual voice quality (G), breathiness (B) and asthenia (A) (Table 4).

However, regardless of nerve injury, by the end of the follow-up period, all changes in the monitored parameters had recovered to preoperative or near-preoperative values with the exception of perceptual evaluation of voice quality.

## 5.3 Endotracheal intubation as a possible etiologic factor for postoperative voice and swallowing disturbances (I)

A total of 203 patients completed the study. The ETI group consisted of 100 patients (25 men, 75 women), age range 21 to 82 years. The LMA group consisted of 103 patients (82 men, 21 women), age range 22 to 82 years. Age distribution between the two anesthesia groups was closely matched ($p = 0.343$). Both groups were comparable in terms of duration of anesthesia and anesthetic management. Since gender distribution was unequal, we divided both groups by gender and compared the results accordingly to avoid a gender bias (Table 9).

**Table 9.** Baseline characteristics of ETI and LMA group patients.

| Characteristic | MEN | | | WOMEN | | |
|---|---|---|---|---|---|---|
| | LMA group (n=82) | ETI group (n=25) | *p* value | LMA group (n=21) | ETI group (n=75) | *p* value |
| Age (years) | 57.3 (±15.2) | 58.9 (±12.8) | 0.627 | 54.0 (±12.9) | 53.0 (±18.2) | 0.815 |
| VHItotal | 8.9 (±10.4) | 7.7 (±8.9) | 0.590 | 8.6 (±8.0) | 11.6 (±14.6) | 0.369 |
| SIS | 1.8 (±2.9) | 2.6 (±3.9) | 0.267 | 3.8 (±4.2) | 3.1 (±4.1) | 0.513 |
| $F_0$ (Hz) | 121.9 (±22.5) | 112.8 (±19.2) | 0.132 | 198.1 (±62.5) | 178.0 (±47.3) | 0.204 |
| Jitter (%) | 1.17 (±1.33) | 0.67 (±0.27) | 0.128 | 1.67 (±3.07) | 1.70 (±1.83) | 0.956 |
| Shimmer (%) | 5.49 (±3.27) | 4.65 (±1.79) | 0.311 | 5.56 (±4.43) | 6.68 (±5.48) | 0.496 |
| NHR (dB) | 0.15 (±0.04) | 0.14 (±0.02) | 0.074 | 0.16 (±0.06) | 0.17 (±0.11) | 0.718 |
| VTI | 0.05 (±0.01) | 0.05 (±0.02) | 0.964 | 0.04 (±0.02) | 0.05 (±0.02) | 0.116 |
| SPI | 17.04 (±9.15) | 17.38 (±9.17) | 0.893 | 20.65 (±17.89) | 16.26 (±7.63) | 0.176 |
| MPT (sec) | 22.7 (±8.9) | 23.2 (±8.6) | 0.857 | 19.2 (±8.5) | 13.6 (±4.3) | **0.001** |

LMA – laryngeal mask airway, ETI – endotracheal intubation, VHI – Voice Handicap Index, SIS – Swallowing Impairment Score, $F_0$ – mean fundamental frequency, NHR – Noise to Harmonics Ratio, VTI – Voice Turbulence Index, SPI – Soft Phonation Index, MPT – Maximum phonation time

VLS showed visual changes in pharyngeal and laryngeal anatomy (vocal fold hyperemia or hematoma, subglottic hematoma, vocal fold vibratory changes, movement disorder of vocal fold etc.) between the baseline and postoperative findings in 4 (4%) patients of the LMA group and 14 (13.6%) patients of the ETI group ($p$=0.02).

Subjective evaluation of voice (VHI) showed no statistically significant postoperative deterioration irrespective of the ventilation method either in male or female patients. Additionally, perceptual evaluation of voice (GRBAS) revealed no voice changes in any patient group. We found a trend of decline in the subjective evaluation of swallowing function (SIS) in female patients in the ETI group ($p$=0.067). In male patients, swallowing function showed no evident postoperative changes in either ventilation group.

Furthermore, in female patients, acoustic voice analysis demonstrated a significant increase of the SPI value in the ETI group ($p$=0.037). In the LMA group, no statistically significant changes were found in any of the investigated acoustic parameters (Table 10). In male patients we noted an increase in mean fundamental frequency ($F_0$) both in the ETI ($p$=0.034) and LMA ($p$=0.055) groups (Table 11).

The MPT values were postoperatively significantly worse in male patients in the case of both ventilation methods (ETI $p$=0.03; LMA $p$<0.001), whereas female patients showed no decrease in MPT values in either group.

When we compared changes from the baseline values in the evaluated parameters and scores between the groups regarding the two anesthesia methods, the only statistically significant difference occurred in SPI for female patients ($p$=0.003) (Table 12). We detected also a marked difference in changes of SIS score in female patients, but it was statistically not significant ($p$=0.07). Evaluation of changes revealed no difference between the two anesthesia methods regarding $F_0$ and MPT values for either gender.

**Table 10.** Comparison of pre- and postoperative acoustic analysis of female patients.

| Variables | ETI group | | | LMA group | | |
|---|---|---|---|---|---|---|
| | Preoperative mean (±SD) | Postoperative mean (±SD) | *p* value | Preoperative mean (±SD) | Postoperative mean (±SD) | *p* value |
| $F_0$ (Hz) | 178.0 (±47.3) | 185.4 (±47.4) | 0.242 | 198.1 (±62.5) | 192.4 (±53.9) | 0.621 |
| Jitter (%) | 1.71 (±1.83) | 1.83 (±2.12) | 0.658 | 1.67 (±3.07) | 1.65 (±2.75) | 0.932 |
| Shimmer (%) | 6.68 (±5.48) | 7.07 (±5.86) | 0.655 | 5.56 (±4.43) | 6.82 (±7.1) | 0.294 |
| NHR (dB) | 0.17 (±0.11) | 0.17 (±0.11) | 0.874 | 0.16 (±0.06) | 0.16 (±0.09) | 0.801 |
| VTI | 0.05 (±0.02) | 0.04 (±0.02) | 0.442 | 0.04 (±0.02) | 0.04 (±0.02) | 0.899 |
| SPI | 16.26 (±7.63) | 18.34 (±8.83) | **0.037** | 20.66 (±17.89) | 14.55 (±5.77) | 0.209 |
| MPT (sec) | 13.6 (±4.3) | 13.19 (±4.2) | 0.350 | 19.2 (±8.5) | 18.3 (±8.9) | 0.440 |

LMA – laryngeal mask airway, ETI – endotracheal intubation, VHI – Voice Handicap Index, SIS – Swallowing Impairment Score, $F_0$ – mean fundamental frequency, NHR – Noise to Harmonics Ratio, VTI – Voice Turbulence Index, SPI – Soft Phonation Index, MPT – Maximum phonation time

**Table 11.** Comparison of pre- and postoperative acoustic analysis of male patients.

| Variables | ETI group | | | LMA group | | |
|---|---|---|---|---|---|---|
| | Preoperative mean (±SD) | Postoperative mean (±SD) | *p* value | Preoperative mean (±SD) | Postoperative mean (±SD) | *p* value |
| $F_0$ (Hz) | 112.8 (±19.2) | 118.6 (±19.2) | **0.034** | 121.9 (±22.5) | 125.3 (±22.1) | 0.055 |
| Jitter (%) | 0.67 (±0.27) | 0.72 (±0.36) | 0.566 | 1.17 (±1.33) | 1.16 (±1.02) | 0.930 |
| Shimmer (%) | 4.65 (±1.79) | 4.64 (±1.80) | 0.992 | 5.49 (±3.27) | 5.64 (±3.27) | 0.507 |
| NHR (dB) | 0.14 (±0.02) | 0.14 (±0.02) | 0.193 | 0.15 (±0.04) | 0.15 (±0.05) | 0.942 |
| VTI | 0.05 (±0.02) | 0.04 (±0.02) | 0.336 | 0.05 (±0.01) | 0.04 (±0.01) | 0.184 |
| SPI | 17.38 (±9.17) | 15.63 (±8.07) | 0.424 | 17.04 (±9.15) | 16.5 (±8.72) | 0.565 |
| MPT (sec) | 23.2 (±8.6) | 18.5 (±5.5) | **0.030** | 22.7 (±8.89) | 20.2 (±7.0) | **<0.001** |

LMA – laryngeal mask airway, ETI – endotracheal intubation, VHI – Voice Handicap Index, SIS – Swallowing Impairment Score, $F_0$ – mean fundamental frequency, NHR – Noise to Harmonics Ratio, VTI – Voice Turbulence Index, SPI – Soft Phonation Index, MPT – Maximum phonation time

**Table 12.** Comparison of changes from the baseline values

| Variables | MEN | | | WOMEN | | |
|---|---|---|---|---|---|---|
| | LMA group mean (±SD) | ETI group mean (±SD) | *p* value | LMA group mean (±SD) | ETI group mean (±SD) | *p* value |
| VHItotal | 1.5 (±7.2) | 1.6 (±4.3) | 0.926 | 2.0 (±5.1) | -1.0 (±10.0) | 0.198 |
| SIS | -0.2 (±1.6) | 0.3 (±2.6) | 0.202 | 0.8 (±2.9) | -0.8 (±3.5) | 0.073 |
| $F_0$ (Hz) | -3.5 (±14.6) | +5.8 (±10.3) | 0.538 | 5.7 (±40.6) | -7.39 (±45.5) | 0.347 |
| Jitter (%) | 0.01 (±1.2) | -0.05 (±0.38) | 0.821 | 0.02 (±0.8) | -0.12 (±1.99) | 0.804 |
| Shimmer (%) | -0.15 (±1.86) | 0.01 (±2.58) | 0.774 | -1.27 (±4.16) | -0.39 (±6.35) | 0.640 |
| NHR (dB) | 0.001 (±0.05) | 0.01 (±0.03) | 0.471 | -0.03 (±0.05) | -0.003 (±0.12) | 0.987 |
| VTI | 0.003 (±0.02) | 0.004 (±0.02) | 0.795 | -0.001 (±0.02) | 0.003 (±0.03) | 0.774 |
| SPI | 0.54 (±7.66) | 1.74 (±8.74) | 0.576 | 6.1 (±15.01) | -2.08 (±7.05) | **0.005** |
| MPT (sec) | 2.6 (±5.7) | 7.7 (±8.2) | 0.205 | 0.9 (±4.2) | 0.4 (±3.2) | 0.631 |

LMA – laryngeal mask airway, ETI – endotracheal intubation, VHI – Voice Handicap Index, SIS – Swallowing Impairment Score, $F_0$ – mean fundamental frequency, NHR – Noise to Harmonics Ratio, VTI – Voice Turbulence Index, SPI – Soft Phonation Index, MPT – Maximum phonation time

# 6. DISCUSSION

Thyroid disease and surgery related voice and swallowing disturbances have been widely investigated. Regarding the different evaluation methods, previous studies have given rather conflicting results. As recurrent laryngeal nerve lies in the close proximity of thyroid gland, contribution of other etiologic factors to these complaints still remains vague. Similarly, the role and duration of laryngeal nerve damage in post-thyroidectomy voice and swallowing changes require clarification.

## 6.1 Preoperative voice and swallowing function in thyroid patients (II)

In our study, thyroidectomy patients showed only mildly detectable voice changes both objectively and subjectively prior to operation. This finding can be explained by the fact that all our patients were preoperatively in a relative euthyroid state. Voice disorders associated with thyroid hormone imbalance are believed to alleviate with treatment within three to six months and all our patients had been medically treated prior to surgery (Kumar *et al*., 2016).

We noted some trend for increased vocal handicap in the emotional subscale of VHI (VHIe), which could be explained by general discomfort and sensory abnormality in the laryngeal region caused by thyroid mass in these patients. Similarly, Viana Baptista *et al.* found that 95% of patients had VHI total scores indicative of only mild handicap and GRBAS-G scores either 0 or 1 in all studied patients (Viana Baptista *et al*., 2020). We also found no correlation between weight of the thyroid gland postoperative histologic specimen and VHI scores, which further confirms the modest role of thyroid compression on voice quality. However, increased jitter and NHR in our study may indicate slight anatomical changes in the vocal folds.

On the other hand, we found more frequently increased impairment of swallowing function in our thyroidectomy patients, which is inconsistent with previous studies (Sorensen *et al*. 2018; Lombardi *et al*., 2006; Lombardi *et al*., 2009, Holler and Anderson, 2014). Previous research has shown that the main reasons for swallowing disturbances are esophageal compression and increased transit time, which are positively correlated with goiter size (Sorensen *et al*., 2018; Scerrino *et al*., 2013). In the present study, we found no correlation between thyroid weight and subjective swallowing impairment. An alternative explanation could be that swallowing disturbances and globus sensation are caused by the impaired innervation of UES. Compression on the nerves innervating the sphincter might result in reduced UES pressure already preoperatively, leading to predisposition to gastric or duodenal reflux. A study by Fiorentino *et al*. reported LPR signs in up to 88% of patients undergoing thyroid surgery for compressive signs (Fiorentino *et al.*, 2011). However, previous

studies involving esophageal manometry have detected a decrease in UES only after thyroid surgery, but not prior to the operation (Sorensen *et al*., 2018; Scerrino *et al*., 2013).

Another explanation is that LPR, instead of thyroid compression, is accountable for swallowing impairment, which has previously been described by Holler and Anderson, as well as by Fiorentino *et al*. (Holler and Anderson, 2014; Fiorentino *et al*., 2011). However, the clinical findings (dependent on RFS scores) indicative of LPR in our study were similar in both groups. According to another theory, the symptoms of thyroid compression mimic the symptoms of LPR disease, which could lead to false positive results of the RSI questionnaire. Analysis of the RSI questionnaire detected higher values for questions addressing general neck discomfort symptoms but not for questions about reflux complaints (heartburn, chest pain, indigestion or stomach acid coming up). The suspicion arises, therefore, that the RSI's questions addressing cough irritation, swallowing difficulties, sensation of lump etc, could alternatively lead to increased scores due to the thyroid gland's compression on the surrounding tissues. However, since ≤50% of LPR patients are estimated to meet gastroesophageal reflux disease (GERD) criteria and complain about gaseous, upright and daytime reflux events rather than about heartburn, chest pain etc., this may not be the correct explanation (Jaspersen *et al*., 2003). The existence of a weak positive correlation between thyroid weight and RFS also supports the explanation that an enlarged thyroid decreases UES pressure and provides a basis for LPR.

An important limitation of our study is the lack of objective evaluation of LPR by means of MII-pH monitoring and UES manometry. LPR is a condition that has proven to be difficult to diagnose due to non-specific symptoms and findings. Currently, 24h multi-channel intraluminal impedance and pH (MII-pH) monitoring are considered to be the gold standard for LPR diagnosis. Due to the absence of specific instruments at our research hospital, it was not possible for us to use either MII-pH or esophageal manometry. In our study, we used the RSI questionnaire and RFS scores to identify local neck symptoms and clinical signs indicative of LPR. A study by Weitzendorfer *et al*. found that subjects with a pathological result in MII-pH showed significant correlation between values of salivary pepsin levels and measurement of RSI score. Additionally, in the same study, higher levels in salivary pepsin test were correlated with RFS score (Weitzendorfer *et al*., 2020). Therefore, patient-reported outcome questionnaires have been advised to use as a diagnostic tool for LPR disease (Lechien *et al*., 2020).

Previous research has shown that glottic insufficiency *per se* can lead to muscle tension resulting in globus sensation during swallowing. Consequently, RSI values can fluctuate in cases of glottic insufficiency regardless of the presence of LPR (Patel *et al.*, 2014). However, our study found no difference in MPT measurement between the study and control group, which could indicate glottic insufficiency in preoperative thyroid patients.

In addition to the subjective evaluation of swallowing, it would have also been useful to use instrumental assessment (functional endoscopic evaluation of swallowing or videofluoroscopy), to differentiate between functional and sensational swallowing disturbances. Therefore, further studies including objective evaluation of LPR and swallowing function are needed.

## 6.2 Voice and swallowing disorders after thyroid surgery (III)

Potential risk factors for postoperative nerve injury are older age, recurrent surgery, large thyroid mass, malignant thyroid disease, inexperienced surgeon etc (Choi *et al*., 2018; Banks *et al*., 2012, Bergenfelz *et al*., 2008). Our study identified large thyroid mass to be the risk factor for nerve injury following thyroid surgery. A large thyroid increases the surgical field and affects the overview of the surgical site, which in turn induces more extensive tissue damage.

In a systematic review by Jeannon *et al*. 9.8% cases of temporary paralysis and 2.3% cases of permanent paralysis were identified after thyroid surgery (Jeannon *et al*., 2009). As different studies use a large variety of methods when diagnosing laryngeal nerve injury, the exact percentage is still unclear. Diagnostic methods vary to a large extent, from the rather unreliable subjective complaints or indirect laryngoscopy to direct laryngoscopy and EMG evaluation (Kim *et al*., 2021). Due to the relatively high dropout rate, we could not identify precise incidence of postoperative vocal fold palsy in our study. In a majority of studies, recurrent laryngeal nerve injury is diagnosed based solely on vocal fold paralysis. In our study, we also included patients with an evident finding of vocal fold motion deficit defined as paresis, which can most likely explain the high incidence of nerve injury among our patients. A study by Dralle *et al*. comprising 16448 thyroidectomy cases found no statistical significance in RLN injury irrespective of IONM usage, therefore the fact that we did not use IONM should not have played a role in these high numbers (Dralle *et al.*, 2004).

In postoperative RLN paralysis, recovery may be anticipated at a rate ranging from 50% to 88% (Choi *et al*., 2018; Wagner *et al*., 2004; Echternach *et al*., 2009). Dynamic evaluation of laryngeal anatomy within 12–18 months postoperatively revealed that in our study 70.4% of the laryngeal nerve injuries turned out to be temporary.

The specific clinical findings of vocal fold tonicity loss and shortening and sluggish motion, which we detected in a considerable number of patients (N14), have previously been described in the context of EBSLN injury. We identified superior laryngeal nerve injury, either uni- or bilateral, in 54% of these patients. As EMG was in most cases conducted on the day of the first-month postoperative follow-up visit, to avoid extra inconvenience for the patient, we might have expected some degree of misdiagnosis due to edema and damage to the surrounding tissues. In addition, it remains unclear how the glottal configuration

and function are affected in concurrent EBSLN and RLN paralysis. As the EMG evaluations with the same clinical finding yielded different results, we could not make any definitive conclusions about the etiopathogenesis of these changes. Orestes and Chettri have alternatively suggested that cricothyroid dysfunction following thyroid surgery can appear due to direct cricothyroid muscle injury and may occur more often than the injury of the EBSLN during isthmus, pyramidal lobe or delphian node dissection (Orestes *et al*., 2006). This supplementary injury could be one alternative explanation for the above contradictory results. Another suggestion might be postoperative hypothyroidism-induced vocal fold myxedema. Histological changes in the vocal folds can develop rapidly in the setting of hypothyroidism and can appear even as early as 36 to 48 hours postoperatively (Birkent *et al*., 2008). This theory is supported by the fact that all the above-mentioned patients in our study had undergone total thyroidectomy. However, previous studies involving postoperative laryngeal evaluation have not reported such findings of vocal fold myxedema, nor is this in accordance with our EMG results.

At the first week evaluation, patients with intact laryngeal nerves had no subjective decline in voice related quality of life. Kletzien *et al*. stated that traditional quantitative methods alone (VHI etc.), when tracking voice disturbances after thyroid surgery, may not capture the burden and dysphonia perceived by the patient adequately (Kletzient *et al*., 2018). Additional patient-reported voice impairment described during interviews might reveal more complaints. However, for the group of patients with laryngeal nerve injury, we found a significant deterioration of both subjective and objective voice quality. Jacobson *et al*. considered a difference of 18 points or higher clinically significant for the total VHI score (Jacobson *et al*., 1997). We found a considerable increase of mean VHI total score for patients with nerve injury from baseline 10.5 to 45.6 (median from 7 to 38) at the first week evaluation, in contrast to a 2.1-point increase (no median rise) for the group of patients with intact nerves. This decline in subjective and objective voice quality is consistent with the insufficient glottal closure pattern, as was also the decline in maximum phonation time. Perceptual voice quality analysis additionally presented disturbances in all evaluated aspects of voice.

Furthermore, evaluation of postoperative swallowing function revealed remarkable disturbances in all postoperative patients regardless of the presence of nerve injury. Patients with postoperatively intact laryngeal nerves showed quick resolution of complaints and swallowing function had even improved in comparison to the pre-operative status by the end of the follow-up period. Similar postoperative improvement in swallowing function was described by Greenblatt and Sabaretnam (Greenblatt *et al*., 2009; Sabaretnam *et al.*, 2012). This confirms that compression by an enlarged thyroid gland can affect swallowing function irrespective of surgical damage and should not be overlooked. Compression can impair UES relaxation and restricted laryngeal elevation affects swallowing irrespective of surgical damage. In contrast, for patients with nerve injury, the values of SIS score were increased during the whole follow-up

period, which indicates that after thyroid surgery both laryngeal nerve injury and compressive symptoms can affect swallowing function irrespective of each other or in combination.

When analyzing the differences between the two groups at different time points, to identify any possible prognostic factors for recovery, we had to admit that the results might have been affected by the relatively low number of patients with permanent laryngeal paralysis, which probably affected the reliability of some statistical analyses. However, although permanent and temporary palsy seem to be clinically similar conditions at the early stage, we detected remarkable differences between the two groups regarding the values of VHI total and physical domain scores, MPT, jitter and GRBAS scale during the follow-up period. Hence, possible indicators of persistent nerve injury can be a drastic decline in subjective and perceptual voice quality, significant increase in glottic insufficiency and delayed recovery of jitter values. Jitter is defined as a parameter of frequency variation and can be affected by the lack of control of the vocal fold vibration. Loss of tonicity and motion, evident in a number of patients with nerve injury in our study, can serve as a basis for increased jitter values. This could also explain why several previous studies have not reported changes in jitter values, as they have concentrated solely on patients with clinical paralysis of the vocal fold, whereas we included also cases of paresis.

Nevertheless, regardless of nerve injury, by the end of the follow-up period, all changes in the monitored parameters had recovered to preoperative or near-preoperative values. Development of efficient laryngeal compensatory mechanisms over time should be expected in a majority of patients with postoperative dysphonia and dysphagia. This data is of vital importance for patients whose quality of life has been affected by post-thyroidectomy nerve injury.

## 6.3 Endotracheal intubation as a possible etiologic factor for postoperative voice and swallowing disturbances (I)

To evaluate the effect of general anesthesia on laryngeal structures, we evaluated clinical picture, voice and swallowing quality of two groups of patients with no surgical interventions in the head and neck region – laparoscopic cholecystectomy with the ETI anesthesia and varicectomy or hernia repair with the LMA. Analysis revealed that although clinical signs indicated more serious trauma in the group of endotracheal intubation, objective measurements and patient subjective evaluation of voice and swallowing function were similar irrespective of the ventilation method used. Postoperative laryngeal injury may be caused either by direct intubation trauma (including hematoma, mucosal edema and dislocation or subluxation of the arytenoids) or by the operation itself when performed in the head and neck regions (Stojadinovic *et al*., 2008; Sariego *et al*., 2010). In our study pathogenesis was most probably related to the pressure and inflammation induced by the tube and the cuff. When pressure

from the unyielding walls of the tube exceeds capillary pressure in the laryngeal mucosa, mucosal ischemia causes irritation, inflammation, congestion, and edema already within the first few hours (Gaynor *et al*., 1985).

Alternatively, postoperative decrease in voice and swallowing quality can be affected by anesthesia, physical pain or analgesia medications. In our study we found increased postoperative fundamental frequency and increased maximum phonation time in male patients with the use of both ventilation methods. This indicates it was caused by general anesthesia medications rather than by the ventilation tube itself. Increased fundamental frequency has previously been explained by lowered sensation of subglottic pressure in the anesthetized larynx, which leads to pressed phonation and a rise in fundamental frequency. Administered anesthetic agents can also interfere with fine neuromuscular control and lead to impairment in voice tonality by this origin (Karcz *et al*., 2013). Furthermore, inhalation of anesthetic gases or intake of drying medications may also lead to desiccation of the vocal fold mucosa, affecting thus the vocal signal. Similar results have been documented also previously by Zimmert *et al*., who found increased $F_0$ in both groups where the studied ventilation methods were employed (Zimmert *et al*., 2007). Likewise, the decreased MPT in our study can be secondary to anesthetic and analgetic management. The post-operative effect of barbiturates, opioids, and pain itself suppresses breathing muscle function and causes restricted or depressed ventilation, which leads to diminished phonation time (Fu *et al*., 2018). Our results are consistent with those of Hamdan *et al*. who also found decreased postoperative values of MPT irrespective of the ventilation method used (Hamdan *et al*., 2008).

The results of acoustic analysis in previous studies have revealed changes in perturbation parameters (shimmer and jitter) and NHR scores; however, none of these studies have documented changes in soft phonation index (SPI) parameter. We found a significant increase in postoperative SPI values in female patients. SPI can be thought of as an indicator of how completely or tightly the vocal folds adduct during phonation (Koreman *et al*., 1997; Mathew *et al*., 2009). Correlations have also been found between SPI and values of perceptual evaluation GRBAS scale Grade (G) and Breathiness (B) (Bhuta *et al*., 2004). Incomplete vocal fold adduction during phonation causes rapid air escape from the lungs, which can also lead to increased MPT values as discussed above. In this study, we found increased postoperative SPI values in female patients who were intubated with the endotracheal tube. Comparison of the results between the two anesthesia methods revealed statistically significant difference. The fact that SPI values were increased only in female patients in the ETI group indicates that it may have been caused by direct damage to the vocal cords. Female larynxes have been found to be more susceptible to mechanical trauma due to differences related to laryngeal physiology, anatomy, hormone differences and other non-laryngeal physiology and behavioral characteristics (Hunter *et al*., 2011). According to the developers of the MDVP software, psychological stress could also be a factor for increase in SPI. This also correlates with female gender, as findings suggest that women tend to report higher levels of anxiety,

which may contribute to their increased vulnerability to emotional stress and related disorders (Bangasser *et al*., 2014; Kessler *et al*., 1981).

Previous studies on swallowing function and dysphagia after general anesthesia have shown rather conflicting results. Dysphagia and odynophagia are generally associated with the trauma caused by high cuff pressure, which leads to edema, inflammation and impaired laryngeal motility. Several studies have associated laryngeal mask airway with higher incidence of dysphagia compared to endotracheal intubation (Rieger *et al*., 1997; Venugopal *et al*., 2016). Our study, however, found no disturbances in swallowing function after general anesthesia.

Consequently, both investigated ventilation methods can be regarded as practically equal. Although clinical signs showed more intense trauma in the ETI group, objective measurements and patient subjective evaluation of voice and swallowing function were similar in both groups.

# CONCLUSIONS

1. Changes in the laryngeal area caused by thyroid disorders do not impact patient's voice related quality of life according to VHI, but do indicate a slight decline in objective voice quality, resulting in increased hoarseness. Thyroid disorders cause marked disturbances in swallowing quality. Higher RSI scores and positive correlation between RFS and thyroid weight indicate a possible role of the enlarged gland in the aggravation of LPR symptoms in thyroid patients. There is no correlation of voice and swallowing disturbances with thyroid pathology or weight, voice use or smoking status.
2. Patients with postoperatively intact laryngeal nerves show a mild decline in subjective evaluation of voice quality (increased perceptual strain in voice) and mild disturbances of voice related quality of life (VHI physical domain). Patients with postoperative laryngeal nerve injury experience substantial deterioration in objective voice quality and voice related quality of life. The characteristics most affected are VHI total score, jitter and MPT. More profound impairment is observed in the patient group with permanent paralysis. Thyroidectomy causes subjective swallowing changes in the early postoperative period, irrespective of laryngeal nerve injury. Large thyroid mass is a risk factor for postoperative laryngeal nerve injury. There is no correlation of older age, smoking status, thyroid disease, the extent of surgery or duration of anesthesia with increased risk of nerve injury.
3. Regardless of postoperative laryngeal nerve injury, most of the monitored parameters recovered to preoperative or near to preoperative values by the end of 12–18-month follow-up period. Patients with laryngeal nerve injury require longer time to recover preoperative function. In patients without laryngeal nerve injury, swallowing function improves following thyroid surgery. Possible indicators for permanent paralysis are delayed recovery in the values of MPT and jitter plus persistent perceptual breathiness and asthenia in voice.
4. We found no substantial role of general anesthesia on postoperative voice and swallowing disturbances within one week of surgery.

# REFERENCES


Alfonso A, Christoudias G, Amaruddin Q, Herbsman H, Gardner B. Tracheal or esophageal compression due to benign thyroid disease. Am J Surg. 1981;142(3):350–4.

Altman KW, Haines GK 3rd, Vakkalanka SK, Keni SP, Kopp PA, Radosevich JA. Identification of thyroid hormone receptors in the human larynx. Laryngoscope. 2003;113(11):1931–4.

Aluffi P, Policarpo M, Cherovac C, Olina M, Dosdegani R, Pia F. Post-thyroidectomy superior laryngeal nerve injury. Eur Arch Otorhinolaryngol. 2001;258(9):451–4.

Bangasser DA, Valentino RJ. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. Front Neuroendocrinol. 2014;35(3):303–319.

Banks CA, Ayers CM, Hornig JD, Lentsch EJ, Day TA, Nguyen SA, Gillespie MB. Thyroid disease and compressive symptoms. Laryngoscope. 2012;122(1):13–6.

Barczyński M, Randolph GW, Cernea CR, Dralle H, Dionigi G, Alesina PF, Mihai R, Finck C, Lombardi D, Hartl DM, Miyauchi A, Serpell J, Snyder S, Volpi E, Woodson G, Kraimps JL, Hisham AN; International Neural Monitoring Study Group. External branch of the superior laryngeal nerve monitoring during thyroid and parathyroid surgery: International Neural Monitoring Study Group standards guideline statement. Laryngoscope. 2013;123(4_ suppl):S1–14.

Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope. 2001;111(8):1313–7.

Belafsky, PC, Postma, GN, Koufman, JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274–7.

Bergenfelz A, Jansson S, Kristoffersson A, et al. Complications to thyroid surgery: results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbecks Arch Surg. 2008;393:667–73.

Bhattacharyya N, Kotz T, Shapiro J. Dysphagia and aspiration with unilateral vocal cord immobility: incidence, characterization, and response to surgical treatment. Ann Otol Rhinol Laryngol 2002;111(8):672–9.

Bhuta T, Patrick L, Garnett JD. Perceptual evaluation of voice quality and its correlation with acoustic measurements. J Voice Off J Voice Found. 2004;18(3):299–304.

Birkent H, Karacalioglu O, Merati AL, Akcam T, Gerek M. Prospective study of the impact of thyroid hormone replacement on objective voice parameters. Ann Otol Rhinol Laryngol. 2008;117(7):523–527.

Bliss RD, Gauger PG, Delbridge LW. Surgeon's approach to the thyroid gland: surgical anatomy and the importance of technique. World J Surg. 2000;24(8):891–7.

Brodsky MB, Akst LM, Jedlanek E, Pandian V, Blackford B, Price C, Cole G, Mendez-Tellez PA, Hillel AT, Best SR, Levy MJ. Laryngeal Injury and Upper Airway Symptoms After Endotracheal Intubation During Surgery: A Systematic Review and Meta-analysis. Anesth Analg. 2021;132(4):1023–1032.

Caroline M, Joglekar SS, Mandel SM, Sataloff RT, Heman-Ackah YD. The predictors of postoperative laryngeal nerve paresis in patients undergoing thyroid surgery: a pilot study. J Voice. 2012;26(2):262–6.

Carrau RL, Pou A, Eibling DE, Murry T, Ferguson BJ. Laryngeal framework surgery for the management of aspiration. Head Neck 1999;21(2):139–45.

Chandrasekhar SS, Randolph GW, Seidman MD, Rosenfeld RM, Angelos P, Barkmeier-Kraemer J, et al. Clinical practice guideline: Improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg. 2013;148 (Suppl. 6):1–37.

Chen AY, Bernet VJ, Carty SE, Davies TF, Ganly I, Inabnet WB, Shaha AR. American thyroid association statement on optimal surgical management of goiter. Thyroid. 2014;24:181–189.

Chiu WY, Yang CC, Huang IC, et al. Dysphagia as a manifestation of thyrotoxicosis: Report of three cases and literature review. Dysphagia. 2004;19(2):120–124.

Choi YS, Joo YH, Park YH, Kim SY, Sun DI. Factors Predicting the Recovery of Unilateral Vocal Fold Paralysis After Thyroidectomy. World J Surg. 2018;42:2117–2122.

Chun BJ, Bae JS, Lee SH, Joo J, Kim ES, Sun DI. A prospective randomized controlled trial of the laryngeal mask airway versus the endotracheal intubation in the thyroid surgery: evaluation of postoperative voice, and laryngopharyngeal symptom. World J Surg. 2015;39(7):1713–20.

Crumley RL. Unilateral recurrent laryngeal nerve paralysis. J Voice. 1994;8(1):79–83.

Cusimano A, Macaione I, Fiorentino E. How uncomplicated total thyroidectomy could aggravate the laryngopharyngeal reflux disease? Eur Arch Otorhinolaryngol. 2016; 273(1):197–202.

de Benoist B, Andersson M, Egli I, Takkouche B, Allen H. Iodine status worldwide. WHO Global Database on Iodine Deficiency. Geneva: World Health Organization; 2004.

Dralle H, Sekulla C, Haerting J, et al. Risk factors of paralysis and functional outcome after recurrent laryngeal nerve monitoring in thyroid surgery. Surgery.2004;136: 1310–1322.

Dursun G, Sataloff RT, Spiegel JR, et al. Superior laryngeal nerve paresis and paralysis. J Voice. 1996;10:206–211.

Echternach M, Maurer CA, Mencke T, Schilling M, Verse T, Richter B. Laryngeal complications after thyroidectomy: is it always the surgeon? Arch Surg. 2009;144: 149–153.

Fiorentino E, Cipolla C, Grceffa G, et al. Local neck symptoms before and after thyroidectomy: a possible correlation with reflux laryngopharyngitis. Eur Arch Otorhinolaryngol. 2011;268(5):715–20.

Flint PW, Downs DH, Coltrera MM. Laryngeal synkinesis following reinnervation in the rat. Ann Otol Rhinol Laryngol. 1991;100:797–806.

Förster G, Müller AH. PCA Atrophy and Synkinesis as the Main Factors for Persistent Vocal Fold Immobility in RLN Paralysis. Laryngoscope. 2021 Apr;131(4):E1244-E1248.

Friedrich T, Hansch U, Eichfeld U, Steinert M, Staemmler A, Schonfelder M. Recurrent laryngeal nerve paralysis as intubation injury?. Chir Z Alle Geb Oper Medizen. 2000;71(5):539–544.

Fu S, Lin W, Zhao X, Ge S, Xue Z. Quantitative Relationships between Pulmonary Function and Residual Neuromuscular Blockade. BioMed Res Int. 2018;2018: 9491750.

Gaynor EB, Greenberg SB. Untoward sequelae of prolonged intubation. The Laryngoscope. 1985;95(12):1461–1467.

Gong Y, Xu X, Wang J, Che L, Wang W, Yi J. Laryngeal mask airway reduces incidence of post-operative sore throat after thyroid surgery compared with endotracheal tube: a single-blinded randomized controlled trial. BMC Anesthesiol. 2020 Jan 14;20(1):16.

Greenblatt DY, Sippel R, Leverson G, Frydman J, Schaefer S, Chen H. Thyroid resection improves perception of swallowing function in patients with thyroid disease. World J Surg. 2009;33:255–60.

Guyton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006

Hamdan AL, Kanazi G, Rameh C, Rifai H, Sibai A. Immediate post-operative vocal changes in patients using laryngeal mask airway versus endotracheal tube. J Laryngol Otol. 2008;122(8):829–35.

Hari Kumar KV, Garg A, Ajai Chandra NS, Singh SP, Datta R. Voice and endocrinology. Indian J Endocrinol Metab. 2016;20(5):590–594.

Heman-Ackah YD, Joglekar SS, Caroline M, Becker C, Kim EJ, Gupta R, Mandel SM, Sataloff RT. The prevalence of undiagnosed thyroid disease in patients with symptomatic vocal fold paresis. J Voice. 2011;25(4):496–500.

Henry LR, Helou LB, Solomon NP, Howard RS, Gurevich-Uvena J, Coppit G, Stojadinovic A. Functional voice outcomes after thyroidectomy: an assessment of the Dsyphonia Severity Index (DSI) after thyroidectomy. Surgery. 2010;147:861–70.

Henry LR, Solomon NP, Howard R, Gurevich-Uvena J, Horst LB, Coppit G, Orlikoff R, Libutti SK, Shaha AR, Stojadinovic A. The functional impact on voice of sternothyroid muscle division during thyroidectomy. Ann Surg Oncol. 2008;15(7):2027–33.

Hirano M. Clinical examination of voice. Disord Hum Commun. 1981;5:1–99.

Holler, T, Anderson J. Prevalence of voice & swallowing complaints in Pre-operative thyroidectomy patients: a prospective cohort study. J Otolaryngol Head Neck Surg. 2014;43(1):28.

Hoyes AD, Kershaw DR. Anatomy and development of the thyroid gland. Ear Nose Throat J. 1985;64(7):318–33.

Hunter EJ, Tanner K, Smith ME. Gender differences affecting vocal health of women in vocally demanding careers. Logoped Phoniatr Vocol. 2011;36(3):128–136.

Husain S, Sadoughi B, Mor N, Levin AM, Sulica L. Time course of recovery of idiopathic vocal fold paralysis. Laryngoscope. 2018;128(1):148–152.

İlhan M, Arabaci E, Turgut S, Karaman O, Danalioglu A, Tasan E. Esophagus motility in overt hypothyroidism. J Endocrinol Invest. 2014;37(7):639–44.

Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS, Newman CW. The Voice Handicap Index (VHI) Development and Validation. Am J Speech Lang Pathol. 1997;6(3):66–70.

Jang YY, Lee SJ, Jeon JY, Lee SJ. Analysis of video fluoroscopic swallowing study in patients with vocal cord paralysis. Dysphagia 2012;27(2):185–90.

Jaspersen D, Kulig M, Labenz J, Leodolter A, Lind T, Meyer-Sabellek W, Vieth M, Willich SN, Lindner D, Stolte M, Malfertheiner P. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. Aliment Pharmacol Ther. 2003;17(12):1515–20.

Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. Int J Clin Pract. 2009;63:624–629.

Karcz M, Papadakos PJ. Respiratory complications in the postanesthesia care unit: A review of pathophysiological mechanisms. Can J Respir Ther CJRT Rev Can Ther Respir RCTR. 2013;49(4):21–29.

Kessler RC, Brown RL, Broman CL. Sex differences in psychiatric help-seeking: evidence from four large-scale surveys. J Health Soc Behav. 1981;22(1):49–64.

Kim SY, Kim GJ, Lee DH, Bae JS, Lee SH, Kim JS, Hwang YS, Shim MR, Park YH, Sun DI. Analysis of voice changes after thyroidectomy using the thyroidectomy-related voice and symptom questionnaire. Auris Nasus Larynx. 2021;48(5):963–972.

Kitahara S, Masuda Y, Kitagawa Y. Vocal fold injury following endotracheal intubation. J Laryngol Otol. 2005;119(10):825–827.

Kletzien H, Macdonald CL, Orne J, Francis DO, Leverson G, Wendt E, Sippel RS, Connor NP. Comparison Between Patient-Perceived Voice Changes and Quantitative Voice Measures in the First Postoperative Year After Thyroidectomy: A Secondary Analysis of a Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2018;144(11):995–1003.

Koreman J, Pützer M. Finding correlates of vocal fold adduction deficiencies. Phonus. 1997;3:155–78.

Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg. 2000;123:385–388.

Kovacic G. Voice and hyperthyroidism: Subjective voice complaints and alterations of the acoustic parameters of the voice. Res Rev Insights. 2018;2(1): 1–4.

Krekeler BN, Wendt E, Macdonald C, Orne J, Francis DO, Sippel R, Connor NP. Patient-Reported Dysphagia After Thyroidectomy: A Qualitative Study. JAMA Otolaryngol Head Neck Surg. 2018;144:342–348.

Krohn K, Wohlgemuth S, Gerber H, Paschke R. Hot 26. microscopic areas of iodine-deficient euthyroid goitres contain constitutively activating TSH receptor mutations. J Pathol. 2000;192:37–42.

Lang BH, Wong CK, Ma EP. A systematic review and meta-analysis on acoustic voice parameters after uncomplicated thyroidectomy. Laryngoscope. 2016;126:528–37.

Lang IM, Shaker R. Anatomy and physiology of the upper esophageal sphincter. Am J Med. 1997;103(5A):50S-55S.

Lechien JR, Akst LM, Hamdan AL, Schindler A, Karkos PD, Barillari MR, Calvo-Henriquez C, Crevier-Buchman L, Finck C, Eun YG, Saussez S, Vaezi MF. Evaluation and Management of Laryngopharyngeal Reflux Disease: State of the Art Review. Otolaryngol Head Neck Surg. 2019;160(5):762–782.

Lechien JR, Saussez S, Muls V, Barillari MR, Chiesa-Estomba CM, Hans S, Karkos PD. Laryngopharyngeal Reflux: A State-of-the-Art Algorithm Management for Primary Care Physicians. J Clin Med. 2020;9(11):3618.

Lee K, Chan Y, Das S. Essential Otolaryngology. 10th ed. New York, NY: McGraw-Hill Medical; 2012.

Lombardi CP, Raffaelli M, De Crea C, D'Alatri L, Maccora D, Marchese MR, Paludetti G, Bellantone R. Long-term outcome of functional post-thyroidectomy voice and swallowing symptoms. Surgery. 2009;146(6):1174–81.

Lombardi CP, Raffaelli M, D'Alatri L, Marchese MR, Rigante M, Paludetti G, Bellantone R. Voice and swallowing changes after thyroidectomy in patients without inferior laryngeal nerve injuries. Surgery. 2006;140(6):1026–32; discussion 1032–4.

Mahmodlou R, Aghasi MR, Sepehrvand N. Idenifying the non-recurrent laryngeal nerve: preventing a major risk of morbidity during thyroidectomy. Int J Prev Med. 2013;4(2):237–40

Maktabi MA, Smith RB, Todd MM. Is routine endotracheal intubation as safe as we think or wish? Anesthesiology. 2003;99(2):247–248.

Martins NMDS, Novalo-Goto ES, Diz-Leme ICM, Goulart T, Ranzatti RP, Leite AKN, Dedivitis RA, Matos LL. Patient Perception of Swallowing after Thyroidectomy in

the Absence of Laryngeal Nerve Injury. ORL J Otorhinolaryngol Relat Spec. 2020;82:274–284.
Mathew MM, Bhat JS. Soft phonation index – a sensitive parameter? Indian J Otolaryngol Head Neck Surg Off Publ Assoc Otolaryngol India. 2009;61(2):127–130.
Mclvor NP, Flint DJ, Gillibrand J, et al. Thyroid surgery and voice-related outcomes. Aust N Z J Surg. 2000;70(3):179–83.
Mencke MD, Thomas, Echternach MD, Mathias, Kleinschmidt MD, Stefan, et al. Laryngeal Morbidity and Quality of Tracheal Intubation A Randomized Controlled Trial. Anesthesiology. 2003;98(5):1049–1056.
Mendels EJ, Brunings JW, Hamaekers AW, Stokroos RJ, Kremer B, Baijens LJ. Adverse laryngeal effects following short-term general anesthesia: A systematic review. Arch Otolaryngol Neck Surg. 2012;138(3):257–264.
Mohebati A, Shaha AR. Anatomy of thyroid and parathyroid glands and neurovascular relations. Clin Anat. 2012;25(1):19–31.
Moini J, Pereira K, Samsam M. Epidemiology of Thyroid Disorders. Elsevier Science Ltd; 2019
Moran RE, Castro AF. The superior laryngeal nerve in thyroid surgery. Ann Surg. 1951;134(6):1018–1021.
Müller AH. Laryngeal Synkinesis: A Viable Condition for Laryngeal Pacing. Adv Otorhinolaryngol. 2020;85:112–119.
Orestes MI, Chhetri DK. Superior laryngeal nerve injury: effects, clinical findings, prognosis, and management options. Curr Opin Otolaryngol Head Neck Surg. 2014;22:439–443.
Park SK, Ko G, Choi GJ, Ahn EJ, Kang H. Comparison between supraglottic airway devices and endotracheal tubes in patients undergoing laparoscopic surgery: A systematic review and meta-analysis. Hanaoka. K, ed. Medicine (Baltimore). 2016; 95(33):e4598.
Pfaff JA, Caruse-Sales H, Jaworek A, Sataloff RT. "The vocal effects of thyroid disorders and their treatment.", Clinical assessment of Voice 2nd ed., edited by Sataloff RT, Plural Publishing, 2017, pp 291–302.
Pröschel U, Eysholdt U. Kurzzeit-Veränderungen an Kehlkopf und Stimme nach Intubation. Laryngo-Rhino-Otol. 2008;72(02):93–97.
Randolph G. 2003. Surgery of the thyroid and parathyroid glands. Third Ed. Philadelphia, PA; [London]: Saunders.
Rieger A, Brunne B, Hass I, Brummer G, Spies C, Striebel HW, Eyrich K. Laryngopharyngeal complaints following laryngeal mask airway and endotracheal intubation. J Clin Anesth. 1997;9(1):42–7.
Roman BR, Randolph GW, Kamani D. Conventional Thyroidectomy in the Treatment of Primary Thyroid Cancer. Endocrinol Metab Clin North Am. 2019;48(1):125–141.
Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, Pelizzo MR, Pezzullo L. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg. 2004;28(3):271–6.
Sabaretnam M, Mishra A, Chand G, Agarwal G, Agarwal A, Verma AK, Mishra SK. Assessment of swallowing function impairment in patients with benign goiters and impact of thyroidectomy: a case control study. World J Surg. 2012;36:1293–9.
Sanders I, Wu B, Mu L, Li Y, Biller HF. The Innervation of the Human Larynx. Arch Otolaryngol Head Neck Surg. 1993;119:934–939.
Sariego J. Vocal fold hypomobility secondary to elective endotracheal intubation: a general surgeon's perspective. J Voice Off J Voice Found. 2010;24(1):110–112.

Sasou S, Nakamura S, Kurihara H. Suspensory ligament of Berry: its relationship to recurrent laryngeal nerve and anatomic examination of 24 autopsies. Head Neck. 1998;20(8):695–8.
Scerrino G, Inviati A, Di Giovanni S, Paladino NC, Di Paola V, Lo Re G, Almasio PL, Cupido F, Gulotta G, Bonventre S. Esophageal motility changes after thyroidectomy; possible associations with postoperative voice and swallowing disorders: preliminary results. Otolaryngol Head Neck Surg. 2013;148(6):926–32.
Sinagra DL, Montesinos MR, Tacchi VA, Moreno JC, Falco JE, Mezzadri NA, Debonis DL, Curutchet HP. Voice changes after thyroidectomy without recurrent laryngeal nerve injury. J Am Coll Surg. 2004;199(4):556–60.
Sorensen JR, Bonnema SJ, Godballe C, Hegedüs L. The Impact of Goiter and Thyroid Surgery on Goiter Related Esophageal Dysfunction. A Systematic Review. Front Endocrinol (Lausanne). 2018;20;9:679.
Soylu L, Ozbas S, Uslu HY, Kocak S. The evaluation of the causes of subjective voice disturbances after thyroid surgery. Am J Surg. 2007;194:317–22.
Stojadinovic A, Henry LR, Howard RS, Gurevich-Uvena J, Makashay MJ, Coppit GL, Shriver CD, Solomon NP. Prospective trial of voice outcomes after thyroidectomy: evaluation of patient-reported and clinician-determined voice assessments in identifying postthyroidectomy dysphonia. Surgery. 2008;143(6):732–42.
Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol. 2018;14(5):301–316.
Teixeira JP, Oliveira C, Lopes C. Vocal acoustic analysis–jitter, shimmer and hnr parameters. Procedia Technology. 2013;9:1112–22.
Van Esch BF, Stegeman I, Smit AL. Comparison of laryngeal mask airway vs tracheal intubation: a systematic review on airway complications. J Clin Anesth. 36:142–150.
Venugopal A, Jacob RM, Koshy RC. A randomized control study comparing the pharyngolaryngeal morbidity of laryngeal mask airway versus endotracheal tube. Anesth Essays Res. 2016;10(2):189–194.
Viana Baptista SIR, Lott DG, Almeida SCC, Cid MO, Vera-Cruz PS, Zagalo C. Preoperative Voice Characteristics in Thyroid Patients. J Voice. 2021;35(5):809.e1–809.e6.
Wagner HE, Seiler C. Recurrent laryngeal nerve palsy after thyroid gland surgery. Br J Surg. 1994;81:226–228.
Weisberg NK, Spengler DM, Netterville JL. Stretch-induced nerve injury as a cause of paralysis secondary to the anterior cervical approach. Otolaryngol Head Neck Surg. 1997;116(3):317–26.
Weitzendorfer M, Antoniou SA, Schredl P, Witzel K, Weitzendorfer IC, Majerus A, Emmanuel K, Koch OO. Pepsin and oropharyngeal pH monitoring to diagnose patients with laryngopharyngeal reflux. Laryngoscope. 2020;130(7):1780–1786.
Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. Thyroid. 2016;26(11):1541–1552.
Zimmert M., Zwirner P., Kruse E., Braun U. Effects on vocal function and incidence of laryngeal disorder when using a laryngeal mask airway in comparison with an endotracheal tube. Eur J Anaesthesiol. 2007;16(8):511–515.

# SUMMARY IN ESTONIAN

## Kilpnäärmehaiguste ja kirurgilise ravi mõju hääle- ja neelamiskvaliteedile

### Sissejuhatus

Kilpnäärme talitlushäired on ühed sagedasemad endokriinhaigused, mis vajavad kirurgilist ~~s~~ekkumist. Hääle- ja neelamishäired on laialt levinud tüsistused, mida võib seostada nii kilpnäärme haiguste enda kui ka nende operatiivse raviga. Kirjanduse andmetel kaebab operatsioonijärgselt ajutist häälekvaliteedi langust 38 – 87% patsientidest ning püsivaid muutuseid 13 – 35% (Soylu *et al*., 2007; Henry *et al.*, 2010; Lombardi *et al.*, 2009; Sinagra *et al.*, 2004). Neelamishäireid esineb vahetul postoperatiivsel perioodil kuni 80% ning aasta pärast võib sama kaebus püsida kuni ühel viiendikul patsientidest ((Lombardi *et al.*, 2009; Krekeler *et al.*, 2018; Martins *et al.*, 2020).

Seoses kilpnäärme paiknemisega *n. vagus*'e tagasikulgeva haru *n. laryngeus recurrens*'i vahetus läheduses, seostatakse antud sümptomaatikat enamasti närvikahjustusest tingitud muutustega. Samal ajal on varasemate uuringute kohaselt postoperatiivse *n. laryngeus recurrens*'i kahjustuse sagedus väga varieeruv – ajutist närvikahjustust võib esineda 1,4 – 38,4% ja püsivat 0 – 18,6% juhtudel (Rosato *et al*., 2004; Bergenfelz *et al*., 2008; Jeannon *et al*., 2009).

Teisteks võimalikeks põhjusteks võivad olla *n. laryngeus superior*'i vigastus, kõri ümbritsevate lihaste posttraumaatiline düsfunktsioon, pehmete kudede turse või hematoom, infektsioon, väljendunud valusündroom vms (Sinagra *et al*., 2004; Stojadinovic *et al.*, 2008; Dursun *et al*. 1996). Varase postoperatiivse perioodi hääle- ja neelamishäirete üheks võimalikuks põhjuseks võib olla ka intubatsioonist tingitud otsene kõri kahjustus. On leitud, et endotrahheaalse intubatsiooni tagajärjel esineb lühiaegseid häälehäireid kuni 69% patsientidest (Brodsky *et al*., 2021; Mendels *et al*., 2012) ja neelamishäireid kuni 43% (Rieger *et al*., 1997; Brodsky *et al*., 2021).

Samas on leitud, et kuni 76% patsientidest on juba kilpnäärme operatsiooni eelselt probleeme häälekvaliteedi ja neelamisega (Fiorentino *et al.*, 2011; Mclvor *et al*., 2000; Viana Baptista *et al*., 2020). Sümptomaatika võib sageli olla tagasihoidlik, kuna enamasti on tegemist aeglaselt progresseeruva protsessiga. Osadel juhtudel võib põhjuseks pidada kilpnäärme ala- või ületalitlust, valdavalt aga peetakse sellistel puhkudel põhjuseks siiski suurenenud kilpnäärme poolt esile kutsutud ümbritsevate kudede kompressiooni. Kompressioonisümptomaatikale väga sarnast kliinilist leidu, nagu tükitunne, neelamistakistus ja -valulikkus ning häälehäired, võib sageli anda ka kõri-neelu reflukshaigus. Lisaks on viimaste uuringute kohaselt jäänud kahtlus, et suurenenud kilpnääre võib olla ~~k~~õri-neelu reflukshaiguse ägenemise üheks põhjuseks (Fiorentino *et al.*, 2011; Holler ja Anderson, 2014).

Kokkuvõtvalt võib öelda, et kilpnäärme patsientide hääle- ja neelamishäirete tekkepõhjused on äärmiselt mitmekesised ja nende väljakujunemises võivad olulist rolli mängida nii operatsioonieelsed kui -järgsed tegurid. Sealjuures on mitmed olulised aspektid hääle- ja neelamishäirete tekkepõhjustes ja kestuses seni teadmata või ebaselged.

## Töö eesmärgid

Doktoritöö üldine eesmärk oli hinnata kilpnäärmeoperatsiooni eelset ja järgset hääle- ja neelamiskvaliteeti, dünaamilisi muutuseid postoperatiivses perioodis ning leida ajutisele ja püsivale häälepaela halvatusele viitavaid tunnuseid.

Eesmärgi saavutamiseks seati tööle neli spetsiifilisemat ülesannet:

1) hinnata hääle- ja neelamiskvaliteeti enne kilpnäärme operatsiooni, häälega seotud mõju elukvaliteedile ja teha kindlaks võimalikud etioloogilised faktorid;
2) hinnata hääle- ja neelamiskvaliteeti peale kilpnäärme operatsiooni, häälega seotud mõju elukvaliteedile ja teha kindlaks võimalikud etioloogilised faktorid;
3) hinnata dünaamilisi muutusi hääle ja neelamiskvaliteedis postoperatiivses perioodis 12–18 kuu jooksul ning leida ajutisele või püsivale häälepaela halvatusele viitavaid tunnuseid;
4) hinnata üldanesteesia võimalikku rolli kilpnäärme operatsiooni järgsete hääle- ja neelamishäirete tekkepõhjusena.

## Uuritavad ja meetodid

Uuringugrupi moodustasid 118 kilpnäärme osalise või totaalse resektsiooni patsienti vanuses 18–83 aastat. Kontrollgrupi moodustasid 110 laparoskoopilise sapipõie eemaldamise patsienti, kelle operatsioon toimus endotrahheaalses intubatsioon-anesteesias vanuses 23–82 aastat ning 103 alajäsemete vaariksite operatsiooni patsienti, kelle operatsioon toimus kõrimask-anesteesias vanuses 22–82 aastat. Kõik patsiendid hospitaliseeriti SA TÜK Kirurgiakliinikusse vahemikus september 2013 kuni detsember 2016. Uuringusse ei kaasatud alla 18 aasta vanuseid patsiente ega eelneva häälepaelte orgaanilise häirega (ka häälepaela halvatus) patsiente. Kilpnäärme patsiendid olid preoperatiivselt eutüreoidses seisundis. Kontrollgrupi patsientidel välistati kaasuv kilpnäärme haigus intervjuu käigus. Kõik uuritavad ja kontrollgruppi kuuluvad patsiendid suunati preoperatiivsele ja esimesel postoperatiivsel nädalal toimuvale kõrva-nina-kurguarsti vastuvõtule. Kõri piirkonna kahjustuse korral viidi läbi täiendavad vastuvõtud 1., 6. ja 12.–18. kuul peale operatsiooni kuni kliinilise paranemiseni. Kilpnäärme grupi patsientidel viidi kõigil läbi 12.–18. kuu vastuvõtt sõltumata kõri piirkonna kahjustusest.

Vastuvõttude ajal täitsid patsiendid ankeedid häälega seotud elukvaliteedi (*Voice Handicap Index* VHI), neelamisfunktsiooni (*Swallowing Impairment*

*Score* SIS) ja kõri-neelu reflukshaiguse hindamiseks (*Reflux Symptom Index* RSI) ning teostati otorinolarüngoloogiline läbivaatus. Viimase käigus hinnati fiiberlarüngoskoopia ja videostroboskoopia abil neelu ja kõri struktuure ja funktsiooni. Lisaks viidi läbi hääle akustiline analüüs (*Multi-Dimensional Voice Program* MDVP), mõõdeti maksimaalne foneerimise aeg ja teostati hääle pertseptiivne hindamine GRBAS skaalal. Fiiberlarüngoskoopia videosalvestisi hinnati kõri-neelu reflukshaiguse tunnuste osas (*Reflux Finding Score* RFS).

Lisaks dokumenteeriti kõigi patsientide demograafilised andmed: kaal, suitsetamine, häälekasutamise koormus, anesteesia meetod, intubatsiooni kestus, intubatsioonitoru ja kõrimaski suurus, intubatsioonitoru ja kõrimaski mansetirõhk, intubatsioonitoru sisestamise katsete arv, kilpnäärme patsientide kilpnäärme histoloogilise preparaadi kaal, histoloogiline diagnoos ja lõikuse ulatus.

Patsientidel, kellel jäi kliiniliselt kahtlus kõrinärvide kahjustusele, teostati neli nädalat peale operatsiooni kõri piirkonna elektromüograafia. Uuringus osalemine oli kõigile patsientidele vabatahtlik ja enne andmete kogumist täitsid kõik patsiendid kirjalikult informeeritud nõusoleku vormi. Uuringul oli Tartu Ülikooli inimuuringute eetikakomitee nõusolek (luba nr. 212/T-7). Statistiliseks analüüsiks kasutati tarkvaraprogramme TIBCO Statistica™ (versioon 10.0) ja R (R Core Team, 2019). Kasutati t-testi, Mann–Whitney U testi, Wilcoxoni märgitesti, $\chi^2$, Fisheri täpset testi, Spearmani korrelatsiooni kordajat, šansside suhet ja Cohen'i kappat. Statistiliselt oluliseks loeti P väärtust alla 0,05.

## Tulemused

Preoperatiivses häälekvaliteedis ei esinenud kilpnäärme patsientide ja kontrollgrupi vahel statistiliselt olulist erinevust ei subjektiivse hinnangu ega objektiivse instrumentaalse hääleanalüüsi põhjal. Kõige märkimisväärsem erinevus ilmnes VHI emotsionaalse hinnangu skaalal, aga ka see osutus statistiliselt mitteoluliseks ($p$=0,074). Hääleanalüüs paljastas siiski kõrgemad väärtused kilpnäärme patsientide hääle sagedushälbes (jitter) ja hääle käheduse indeksis (NHR), mis võivad viidata anatoomilistele muutustele häälepaeltes. Lisaks ei toonud ka spetsialisti pertseptiivne hinnang häälekvaliteedile GRBAS skaalal kahe grupi vahel erinevust välja.

Subjektiivne neelamiskvaliteedi küsimustik (SIS) paljastas postoperatiivselt statistiliselt olulise neelamiskvaliteedi languse kilpnäärme patsientide seas ($p$=0,006). 73,3% patsientidest kaebas vähemalt mõnel korral neelamishäirete esinemist, võrreldes 57,3% kontrollgrupi patsientidega. Kilpnäärme kaalu ja neelamishäirete vaheline seos käesolevas uuringus kinnitust ei leidnud ($\rho$= -0,082). Subjektiivsete refluksikaebuste hinnangulehe (RSI) kohaselt esines kilpnäärme patsientide seas oluliselt kõrgemaid väärtusi kui kontrollgrupil ($p$= 0,001). 31% kilpnäärme patsientide ankeetide tulemused ületasid normi piirid, võrreldes 19% kontrollgrupis. Endoskoopilise uuringu põhjal hinnatud kliinilise leiu alusel (RFS) sealjuures kahe grupi vahel olulist erinevust ei ilmnenud.

Uurides seoseid RSI ja SIS vahel kilpnäärme patsientide grupis, leidsime me tugeva positiivse korrelatsiooni ((ρ=0,641). Lisaks leidsime nõrga positiivse korrelatsiooni kilpnäärme kaalu ja RFS vahel (ρ=0,379). Kõrgemad väärtused refluksi kaebuste ankeetide tulemustes ja positiivne seos refluksile viitava kliinilise leiu ja kilpnäärme kaalu vahel võivad viidata kilpnäärme rollile kõri-neelu refluksi kaebuste ägenemises.

Kilpnäärme operatsiooni järgselt esines kõrinärvi kahjustusega patsientidel oluliselt väljendunum häälekvaliteedi langus nii subjektiivsete kui objektiivsete hinnangute põhjal. Kõige enam olid haaratud VHI, sagedushälve (jitter) ja maksimaalne foneerimise aeg. Enam väljendunud kaebused esinesid püsiva häälepaela halvatusega patsientidel. Lisaks leidsime, et kilpnäärme operatsiooni järgselt esineb neelamiskvaliteedi langus nii närvikahjustusega ($p$=0,001) kui -kahjustuseta ($p$=0,014) patsientidel. Sealjuures võtab närvikahjustusega patsientidel paranemine preoperatiivsele tasemele kauem aega. Vaatamata sellele, sõltumata närvikahjustuse puudumisest või olemasolust, taastus jälgimisaja lõpuks valdav enamus mõõdetud parameetritest preoperatiivsele tasemele. Post-operatiivse närvikahjustuseta patsientide seas täheldasime jälgimisaja lõpuks neelamiskvaliteedis isegi statistiliselt olulist paranemist võrreldes preoperatiivse tasemega ($p$=0,008). Võimalikud indikaatorid, mis viitavad püsivale häälepaela halvatusele, on maksimaalse foneerimise aja ja sagedushälbe väärtuste aeglasem taastumine ning püsiv pertseptiivne kahin ja jõuetus hääles.

Võrreldes intubatsioonanesteesia ja kõrimasknarkoosi mõju kõri piirkonna anatoomiale, hääle- ja neelamiskvaliteedile järeldasime, et esimese nädala jooksul peale operatiivset ravi võib mõlemad anesteesia meetodid lugeda võrdväärseteks. Kuigi kliiniline pilt viitas küll intubatsioonitoru puhul suuremale kõri piirkonna vigastuse võimalusele, siis objektiivsed ega subjektiivsed hääle- ja neelamiskvaliteedi mõõtmisvahendid kahe grupi vahel erinevusi välja ei toonud.

## Uurimistöö järeldused

1. Kilpnäärme haigustest tingitud muutused kõri piirkonnas ei mõjuta oluliselt patsiendi häälega seotud elukvaliteeti, aga esinevad viited suurenenud kähedusele hääles. Kilpnäärme haigused põhjustavad olulisi muutusi neelamiskvaliteedis. Kõrgemad väärtused kõri-neelu reflukshaiguse hinnangulehtedel ja positiivne seos refluksile viitava kliinilise leiu ja kilpnäärme kaalu vahel viitavad suurenenud kilpnäärme võimalikule rollile kõri-neelu reflukshaiguse ägenemises. Seost hääle- ja neelamishäirete ning suurenenud kilpnäärme kaalu, kilpnäärme haiguse olemuse, suitsetamise või häälekasutuse osas ei ilmnenud.
2. Kõrinärvide kahjustusega patsientidel esineb postoperatiivselt oluline häälekvaliteedi ja häälega seotud elukvaliteedi langus. Enam haaratud parameetrid on VHI koguskoor, sagedushälve (jitter) ja maksimaalne foneerimise aeg. Enam väljendunud on muutused püsiva häälepaela halvatusega patsientidel. Ka ilma kõrinärvi kahjustuseta patsientidel võib operatsioonijärgselt

täheldada häälega seotud elukvaliteedi langust ja hääles enam pertseptiivset pinget. Neelamiskvaliteedi langus esineb postoperatiivselt nii närvikahjustusega kui -kahjustuseta patsientidel. Operatsioonijärgse kõrinärvi kahjustuse riskifaktoriks on suur kilpnäärme mass. Seost vanuse, suitsetamisharjumuste, kilpnäärme haiguse olemuse, anesteesia kestuse ja operatsioonijärgse närvivigastuse vahel ei ilmnenud.

3. Sõltumata postoperatiivsest kõrinärvi vigastuse olemasolust paranes jälgimisaja lõpuks mõlema grupi patsientidel enamik hinnatud parameetritest preoperatiivsele tasemele. Püsiva närvikahjustusega patsientidel kulus paranemiseks kauem aega. Kõrinärvide vigastuseta patsientide neelamisfunktsioon paranes võrreldes operatsioonieelse hinnanguga. Püsiva häälepaela halvatuse võimalikud indikaatorid on maksimaalse foneerimise aja ja sagedushälbe väärtuste aeglasem taastumine ning püsiv pertseptiivne kahin ja jõuetus hääles.
4. Nädal peale lõikust ei ole üldanesteesial postoperatiivsete hääle- ja neelamishäirete tekkes olulist rolli.

# ACKNOWLEDGEMENTS

I wish to express my deepest gratitude to:

- My supervisors Prof. Urmas Lepner and Dr. Priit Kasenõmm for never fading support and encouragement. I would like to extend my very special thanks to Prof. Lepner for generating the idea of the study and never losing faith in me for finalizing the work, and to Dr. Priit Kasenõmm for devotion while supervising the work and for giving comprehensive instructions and constructive feedback.
- Prof. Pille Taba and Prof. Aare Märtson for thorough reviewing and providing their guidance in improving the quality of my dissertation.
- Mrs. Ülle Kirsimägi for collaboration and help in navigating the complex world of statistics.
- Mrs. Ester Jaigma for her kind help in improving the English text of my manuscript.
- All patients who participated in the research and thus made this work possible.
- All my colleagues and friends of the Ear Clinic of Tartu University Hospital. My warmest gratitude goes to research nurses Sille Ilus and Ene Kukin for their assistance and dedication during data collection.
- I would particularly like to thank Lagle Lehes for being there for me during the whole journey. Whether it was a shoulder to lean on and blow off the steam, or just to have a good laugh together. Thank You for encouraging and pushing me towards the goal.
- Finally, I am very grateful to my loving family for their support and patience all through this long journey. Your support means the world.

# PUBLICATIONS

# CURRICULUM VITAE


Name: Linda Sõber
Date of birth: February 13, 1983
Citizenship: Estonian
E-mail: linda.sober@kliinikum.ee


**Education:**

| | |
|---|---|
| 2012–2022 | Tartu University, Faculty of Medicine, PhD studies |
| 2007–2010 | Tartu University, Faculty of Medicine, Postgraduate medical training (residency) in otorhinolaryngology |
| 2001–2007 | Tartu University, Faculty of Medicine (MD) |
| 1990–2001 | Tartu Kivilinna Grammar School |
| 1989–1990 | Himmaste Preliminary School |

**Professional employment:**

| | |
|---|---|
| 2022– | University of Tartu, Faculty of Medicine, Institute of Clinical Medicine, assistant in otorhinolaryngology |
| 2007– | Tartu University Hospital, ENT Clinic, otorhinolaryngologist |

**Research and developmental work:**

I. Main fields of interests: Thyroid disease and surgery related voice and swallowing disorders, vocal fold palsy

II. Publications:


- Sõber L, Lepner U, Kirsimägi Ü, Puksa L, Kasenõmm P. Voice and Swallowing Disorders After Thyroid Surgery. J Voice. 2022 Apr 8: S0892–1997(22)00077–7. doi:10.1016/j.jvoice.2022.03.013.
- Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Prethyroidectomy voice and swallowing disorders and the possible role of laryngopharyngeal reflux disease. Logoped Phoniatr Vocol. 2021 Dec 23:1–6. doi:10.1080/14015439.2021.2020894.
- Lehes L, Numa J, Sober L, Padrik M, Kasenõmm P, Jagomägi T. The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. Clin Linguist Phon. 2021;35(5):393–404. doi:10.1080/02699206.2020.1780323.
- Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Effect of endotracheal intubation versus laryngeal mask airway on patient's quality of voice and swallowing. Int J Otorhinolaryngol Head Neck Surg 2019 Jul 5(4)820–825. doi:10.18203/issn.2454–5929.ijohns20192699

III. Supervising:

- May 2017 Mari Kabel, Tartu University, Institute of Education, Department of Special Education, MA thesis "The impact of laryngopharyngeal reflux on patient's quality of voice".
- May 2019 Signe Süvaorg, Tartu University, Institute of Education, Department of Special Education, MA thesis „Voice and swallowing disorders in pre-operative thyroidectomy patients".

IV. Professional organisations:

- Estonian Society of Otorhinolaryngologists and Head and Neck Surgeons (vice president)
- European Society for Swallowing Disorders (member)
- European Laryngological Society (member)
- Estonian Medical Association (member)

# ELULOOKIRJELDUS


Nimi: Linda Sõber
Sünniaeg: 13. veebruar 1983
Kodakondsus: Eesti
E-mail: linda.sober@kliinikum.ee


**Hariduskäik:**

| | |
|---|---|
| 2012–2022 | Tartu Ülikool, Arstiteaduskond, doktoriõpe |
| 2007–2010 | Tartu Ülikool, Arstiteaduskond, otorinolarüngoloogia residentuur |
| 2001–2007 | Tartu Ülikool, Arstiteaduskond, arstiteaduse põhiõpe |
| 1990–2001 | Tartu Kivilinna Gümnaasium |
| 1989–1990 | Himmaste Algkool |

**Teenistuskäik:**

| | |
|---|---|
| 2022– | Tartu Ülikool, Meditsiiniteaduste valdkond, kliinilise meditsiini instituut, otorinolarüngoloogia assistent |
| 2007– | Tartu Ülikooli Kliinikum, Kõrvakliinik, otorinolarüngoloogia arst-õppejõud |

**Teaduslik ja arendustegevus**:

I. Peamised uurimisvaldkonnad: Kilpnäärme haiguste ja kirurgiaga seotud hääle- ja neelamishäired, häälepaela paralüüs

II. Publikatsioonide loetelu:

- Sõber L, Lepner U, Kirsimägi Ü, Puksa L, Kasenõmm P. Voice and Swallowing Disorders After Thyroid Surgery. J Voice. 2022 Apr 8: S0892–1997(22)00077–7. doi:10.1016/j.jvoice.2022.03.013.
- Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Prethyroidectomy voice and swallowing disorders and the possible role of laryngopharyngeal reflux disease. Logoped Phoniatr Vocol. 2021 Dec 23:1–6. doi:10.1080/14015439.2021.2020894.
- Lehes L, Numa J, Sober L, Padrik M, Kasenõmm P, Jagomägi T. The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. Clin Linguist Phon. 2021;35(5):393–404. doi:10.1080/02699206.2020.1780323.
- Sõber L, Lepner U, Kirsimägi Ü, Kasenõmm P. Effect of endotracheal intubation versus laryngeal mask airway on patient's quality of voice and swallowing. Int J Otorhinolaryngol Head Neck Surg 2019 Jul 5(4)820–825. doi:10.18203/issn.2454–5929.ijohns20192699

III. Juhendamised:

- Mai 2017 Mari Kabel, Tartu Ülikool, Sotsiaalteaduste valdkond, Haridusteaduste instituut, magistritöö “Larüngofarüngeaalse refluksi mõju patsiendi hääle kvaliteedile”.
- May 2019 Signe Süvaorg, Tartu Ülikool, Sotsiaalteaduste valdkond, Haridusteaduste instituut, magistritöö “Kilpnäärme operatsioonieelsete patsientide hääle- ja neelamishäired”.

IV. Kutseorganisatsioonid:

- Eesti Kõrva-nina-kurguarstide ja Pea- ja Kaelakirurgide Selts (asepresident)
- European Laryngeal Society (liige)
- European Society for Swallowing Disorders (liige)
- Eesti Nooremarstide Ühendus (liige)

# DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar**. Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik**. Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu**. Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
6. **Marika Mikelsaar**. Evaluation of the gastrointestinal microbial ecosystem in health and disease. Tartu, 1992.
7. **Hele Everaus**. Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar**. Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm**. On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross**. Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
11. **Oivi Uibo**. Childhood coeliac disease in Estonia: occurrence, screening, diagnosis and clinical characterization. Tartu, 1994.
12. **Viiu Tuulik**. The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
13. **Margus Viigimaa**. Primary haemostasis, antiaggregative and anticoagulant treatment of acute myocardial infarction. Tartu, 1994.
14. **Rein Kolk**. Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar**. Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi**. The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.
17. **Irja Lutsar**. Infections of the central nervous system in children (epidemiologic, diagnostic and therapeutic aspects, long term outcome). Tartu, 1995.
18. **Aavo Lang**. The role of dopamine, 5-hydroxytryptamine, sigma and NMDA receptors in the action of antipsychotic drugs. Tartu, 1995.
19. **Andrus Arak**. Factors influencing the survival of patients after radical surgery for gastric cancer. Tartu, 1996.

20. **Tõnis Karki**. Quantitative composition of the human lactoflora and method for its examination. Tartu, 1996.
21. **Reet Mändar**. Vaginal microflora during pregnancy and its transmission to newborn. Tartu, 1996.
22. **Triin Remmel**. Primary biliary cirrhosis in Estonia: epidemiology, clinical characterization and prognostication of the course of the disease. Tartu, 1996.
23. **Toomas Kivastik**. Mechanisms of drug addiction: focus on positive reinforcing properties of morphine. Tartu, 1996.
24. **Paavo Pokk**. Stress due to sleep deprivation: focus on $GABA_A$ receptor-chloride ionophore complex. Tartu, 1996.
25. **Kristina Allikmets**. Renin system activity in essential hypertension. Associations with atherothrombogenic cardiovascular risk factors and with the efficacy of calcium antagonist treatment. Tartu, 1996.
26. **Triin Parik**. Oxidative stress in essential hypertension: Associations with metabolic disturbances and the effects of calcium antagonist treatment. Tartu, 1996.
27. **Svetlana Päi**. Factors promoting heterogeneity of the course of rheumatoid arthritis. Tartu, 1997.
28. **Maarike Sallo**. Studies on habitual physical activity and aerobic fitness in 4 to 10 years old children. Tartu, 1997.
29. **Paul Naaber**. *Clostridium difficile* infection and intestinal microbial ecology. Tartu, 1997.
30. **Rein Pähkla**. Studies in pinoline pharmacology. Tartu, 1997.
31. **Andrus Juhan Voitk**. Outpatient laparoscopic cholecystectomy. Tartu, 1997.
32. **Joel Starkopf**. Oxidative stress and ischaemia-reperfusion of the heart. Tartu, 1997.
33. **Janika Kõrv**. Incidence, case-fatality and outcome of stroke. Tartu, 1998.
34. **Ülla Linnamägi**. Changes in local cerebral blood flow and lipid peroxidation following lead exposure in experiment. Tartu, 1998.
35. **Ave Minajeva**. Sarcoplasmic reticulum function: comparison of atrial and ventricular myocardium. Tartu, 1998.
36. **Oleg Milenin**. Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev**. Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
38. **Allen Kaasik**. Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
39. **Vallo Matto**. Pharmacological studies on anxiogenic and antiaggressive properties of antidepressants. Tartu, 1998.
40. **Maire Vasar**. Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.
41. **Kaja Julge**. Humoral immune responses to allergens in early childhood. Tartu, 1998.

42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp**. Formation of intestinal microbial ecosystem in children. Tartu, 1998.
44. **Mai Ots**. Characteristics of the progression of human and experimental glomerulopathies. Tartu, 1998.
45. **Tiina Ristimäe**. Heart rate variability in patients with coronary artery disease. Tartu, 1998.
46. **Leho Kõiv**. Reaction of the sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in the acute stage of head injury. Tartu, 1998.
47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand**. Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi**. Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask**. Behavioural studies on neuropeptide Y. Tartu, 1999.
52. **Ello-Rahel Karelson**. Modulation of adenylate cyclase activity in the rat hippocampus by neuropeptide galanin and its chimeric analogs. Tartu, 1999.
53. **Tanel Laisaar**. Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
54. **Eve Pihl**. Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
55. **Katrin Õunap**. Phenylketonuria in Estonia: incidence, newborn screening, diagnosis, clinical characterization and genotype/phenotype correlation. Tartu, 1999.
56. **Siiri Kõljalg**. *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
57. **Helle Karro**. Reproductive health and pregnancy outcome in Estonia: association with different factors. Tartu, 1999.
58. **Heili Varendi**. Behavioral effects observed in human newborns during exposure to naturally occurring odors. Tartu, 1999.
59. **Anneli Beilmann**. Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
60. **Vallo Volke**. Pharmacological and biochemical studies on nitric oxide in the regulation of behaviour. Tartu, 1999.
61. **Pilvi Ilves**. Hypoxic-ischaemic encephalopathy in asphyxiated term infants. A prospective clinical, biochemical, ultrasonographical study. Tartu, 1999.
62. **Anti Kalda**. Oxygen-glucose deprivation-induced neuronal death and its pharmacological prevention in cerebellar granule cells. Tartu, 1999.
63. **Eve-Irene Lepist**. Oral peptide prodrugs – studies on stability and absorption. Tartu, 2000.

64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
68. **Ruth Kalda**. Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.
69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
70. **Marlit Veldi**. Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.
71. **Anneli Uusküla**. Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.
72. **Ade Kallas**. Characterization of antibodies to coagulation factor VIII. Tartu, 2002.
73. **Heidi Annuk**. Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.
74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.
75. **Maigi Eisen**. Pathogenesis of Contact Dermatitis: participation of Oxidative Stress. A clinical – biochemical study. Tartu, 2002.
76. **Piret Hussar**. Histology of the post-traumatic bone repair in rats. Elaboration and use of a new standardized experimental model – bicortical perforation of tibia compared to internal fracture and resection osteotomy. Tartu, 2002.
77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
78. **Marju Herodes**. Quality of life of people with epilepsy in Estonia. Tartu, 2003.
79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.
82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

83. **Helgi Kolk**. Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.
84. **Helena Soomer**. Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.
85. **Kersti Oselin**. Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.
86. **Jaan Soplepmann**. Peptic ulcer haemorrhage in Estonia: epidemiology, prognostic factors, treatment and outcome. Tartu, 2003.
87. **Margot Peetsalu**. Long-term follow-up after vagotomy in duodenal ulcer disease: recurrent ulcer, changes in the function, morphology and *Helicobacter pylori* colonisation of the gastric mucosa. Tartu, 2003.
88. **Kersti Klaamas**. Humoral immune response to *Helicobacter pylori* a study of host-dependent and microbial factors. Tartu, 2003.
89. **Pille Taba**. Epidemiology of Parkinson's disease in Tartu, Estonia. Prevalence, incidence, clinical characteristics, and pharmacoepidemiology. Tartu, 2003.
90. **Alar Veraksitš**. Characterization of behavioural and biochemical phenotype of cholecystokinin-2 receptor deficient mice: changes in the function of the dopamine and endopioidergic system. Tartu, 2003.
91. **Ingrid Kalev**. CC-chemokine receptor 5 (CCR5) gene polymorphism in Estonians and in patients with Type I and Type II diabetes mellitus. Tartu, 2003.
92. **Lumme Kadaja**. Molecular approach to the regulation of mitochondrial function in oxidative muscle cells. Tartu, 2003.
93. **Aive Liigant**. Epidemiology of primary central nervous system tumours in Estonia from 1986 to 1996. Clinical characteristics, incidence, survival and prognostic factors. Tartu, 2004.
94. **Andres, Kulla**. Molecular characteristics of mesenchymal stroma in human astrocytic gliomas. Tartu, 2004.
95. **Mari Järvelaid**. Health damaging risk behaviours in adolescence. Tartu, 2004.
96. **Ülle Pechter**. Progression prevention strategies in chronic renal failure and hypertension. An experimental and clinical study. Tartu, 2004.
97. **Gunnar Tasa**. Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.
98. **Tuuli Käämbre**. Intracellular energetic unit: structural and functional aspects. Tartu, 2004.
99. **Vitali Vassiljev**. Influence of nitric oxide syntase inhibitors on the effects of ethanol after acute and chronic ethanol administration and withdrawal. Tartu, 2004.

100. **Aune Rehema**. Assessment of nonhaem ferrous iron and glutathione redox ratio as markers of pathogeneticity of oxidative stress in different clinical groups. Tartu, 2004.
101. **Evelin Seppet**. Interaction of mitochondria and ATPases in oxidative muscle cells in normal and pathological conditions. Tartu, 2004.
102. **Eduard Maron**. Serotonin function in panic disorder: from clinical experiments to brain imaging and genetics. Tartu, 2004.
103. **Marje Oona**. *Helicobacter pylori* infection in children: epidemiological and therapeutic aspects. Tartu, 2004.
104. **Kersti Kokk**. Regulation of active and passive molecular transport in the testis. Tartu, 2005.
105. **Vladimir Järv**. Cross-sectional imaging for pretreatment evaluation and follow-up of pelvic malignant tumours. Tartu, 2005.
106. **Andre Õun**. Epidemiology of adult epilepsy in Tartu, Estonia. Incidence, prevalence and medical treatment. Tartu, 2005.
107. **Piibe Muda**. Homocysteine and hypertension: associations between homocysteine and essential hypertension in treated and untreated hypertensive patients with and without coronary artery disease. Tartu, 2005.
108. **Külli Kingo**. The interleukin-10 family cytokines gene polymorphisms in plaque psoriasis. Tartu, 2005.
109. **Mati Merila**. Anatomy and clinical relevance of the glenohumeral joint capsule and ligaments. Tartu, 2005.
110. **Epp Songisepp**. Evaluation of technological and functional properties of the new probiotic *Lactobacillus fermentum* ME-3. Tartu, 2005.
111. **Tiia Ainla**. Acute myocardial infarction in Estonia: clinical characteristics, management and outcome. Tartu, 2005.
112. **Andres Sell**. Determining the minimum local anaesthetic requirements for hip replacement surgery under spinal anaesthesia – a study employing a spinal catheter. Tartu, 2005.
113. **Tiia Tamme**. Epidemiology of odontogenic tumours in Estonia. Pathogenesis and clinical behaviour of ameloblastoma. Tartu, 2005.
114. **Triine Annus**. Allergy in Estonian schoolchildren: time trends and characteristics. Tartu, 2005.
115. **Tiia Voor**. Microorganisms in infancy and development of allergy: comparison of Estonian and Swedish children. Tartu, 2005.
116. **Priit Kasenõmm**. Indicators for tonsillectomy in adults with recurrent tonsillitis – clinical, microbiological and pathomorphological investigations. Tartu, 2005.
117. **Eva Zusinaite**. Hepatitis C virus: genotype identification and interactions between viral proteases. Tartu, 2005.
118. **Piret Kõll**. Oral lactoflora in chronic periodontitis and periodontal health. Tartu, 2006.
119. **Tiina Stelmach**. Epidemiology of cerebral palsy and unfavourable neurodevelopmental outcome in child population of Tartu city and county, Estonia Prevalence, clinical features and risk factors. Tartu, 2006.

120. **Katrin Pudersell**. Tropane alkaloid production and riboflavine excretion in the field and tissue cultures of henbane (*Hyoscyamus niger* L.). Tartu, 2006.
121. **Külli Jaako**. Studies on the role of neurogenesis in brain plasticity. Tartu, 2006.
122. **Aare Märtson**. Lower limb lengthening: experimental studies of bone regeneration and long-term clinical results. Tartu, 2006.
123. **Heli Tähepõld**. Patient consultation in family medicine. Tartu, 2006.
124. **Stanislav Liskmann**. Peri-implant disease: pathogenesis, diagnosis and treatment in view of both inflammation and oxidative stress profiling. Tartu, 2006.
125. **Ruth Rudissaar**. Neuropharmacology of atypical antipsychotics and an animal model of psychosis. Tartu, 2006.
126. **Helena Andreson**. Diversity of *Helicobacter pylori* genotypes in Estonian patients with chronic inflammatory gastric diseases. Tartu, 2006.
127. **Katrin Pruus**. Mechanism of action of antidepressants: aspects of serotoninergic system and its interaction with glutamate. Tartu, 2006.
128. **Priit Põder**. Clinical and experimental investigation: relationship of ischaemia/reperfusion injury with oxidative stress in abdominal aortic aneurysm repair and in extracranial brain artery endarterectomy and possibilities of protection against ischaemia using a glutathione analogue in a rat model of global brain ischaemia. Tartu, 2006.
129. **Marika Tammaru**. Patient-reported outcome measurement in rheumatoid arthritis. Tartu, 2006.
130. **Tiia Reimand**. Down syndrome in Estonia. Tartu, 2006.
131. **Diva Eensoo**. Risk-taking in traffic and Markers of Risk-Taking Behaviour in Schoolchildren and Car Drivers. Tartu, 2007.
132. **Riina Vibo**. The third stroke registry in Tartu, Estonia from 2001 to 2003: incidence, case-fatality, risk factors and long-term outcome. Tartu, 2007.
133. **Chris Pruunsild**. Juvenile idiopathic arthritis in children in Estonia. Tartu, 2007.
134. **Eve Õiglane-Šlik**. Angelman and Prader-Willi syndromes in Estonia. Tartu, 2007.
135. **Kadri Haller**. Antibodies to follicle stimulating hormone. Significance in female infertility. Tartu, 2007.
136. **Pille Ööpik**. Management of depression in family medicine. Tartu, 2007.
137. **Jaak Kals**. Endothelial function and arterial stiffness in patients with atherosclerosis and in healthy subjects. Tartu, 2007.
138. **Priit Kampus**. Impact of inflammation, oxidative stress and age on arterial stiffness and carotid artery intima-media thickness. Tartu, 2007.
139. **Margus Punab**. Male fertility and its risk factors in Estonia. Tartu, 2007.
140. **Alar Toom**. Heterotopic ossification after total hip arthroplasty: clinical and pathogenetic investigation. Tartu, 2007.

141. **Lea Pehme**. Epidemiology of tuberculosis in Estonia 1991–2003 with special regard to extrapulmonary tuberculosis and delay in diagnosis of pulmonary tuberculosis. Tartu, 2007.
142. **Juri Karjagin**. The pharmacokinetics of metronidazole and meropenem in septic shock. Tartu, 2007.
143. **Inga Talvik**. Inflicted traumatic brain injury shaken baby syndrome in Estonia – epidemiology and outcome. Tartu, 2007.
144. **Tarvo Rajasalu**. Autoimmune diabetes: an immunological study of type 1 diabetes in humans and in a model of experimental diabetes (in RIP-B7.1 mice). Tartu, 2007.
145. **Inga Karu**. Ischaemia-reperfusion injury of the heart during coronary surgery: a clinical study investigating the effect of hyperoxia. Tartu, 2007.
146. **Peeter Padrik**. Renal cell carcinoma: Changes in natural history and treatment of metastatic disease. Tartu, 2007.
147. **Neve Vendt**. Iron deficiency and iron deficiency anaemia in infants aged 9 to 12 months in Estonia. Tartu, 2008.
148. **Lenne-Triin Heidmets**. The effects of neurotoxins on brain plasticity: focus on neural Cell Adhesion Molecule. Tartu, 2008.
149. **Paul Korrovits**. Asymptomatic inflammatory prostatitis: prevalence, etiological factors, diagnostic tools. Tartu, 2008.
150. **Annika Reintam**. Gastrointestinal failure in intensive care patients. Tartu, 2008.
151. **Kristiina Roots**. Cationic regulation of Na-pump in the normal, Alzheimer's and $CCK_2$ receptor-deficient brain. Tartu, 2008.
152. **Helen Puusepp**. The genetic causes of mental retardation in Estonia: fragile X syndrome and creatine transporter defect. Tartu, 2009.
153. **Kristiina Rull**. Human chorionic gonadotropin beta genes and recurrent miscarriage: expression and variation study. Tartu, 2009.
154. **Margus Eimre**. Organization of energy transfer and feedback regulation in oxidative muscle cells. Tartu, 2009.
155. **Maire Link**. Transcription factors FoxP3 and AIRE: autoantibody associations. Tartu, 2009.
156. **Kai Haldre**. Sexual health and behaviour of young women in Estonia. Tartu, 2009.
157. **Kaur Liivak**. Classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Estonia: incidence, genotype and phenotype with special attention to short-term growth and 24-hour blood pressure. Tartu, 2009.
158. **Kersti Ehrlich**. Antioxidative glutathione analogues (UPF peptides) – molecular design, structure-activity relationships and testing the protective properties. Tartu, 2009.
159. **Anneli Rätsep**. Type 2 diabetes care in family medicine. Tartu, 2009.
160. **Silver Türk**. Etiopathogenetic aspects of chronic prostatitis: role of mycoplasmas, coryneform bacteria and oxidative stress. Tartu, 2009.

161. **Kaire Heilman**. Risk markers for cardiovascular disease and low bone mineral density in children with type 1 diabetes. Tartu, 2009.
162. **Kristi Rüütel**. HIV-epidemic in Estonia: injecting drug use and quality of life of people living with HIV. Tartu, 2009.
163. **Triin Eller**. Immune markers in major depression and in antidepressive treatment. Tartu, 2009.
164. **Siim Suutre**. The role of TGF-β isoforms and osteoprogenitor cells in the pathogenesis of heterotopic ossification. An experimental and clinical study of hip arthroplasty. Tartu, 2010.
165. **Kai Kliiman**. Highly drug-resistant tuberculosis in Estonia: Risk factors and predictors of poor treatment outcome. Tartu, 2010.
166. **Inga Villa**. Cardiovascular health-related nutrition, physical activity and fitness in Estonia. Tartu, 2010.
167. **Tõnis Org**. Molecular function of the first PHD finger domain of Autoimmune Regulator protein. Tartu, 2010.
168. **Tuuli Metsvaht**. Optimal antibacterial therapy of neonates at risk of early onset sepsis. Tartu, 2010.
169. **Jaanus Kahu**. Kidney transplantation: Studies on donor risk factors and mycophenolate mofetil. Tartu, 2010.
170. **Koit Reimand**. Autoimmunity in reproductive failure: A study on associated autoantibodies and autoantigens. Tartu, 2010.
171. **Mart Kull**. Impact of vitamin D and hypolactasia on bone mineral density: a population based study in Estonia. Tartu, 2010.
172. **Rael Laugesaar**. Stroke in children – epidemiology and risk factors. Tartu, 2010.
173. **Mark Braschinsky**. Epidemiology and quality of life issues of hereditary spastic paraplegia in Estonia and implemention of genetic analysis in everyday neurologic practice. Tartu, 2010.
174. **Kadri Suija**. Major depression in family medicine: associated factors, recurrence and possible intervention. Tartu, 2010.
175. **Jarno Habicht**. Health care utilisation in Estonia: socioeconomic determinants and financial burden of out-of-pocket payments. Tartu, 2010.
176. **Kristi Abram**. The prevalence and risk factors of rosacea. Subjective disease perception of rosacea patients. Tartu, 2010.
177. **Malle Kuum**. Mitochondrial and endoplasmic reticulum cation fluxes: Novel roles in cellular physiology. Tartu, 2010.
178. **Rita Teek**. The genetic causes of early onset hearing loss in Estonian children. Tartu, 2010.
179. **Daisy Volmer**. The development of community pharmacy services in Estonia – public and professional perceptions 1993–2006. Tartu, 2010.
180. **Jelena Lissitsina**. Cytogenetic causes in male infertility. Tartu, 2011.
181. **Delia Lepik**. Comparison of gunshot injuries caused from Tokarev, Makarov and Glock 19 pistols at different firing distances. Tartu, 2011.
182. **Ene-Renate Pähkla**. Factors related to the efficiency of treatment of advanced periodontitis. Tartu, 2011.

183. **Maarja Krass**. L-Arginine pathways and antidepressant action. Tartu, 2011.
184. **Taavi Lai**. Population health measures to support evidence-based health policy in Estonia. Tartu, 2011.
185. **Tiit Salum**. Similarity and difference of temperature-dependence of the brain sodium pump in normal, different neuropathological, and aberrant conditions and its possible reasons. Tartu, 2011.
186. **Tõnu Vooder**. Molecular differences and similarities between histological subtypes of non-small cell lung cancer. Tartu, 2011.
187. **Jelena Štšepetova**. The characterisation of intestinal lactic acid bacteria using bacteriological, biochemical and molecular approaches. Tartu, 2011.
188. **Radko Avi**. Natural polymorphisms and transmitted drug resistance in Estonian HIV-1 CRF06_cpx and its recombinant viruses. Tartu, 2011, 116 p.
189. **Edward Laane**. Multiparameter flow cytometry in haematological malignancies. Tartu, 2011, 152 p.
190. **Triin Jagomägi**. A study of the genetic etiology of nonsyndromic cleft lip and palate. Tartu, 2011, 158 p.
191. **Ivo Laidmäe**. Fibrin glue of fish (*Salmo salar*) origin: immunological study and development of new pharmaceutical preparation. Tartu, 2012, 150 p.
192. **Ülle Parm**. Early mucosal colonisation and its role in prediction of invasive infection in neonates at risk of early onset sepsis. Tartu, 2012, 168 p.
193. **Kaupo Teesalu**. Autoantibodies against desmin and transglutaminase 2 in celiac disease: diagnostic and functional significance. Tartu, 2012, 142 p.
194. **Maksim Zagura**. Biochemical, functional and structural profiling of arterial damage in atherosclerosis. Tartu, 2012, 162 p.
195. **Vivian Kont**. Autoimmune regulator: characterization of thymic gene regulation and promoter methylation. Tartu, 2012, 134 p.
196. **Pirje Hütt**. Functional properties, persistence, safety and efficacy of potential probiotic lactobacilli. Tartu, 2012, 246 p.
197. **Innar Tõru**. Serotonergic modulation of CCK-4- induced panic. Tartu, 2012, 132 p.
198. **Sigrid Vorobjov**. Drug use, related risk behaviour and harm reduction interventions utilization among injecting drug users in Estonia: implications for drug policy. Tartu, 2012, 120 p.
199. **Martin Serg**. Therapeutic aspects of central haemodynamics, arterial stiffness and oxidative stress in hypertension. Tartu, 2012, 156 p.
200. **Jaanika Kumm**. Molecular markers of articular tissues in early knee osteoarthritis: a population-based longitudinal study in middle-aged subjects. Tartu, 2012, 159 p.
201. **Kertu Rünkorg**. Functional changes of dopamine, endopioid and endocannabinoid systems in CCK2 receptor deficient mice. Tartu, 2012, 125 p.
202. **Mai Blöndal**. Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia. Tartu, 2012, 127 p.

203. **Jana Lass**. Epidemiological and clinical aspects of medicines use in children in Estonia. Tartu, 2012, 170 p.
204. **Kai Truusalu**. Probiotic lactobacilli in experimental persistent *Salmonella* infection. Tartu, 2013, 139 p.
205. **Oksana Jagur**. Temporomandibular joint diagnostic imaging in relation to pain and bone characteristics. Long-term results of arthroscopic treatment. Tartu, 2013, 126 p.
206. **Katrin Sikk**. Manganese-ephedrone intoxication – pathogenesis of neurological damage and clinical symptomatology. Tartu, 2013, 125 p.
207. **Kai Blöndal**. Tuberculosis in Estonia with special emphasis on drug-resistant tuberculosis: Notification rate, disease recurrence and mortality. Tartu, 2013, 151 p.
208. **Marju Puurand**. Oxidative phosphorylation in different diseases of gastric mucosa. Tartu, 2013, 123 p.
209. **Aili Tagoma**. Immune activation in female infertility: Significance of autoantibodies and inflammatory mediators. Tartu, 2013, 135 p.
210. **Liis Sabre**. Epidemiology of traumatic spinal cord injury in Estonia. Brain activation in the acute phase of traumatic spinal cord injury. Tartu, 2013, 135 p.
211. **Merit Lamp**. Genetic susceptibility factors in endometriosis. Tartu, 2013, 125 p.
212. **Erik Salum**. Beneficial effects of vitamin D and angiotensin II receptor blocker on arterial damage. Tartu, 2013, 167 p.
213. **Maire Karelson**. Vitiligo: clinical aspects, quality of life and the role of melanocortin system in pathogenesis. Tartu, 2013, 153 p.
214. **Kuldar Kaljurand**. Prevalence of exfoliation syndrome in Estonia and its clinical significance. Tartu, 2013, 113 p.
215. **Raido Paasma**. Clinical study of methanol poisoning: handling large outbreaks, treatment with antidotes, and long-term outcomes. Tartu, 2013, 96 p.
216. **Anne Kleinberg**. Major depression in Estonia: prevalence, associated factors, and use of health services. Tartu, 2013, 129 p.
217. **Triin Eglit**. Obesity, impaired glucose regulation, metabolic syndrome and their associations with high-molecular-weight adiponectin levels. Tartu, 2014, 115 p.
218. **Kristo Ausmees**. Reproductive function in middle-aged males: Associations with prostate, lifestyle and couple infertility status. Tartu, 2014, 125 p.
219. **Kristi Huik**. The influence of host genetic factors on the susceptibility to HIV and HCV infections among intravenous drug users. Tartu, 2014, 144 p.
220. **Liina Tserel**. Epigenetic profiles of monocytes, monocyte-derived macrophages and dendritic cells. Tartu, 2014, 143 p.
221. **Irina Kerna**. The contribution of *ADAM12* and *CILP* genes to the development of knee osteoarthritis. Tartu, 2014, 152 p.

222. **Ingrid Liiv**. Autoimmune regulator protein interaction with DNA-dependent protein kinase and its role in apoptosis. Tartu, 2014, 143 p.
223. **Liivi Maddison**. Tissue perfusion and metabolism during intra-abdominal hypertension. Tartu, 2014, 103 p.
224. **Krista Ress**. Childhood coeliac disease in Estonia, prevalence in atopic dermatitis and immunological characterisation of coexistence. Tartu, 2014, 124 p.
225. **Kai Muru**. Prenatal screening strategies, long-term outcome of children with marked changes in maternal screening tests and the most common syndromic heart anomalies in Estonia. Tartu, 2014, 189 p.
226. **Kaja Rahu**. Morbidity and mortality among Baltic Chernobyl cleanup workers: a register-based cohort study. Tartu, 2014, 155 p.
227. **Klari Noormets**. The development of diabetes mellitus, fertility and energy metabolism disturbances in a Wfs1-deficient mouse model of Wolfram syndrome. Tartu, 2014, 132 p.
228. **Liis Toome**. Very low gestational age infants in Estonia. Tartu, 2014, 183 p.
229. **Ceith Nikkolo**. Impact of different mesh parameters on chronic pain and foreign body feeling after open inguinal hernia repair. Tartu, 2014, 132 p.
230. **Vadim Brjalin**. Chronic hepatitis C: predictors of treatment response in Estonian patients. Tartu, 2014, 122 p.
231. **Vahur Metsna**. Anterior knee pain in patients following total knee arthroplasty: the prevalence, correlation with patellar cartilage impairment and aspects of patellofemoral congruence. Tartu, 2014, 130 p.
232. **Marju Kase**. Glioblastoma multiforme: possibilities to improve treatment efficacy. Tartu, 2015, 137 p.
233. **Riina Runnel**. Oral health among elementary school children and the effects of polyol candies on the prevention of dental caries. Tartu, 2015, 112 p.
234. **Made Laanpere**. Factors influencing women's sexual health and reproductive choices in Estonia. Tartu, 2015, 176 p.
235. **Andres Lust**. Water mediated solid state transformations of a polymorphic drug – effect on pharmaceutical product performance. Tartu, 2015, 134 p.
236. **Anna Klugman**. Functionality related characterization of pretreated wood lignin, cellulose and polyvinylpyrrolidone for pharmaceutical applications. Tartu, 2015, 156 p.
237. **Triin Laisk-Podar**. Genetic variation as a modulator of susceptibility to female infertility and a source for potential biomarkers. Tartu, 2015, 155 p.
238. **Mailis Tõnisson**. Clinical picture and biochemical changes in blood in children with acute alcohol intoxication. Tartu, 2015, 100 p.
239. **Kadri Tamme**. High volume haemodiafiltration in treatment of severe sepsis – impact on pharmacokinetics of antibiotics and inflammatory response. Tartu, 2015, 133 p.

240. **Kai Part**. Sexual health of young people in Estonia in a social context: the role of school-based sexuality education and youth-friendly counseling services. Tartu, 2015, 203 p.
241. **Urve Paaver**. New perspectives for the amorphization and physical stabilization of poorly water-soluble drugs and understanding their dissolution behavior. Tartu, 2015, 139 p.
242. **Aleksandr Peet**. Intrauterine and postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes. Tartu. 2015, 146 p.
243. **Piret Mitt**. Healthcare-associated infections in Estonia – epidemiology and surveillance of bloodstream and surgical site infections. Tartu, 2015, 145 p.
244. **Merli Saare**. Molecular Profiling of Endometriotic Lesions and Endometria of Endometriosis Patients. Tartu, 2016, 129 p.
245. **Kaja-Triin Laisaar**. People living with HIV in Estonia: Engagement in medical care and methods of increasing adherence to antiretroviral therapy and safe sexual behavior. Tartu, 2016, 132 p.
246. **Eero Merilind**. Primary health care performance: impact of payment and practice-based characteristics. Tartu, 2016, 120 p.
247. **Jaanika Kärner**. Cytokine-specific autoantibodies in AIRE deficiency. Tartu, 2016, 182 p.
248. **Kaido Paapstel**. Metabolomic profile of arterial stiffness and early biomarkers of renal damage in atherosclerosis. Tartu, 2016, 173 p.
249. **Liidia Kiisk**. Long-term nutritional study: anthropometrical and clinico-laboratory assessments in renal replacement therapy patients after intensive nutritional counselling. Tartu, 2016, 207 p.
250. **Georgi Nellis**. The use of excipients in medicines administered to neonates in Europe. Tartu, 2017, 159 p.
251. **Aleksei Rakitin**. Metabolic effects of acute and chronic treatment with valproic acid in people with epilepsy. Tartu, 2017, 125 p.
252. **Eveli Kallas**. The influence of immunological markers to susceptibility to HIV, HBV, and HCV infections among persons who inject drugs. Tartu, 2017, 138 p.
253. **Tiina Freimann**. Musculoskeletal pain among nurses: prevalence, risk factors, and intervention. Tartu, 2017, 125 p.
254. **Evelyn Aaviksoo**. Sickness absence in Estonia: determinants and influence of the sick-pay cut reform. Tartu, 2017, 121 p.
255. **Kalev Nõupuu**. Autosomal-recessive Stargardt disease: phenotypic heterogeneity and genotype-phenotype associations. Tartu, 2017, 131 p.
256. **Ho Duy Binh**. Osteogenesis imperfecta in Vietnam. Tartu, 2017, 125 p.
257. **Uku Haljasorg**. Transcriptional mechanisms in thymic central tolerance. Tartu, 2017, 147 p.
258. **Živile Riispere**. IgA Nephropathy study according to the Oxford Classification: IgA Nephropathy clinical-morphological correlations, disease progression and the effect of renoprotective therapy. Tartu, 2017, 129 p.

259. **Hiie Soeorg**. Coagulase-negative staphylococci in gut of preterm neonates and in breast milk of their mothers. Tartu, 2017, 216 p.
260. **Anne-Mari Anton Willmore**. Silver nanoparticles for cancer research. Tartu, 2017, 132 p.
261. **Ott Laius**. Utilization of osteoporosis medicines, medication adherence and the trend in osteoporosis related hip fractures in Estonia. Tartu, 2017, 134 p.
262. **Alar Aab**. Insights into molecular mechanisms of asthma and atopic dermatitis. Tartu, 2017, 164 p.
263. **Sander Pajusalu**. Genome-wide diagnostics of Mendelian disorders: from chromosomal microarrays to next-generation sequencing. Tartu, 2017, 146 p.
264. **Mikk Jürisson**. Health and economic impact of hip fracture in Estonia. Tartu, 2017, 164 p.
265. **Kaspar Tootsi**. Cardiovascular and metabolomic profiling of osteoarthritis. Tartu, 2017, 150 p.
266. **Mario Saare**. The influence of AIRE on gene expression – studies of transcriptional regulatory mechanisms in cell culture systems. Tartu, 2017, 172 p.
267. **Piia Jõgi**. Epidemiological and clinical characteristics of pertussis in Estonia. Tartu, 2018, 168 p.
268. **Elle Põldoja**. Structure and blood supply of the superior part of the shoulder joint capsule. Tartu, 2018, 116 p.
269. **Minh Son Nguyen**. Oral health status and prevalence of temporomandibular disorders in 65–74-year-olds in Vietnam. Tartu, 2018, 182 p.
270. **Kristian Semjonov**. Development of pharmaceutical quench-cooled molten and melt-electrospun solid dispersions for poorly water-soluble indomethacin. Tartu, 2018, 125 p.
271. **Janne Tiigimäe-Saar**. Botulinum neurotoxin type A treatment for sialorrhea in central nervous system diseases. Tartu, 2018, 109 p.
272. **Veiko Vengerfeldt**. Apical periodontitis: prevalence and etiopathogenetic aspects. Tartu, 2018, 150 p.
273. **Rudolf Bichele**. TNF superfamily and AIRE at the crossroads of thymic differentiation and host protection against *Candida albicans* infection. Tartu, 2018, 153 p.
274. **Olga Tšuiko**. Unravelling Chromosomal Instability in Mammalian Preimplantation Embryos Using Single-Cell Genomics. Tartu, 2018, 169 p.
275. **Kärt Kriisa**. Profile of acylcarnitines, inflammation and oxidative stress in first-episode psychosis before and after antipsychotic treatment. Tartu, 2018, 145 p.
276. **Xuan Dung Ho**. Characterization of the genomic profile of osteosarcoma. Tartu, 2018, 144 p.
277. **Karit Reinson**. New Diagnostic Methods for Early Detection of Inborn Errors of Metabolism in Estonia. Tartu, 2018, 201 p.

278. **Mari-Anne Vals**. Congenital N-glycosylation Disorders in Estonia. Tartu, 2019, 148 p.
279. **Liis Kadastik-Eerme**. Parkinson's disease in Estonia: epidemiology, quality of life, clinical characteristics and pharmacotherapy. Tartu, 2019, 202 p.
280. **Hedi Hunt**. Precision targeting of intraperitoneal tumors with peptide-guided nanocarriers. Tartu, 2019, 179 p.
281. **Rando Porosk**. The role of oxidative stress in Wolfram syndrome 1 and hypothermia. Tartu, 2019, 123 p.
282. **Ene-Ly Jõgeda**. The influence of coinfections and host genetic factor on the susceptibility to HIV infection among people who inject drugs. Tartu, 2019, 126 p.
283. **Kristel Ehala-Aleksejev**. The associations between body composition, obesity and obesity-related health and lifestyle conditions with male reproductive function. Tartu, 2019, 138 p.
284. **Aigar Ottas**. The metabolomic profiling of psoriasis, atopic dermatitis and atherosclerosis. Tartu, 2019, 136 p.
285. **Elmira Gurbanova**. Specific characteristics of tuberculosis in low default, but high multidrug–resistance prison setting. Tartu, 2019, 129 p.
286. **Van Thai Nguyeni**. The first study of the treatment outcomes of patients with cleft lip and palate in Central Vietnam. Tartu, 2019, 144 p.
287. **Maria Yakoreva**. Imprinting Disorders in Estonia. Tartu, 2019, 187 p.
288. **Kadri Rekker**. The putative role of microRNAs in endometriosis pathogenesis and potential in diagnostics. Tartu, 2019, 140 p.
289. **Ülle Võhma**. Association between personality traits, clinical characteristics and pharmacological treatment response in panic disorder. Tartu, 2019, 121 p.
290. **Aet Saar**. Acute myocardial infarction in Estonia 2001–2014: towards risk-based prevention and management. Tartu, 2019, 124 p.
291. **Toomas Toomsoo**. Transcranial brain sonography in the Estonian cohort of Parkinson's disease. Tartu, 2019, 114 p.
292. **Lidiia Zhytnik**. Inter- and intrafamilial diversity based on genotype and phenotype correlations of Osteogenesis Imperfecta. Tartu, 2019, 224 p.
293. **Pilleriin Soodla**. Newly HIV-infected people in Estonia: estimation of incidence and transmitted drug resistance. Tartu, 2019, 194 p.
294. **Kristiina Ojamaa**. Epidemiology of gynecological cancer in Estonia. Tartu, 2020, 133 p.
295. **Marianne Saard**. Modern Cognitive and Social Intervention Techniques in Paediatric Neurorehabilitation for Children with Acquired Brain Injury. Tartu, 2020, 168 p.
296. **Julia Maslovskaja**. The importance of DNA binding and DNA breaks for AIRE-mediated transcriptional activation. Tartu, 2020, 162 p.
297. **Natalia Lobanovskaya**. The role of PSA-NCAM in the survival of retinal ganglion cells. Tartu, 2020, 105 p.

298. **Madis Rahu**. Structure and blood supply of the postero-superior part of the shoulder joint capsule with implementation of surgical treatment after anterior traumatic dislocation. Tartu, 2020, 104 p.
299. **Helen Zirnask**. Luteinizing hormone (LH) receptor expression in the penis and its possible role in pathogenesis of erectile disturbances. Tartu, 2020, 87 p.
300. **Kadri Toome**. Homing peptides for targeting of brain diseases. Tartu, 2020, 152 p.
301. **Maarja Hallik**. Pharmacokinetics and pharmacodynamics of inotropic drugs in neonates. Tartu, 2020, 172 p.
302. **Raili Müller**. Cardiometabolic risk profile and body composition in early rheumatoid arthritis. Tartu, 2020, 133 p.
303. **Sergo Kasvandik**. The role of proteomic changes in endometrial cells – from the perspective of fertility and endometriosis. Tartu, 2020, 191 p.
304. **Epp Kaleviste**. Genetic variants revealing the role of STAT1/STAT3 signaling cytokines in immune protection and pathology. Tartu, 2020, 189 p.
305. **Sten Saar**. Epidemiology of severe injuries in Estonia. Tartu, 2020, 104 p.
306. **Kati Braschinsky**. Epidemiology of primary headaches in Estonia and applicability of web-based solutions in headache epidemiology research. Tartu, 2020, 129 p.
307. **Helen Vaher**. MicroRNAs in the regulation of keratinocyte responses in *psoriasis vulgaris* and atopic dermatitis. Tartu, 2020, 242 p.
308. **Liisi Raam**. Molecular Alterations in the Pathogenesis of Two Chronic Dermatoses – Vitiligo and Psoriasis. Tartu, 2020, 164 p.
309. **Artur Vetkas**. Long-term quality of life, emotional health, and associated factors in patients after aneurysmal subarachnoid haemorrhage. Tartu, 2020, 127 p.
310. **Teele Kasepalu**. Effects of remote ischaemic preconditioning on organ damage and acylcarnitines' metabolism in vascular surgery. Tartu, 2020, 130 p.
311. **Prakash Lingasamy**. Development of multitargeted tumor penetrating peptides. Tartu, 2020, 246 p.
312. **Lille Kurvits.** Parkinson's disease as a multisystem disorder: whole transcriptome study in Parkinson's disease patients' skin and blood. Tartu, 2021, 142 p.
313. **Mariliis Põld.** Smoking, attitudes towards smoking behaviour, and nicotine dependence among physicians in Estonia: cross-sectional surveys 1982–2014. Tartu, 2021, 172 p.
314. **Triin Kikas**. Single nucleotide variants affecting placental gene expression and pregnancy outcome. Tartu, 2021, 160 p.
315. **Hedda Lippus-Metsaots**. Interpersonal violence in Estonia: prevalence, impact on health and health behaviour. Tartu, 2021, 172 p.

316. **Georgi Dzaparidze.** Quantification and evaluation of the diagnostic significance of adenocarcinoma-associated microenvironmental changes in the prostate using modern digital pathology solutions. Tartu, 2021, 132 p.
317. **Tuuli Sedman.** New avenues for GLP1 receptor agonists in the treatment of diabetes. Tartu, 2021, 118 p.
318. **Martin Padar.** Enteral nutrition, gastrointestinal dysfunction and intestinal biomarkers in critically ill patients. Tartu, 2021, 189 p.
319. **Siim Schneider.** Risk factors, etiology and long-term outcome in young ischemic stroke patients in Estonia. Tartu, 2021, 131 p.
320. **Konstantin Ridnõi.** Implementation and effectiveness of new prenatal diagnostic strategies in Estonia. Tartu, 2021, 191 p.
321. **Risto Vaikjärv.** Etiopathogenetic and clinical aspects of peritonsillar abscess. Tartu, 2021, 115 p.
322. **Liis Preem.** Design and characterization of antibacterial electrospun drug delivery systems for wound infections. Tartu, 2022, 220 p.
323. **Keerthie Dissanayake.** Preimplantation embryo-derived extracellular vesicles: potential as an embryo quality marker and their role during the embryo-maternal communication. Tartu, 2022, 203 p.
324. **Laura Viidik.** 3D printing in pharmaceutics: a new avenue for fabricating therapeutic drug delivery systems. Tartu, 2022, 139 p.
325. **Kasun Godakumara.** Extracellular vesicle mediated embryo-maternal communication – A tool for evaluating functional competency of preimplantation embryos. Tartu, 2022, 176 p.
326. **Hindrek Teder.** Developing computational methods and workflows for targeted and whole-genome sequencing based non-invasive prenatal testing. Tartu, 2022, 138 p.
327. **Jana Tuusov.** Deaths caused by alcohol, psychotropic and other substances in Estonia: evidence based on forensic autopsies. Tartu, 2022, 157 p.
328. **Heigo Reima.** Colorectal cancer care and outcomes – evaluation and possibilities for improvement in Estonia. Tartu, 2022, 146 p.
329. **Liisa Kuhi.** A contribution of biomarker collagen type II neoepitope C2C in urine to the diagnosis and prognosis of knee osteoarthritis. Tartu, 2022, 157 p.
330. **Reeli Tamme.** Associations between pubertal hormones and physical activity levels, and subsequent bone mineral characteristics: a longitudinal study of boys aged 12–18. Tartu, 2022, 118 p.
331. **Deniss Sõritsa.** The impact of endometriosis and physical activity on female reproduction. Tartu, 2022, 152 p.
332. **Mohammad Mehedi Hasan.** Characterization of follicular fluid-derived extracellular vesicles and their contribution to periconception environment. Tartu, 2022, 194 p.
333. **Priya Kulkarni.** Osteoarthritis pathogenesis: an immunological passage through synovium-synovial fluid axis. Tartu, 2022, 268 p.

334. **Nigul Ilves.** Brain plasticity and network reorganization in children with perinatal stroke: a functional magnetic resonance imaging study. Tartu, 2022, 169 p.
335. **Marko Murruste.** Short- and long-term outcomes of surgical management of chronic pancreatitis. Tartu, 2022, 180 p.
336. **Marilin Ivask.** Transcriptomic and metabolic changes in the WFS1-deficient mouse model. Tartu, 2022, 158 p.
337. **Jüri Lieberg.** Results of surgical treatment and role of biomarkers in pathogenesis and risk prediction in patients with abdominal aortic aneurysm and peripheral artery disease. Tartu, 2022, 160 p.
338. **Sanna Puusepp.** Comparison of molecular genetics and morphological findings of childhood-onset neuromuscular disorders. Tartu, 2022, 216 p.
339. **Khan Nguyen Viet.** Chemical composition and bioactivity of extracts and constituents isolated from the medicinal plants in Vietnam and their nanotechnology-based delivery systems. Tartu, 2023, 172 p.
340. **Getnet Balcha Midekessa.** Towards understanding the colloidal stability and detection of Extracellular Vesicles. Tartu, 2023, 172 p.
341. **Kristiina Sepp.** Competency-based and person-centred community pharmacy practice – development and implementation in Estonia. Tartu, 2023, 242 p.