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Introducing an Innovative Oral Neuromuscular Treatment of the Underlying Reason for Reflux Caused by Hiatus Hernia: An Aggravating Factor in Esophagitis

Mary Hägg and Thomas Franzén

Abstract

Esophagitis is a debilitating disease often leading to more serious conditions. It is aggravated by refluxed stomach acids for which the usual treatment is PPI drugs that at best treat the symptoms, not the underlying cause of reflux. Surgical interventions address the root - Hiatal muscular incompetence - but are invasive and expensive. Both treatments have proven unwanted side-effects. Neuromuscular treatment is a new and innovative alternative that addresses the root cause of reflux. The science and evidence behind this treatment is presented here. Reflux cannot happen when the diaphragm functions properly and maintains adequate pressure in the Hiatal canal, otherwise the neck of the stomach can intrude through the diaphragm into the chest cavity allowing reflux and conditions such as GERD, LPR, silent reflux, dyspepsia and more. This is especially common at night, when in bed. Training with a simple and inexpensive neuromuscular medical device takes 90 seconds per day, self-administered by the patient without medication or surgical intervention. No negative side effects are recorded for this treatment. Currently, 40 000 individuals have treated with the device. It is deployed in healthcare institutions in several countries and is recognised in the UK by NICE in a briefing to the NHS as a treatment for Hiatal hernia.

Keywords: dysphagia, esophagitis, GERD, hiatal hernia, hiatal incompetence, manometry, neuromuscular treatment, obesity, PPI medication, reflux

1. Introduction

Esophagitis is thoroughly explained as a condition elsewhere in this book and its various causes discussed. There can be a variety of causes of esophagitis but in all cases it is aggravated if Gastro Oesophageal Reflux Disease (GERD) is present. It is that condition, reflux that will be discussed here: its treatments, causes, similar conditions, and a new and innovative treatment that simply and effectively addresses the root cause of reflux – not just its symptoms. Damage caused by reflux to the lining of the oesophagus can lead to the condition of Barrett's oesophagus in which cell changes indicate a pre-cancerous condition [1, 2]. This chapter will

explain what Hiatal hernia (HH) is and why it is near-exclusively [3, 4] responsible for all reflux-related conditions. It will be seen that the current most common active treatment for the symptoms of reflux is the administration of medication, often Proton Pump Inhibitor (PPI) drugs. These successfully alleviate the symptoms by reducing stomach acid production and its efficacy but, because they do not address the underlying cause of the condition, they are often prescribed for many years or even to end-of life. Their unwanted side-effects are well documented and referenced here. Medical science and healthcare professionals concerned with treating all symptoms caused by reflux should be excited and interested in a new, but proven, treatment that is simple, cheap, self-administered and with no negative side-effects. This disruptive technology to drug research and development is presented here.

2. Current treatments

In most cases clinicians first advise patients who present with reflux and the symptoms of reflux to implement lifestyle changes. These include changes in eating and drinking habits: lose weight, drink less alcohol, stop smoking, do not eat too close to bedtime, and more. Doctors also advise sleeping with the head of the bed raised, this encourages the neck of the stomach to remain correctly positioned and not intrude through the diaphragm at night allowing reflux. Changes in diet are often popular with patients with certain foods being excluded or included in their symptom-management routines.

The second, and most common type of treatment administered, is medication. This can be mild, over-the-counter (OTC) drugs, but is usually prescription drugs from the Proton Pump Inhibitor (PPI) class.

The third and last widely used type of intervention is surgery. Laparoscopic fundoplication is common, as are magnetic bands around the hiatal canal, and other operations. In essence each of these interventions is designed to compensate for the muscular incompetence in the diaphragm that allows the stomach neck to herniate into the chest cavity and reflux stomach contents.

2.1 Shortcomings of current treatments

Lifestyle changes are the most innocuous treatment and suffice for some people. Evidence [5] shows however, that their effect is weak.

Many OTC medications have a base pH and address the problem of reflux by reducing the acidity of the stomach acids which are being refluxed. Although the unpleasant sensations of reflux are reduced, the harmful effects on the vulnerable oesophagus and other organs continues. Long-term use of OTC medication is generally regarded to be free from harmful side-effects.

PPI medications act by inhibiting the amount and strength of the acids produced in the stomach. In the case of all medications there is no expectation that the underlying cause of the reflux – the weakened diaphragm musculature – will be addressed, merely the severity of the reflux symptoms.

However, in the case of the latter drug class there are significant known side effects. Long-term PPI usage is generally discouraged and several countries insist that clinicians perform a medication review before renewing PPI prescriptions. At least once per year is recommended in the UK [6]. PPI medication is usually not expensive, but the costs of repeat Healthcare Professional (HCP) interventions build to a considerable amount when prescribed for rest-of-life.

PPI drugs belong to one of the safest medication groups, but some research suggests a list of unwanted side effects [7, 8] include increased risk of cardiovascular disease, osteoporosis, dementia, male infertility, diabetes, increased vulnerability to severe covid19 infection.

In addition, harmful bacteria in the stomach like *Helicobacter pylori* (HP) that would not survive in normal circumstances, can thrive in the weakened acids after PPI treatment. These germs can enter the body and live in the digestive tract. After many years, they can cause sores, called ulcers, in the lining of the stomach or the upper part of the small intestine. For some people, an infection can lead to stomach cancer.

In the UK there are several initiatives in the NHS to reduce PPI prescription, Rotherham [9], All Wales [10] etc.

The final class of treatment is that of surgical intervention. Laparoscopic operations are minimally invasive, whilst other procedures can be more traumatic, all surgical operations carry risks [11]. Such operations require hospitalisation and the National Institute for Health and Care Excellence (NICE) in the UK advise that the cost is GBP 2076 [12].

The prevalence of success of these operations [13] is not 100%. In some cases the remedy is not long lasting and a second operation is required, or the patient will return to PPI medication. Some patients are not deemed suitable for surgery because of other pre-existing factors, and in periods like the Covid19 pandemic such interventions are not prioritised and can be delayed by years.

3. There are several related reflux conditions

Esophagitis is aggravated by acidic reflux and several other conditions are also caused by this condition. All except esophagitis have similar characteristics and treatments.

Reflux is a condition in which stomach acids sometimes bubble up from the stomach, through the oesophagus and into throat, larynx and pharynx. The effect of these acids is to cause the symptoms [14] of:

- Heartburn
- Burning sensation in the chest
- Acidic reflux
- Swallowing difficulties
- Feeling of a lump in the throat
- Feeling of a blockage in the chest when eating
- Chest pains
- Pain under the breastbone (sternum)
- Stomach pains before eating
- Stomach pains after eating
- Reduced appetite
- Early 'Full up' feeling
- Feeling sick
- Constipated, gassy
- Vomiting
- Persistent dry or phlegmy cough
- Food or drink 'goes down the wrong way'
- Hoarseness
- Breathing difficulties

It should be noted that if some of the above symptoms are chronic, and especially if they do not respond to medication, they could be caused by cancer or other diseases and these should be considered before diagnosing reflux as the sole cause.

Refluxing stomach acids is the underlying cause of several conditions: LPR, GERD (or GORD), Silent Reflux, IED. These conditions are sometimes known by their full names: Laryngopharyngeal Reflux, Gastroesophageal Reflux Disease, and Intermittent Oesophageal Dysphagia. These various conditions exhibit some or all of the symptoms listed above, they vary slightly but are all caused by the corrosive effect of the refluxed stomach acids. Reflux has an aggravating effect on those with esophagitis.

Another form of reflux is non-acid reflux, this can be diagnosed by impedance and 24-hour pH study. Even though the refluxed stomach contents are not acidic – perhaps due to PPI suppression medication – it is still an unwanted symptom. For this reason, the HH should still be treated even though non-acid reflux is not thought to aggravate esophagitis.

If untreated, the effect of these acids on the oesophagus can lead to inflammation and Barrett's oesophagus. These altered cells can be a sign that they have entered a pre-cancerous phase. It has been shown that even after PPI medication that relieves symptoms, the cancer risk is undiminished [15]. It may be useful to describe the similarities and differences between the various conditions listed.

3.1 GERD

GERD and GORD are the same thing and the name varies only because people spell (o) oesophagus with or without an 'O' in the beginning. It is an abbreviation for Gastroesophageal Reflux Disease.

This condition means that stomach acids bubble up from the stomach, into the oesophagus and up to the throat, larynx and pharynx. The effect of these acids is to cause persistent symptoms like heartburn, a feeling of something stuck in the throat, pain behind the breastbone, difficulties in swallowing some foods, persistent non-productive cough, thick phlegm or frothy saliva, and regurgitation.

3.2 LPR

LPR is an abbreviation for LaryngoPharyngeal Reflux. In this condition stomach acids sometimes bubble up as described earlier and cause the symptoms of heartburn, sore throat, irritation in the larynx and vocal cords, and hoarseness. When the symptoms do not include heartburn, it is often called Silent Reflux instead.

With LPR, unlike similar oesophageal conditions like GERD, the oesophagus itself is not usually irritated, nor does one usually suffer from the impression of something stuck in the throat or behind the breastbone.

3.3 Silent reflux

In this condition stomach acids sometimes bubble up as described earlier and cause the symptoms of sore throat, irritation in the larynx and vocal cords, and hoarseness.

With Silent Reflux, unlike similar oesophageal conditions like GERD, the oesophagus itself is not usually irritated, nor does one usually suffer from the impression of something stuck in the throat or behind the breastbone. Because the symptoms are less obvious than GERD, the condition is known as Silent Reflux. If heartburn is present in addition to the above symptoms the condition is more often described as LPR.

3.4 Heartburn

Heartburn is a condition that everybody experiences occasionally. It is normal after, for example, a heavy meal or fizzy drinks. Constant or persistent heartburn is

SYMPTOM	GERD/GORD	LPR	SILENT REFLUX
Heartburn	●	●	
Lump in the throat	●		
Pain behind the breastbone	●		
Swallowing difficulties	●		
Thick phlegm or frothy saliva	●		
Regurgitation	●		
Persistent cough	●		
Sore throat		●	●
Irritation in the larynx/vocal cords		●	●
Hoarseness		●	●
WHERE?			
Throat	●	●	●
Chest	●		

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Figure 1.
Symptom comparisons in reflux diseases.

usually diagnosed by doctors as being caused by reflux which sometimes has the related symptoms of sore throat, irritation in the larynx and vocal cords and hoarseness (**Figure 1**).

4. Hiatus hernia: the root cause of reflux

Reflux of stomach contents can allow the body’s own acids to attack the vulnerable soft membranes and tissues in the oesophagus, pharynx, larynx, throat, vocal cords, tongue, and more. Refluxed stomach acids can worsen a pre-existing condition of esophagitis.

The underlying cause of reflux is a muscular weakness in and around the diaphragm where the oesophagus passes through it; this is a Hiatal hernia (HH). Medication will not address this, whereas surgical intervention will, and we will describe later how a new, non-invasive neuromuscular treatment will allow these delinquent muscles to be strengthened and rebuilt as an alternative to surgical intervention.

Many people suffer from reflux but were never diagnosed with HH in earlier internal examinations. The condition is difficult to diagnose with certainty, a sliding HH (90% of all cases) [3, 4] is by its nature intermittent and does not always exhibit at the time of examination. Cuffing of the abdomen to try to provoke herniation is sometimes required to make a diagnosis more certain, especially when using hypopharynx-oesophageal X-ray. It is also the case that the main reason for an internal examination using gastroscopy with biopsy will have been to rule out other serious conditions; not to confirm a HH. Continual pH-monitoring is also used to measure prevalence of acidic reflux but does not aim to identify its cause.

Scientific studies [16–18] have looked at treatment of HH. When recruiting patients to these studies the researchers have always distinguished between those with the symptoms of a HH and a confirmed diagnosis; and those with the symptoms but no confirmation. In these studies, these two groups have the same symptoms, treatment and positive results. In reality there is no difference between the two groups.

In an IQoro customer questionnaire analysis [19] in June 2020 directed at people in Sweden and the UK, self-treating the symptoms of reflux with a neuromuscular device, they were asked how many knew that they had a HH. Most had reflux symptoms and were asked if they had a confirmed diagnosis. More than 2 700 responded: 37% had a confirmation of the condition after examination, and 37% suspected a Hiatal hernia or did not know and had no confirmed diagnosis. In other words, less than 40% of a cohort that probably had a HH had had it confirmed by examination. To add to this uncertainty people were 25% more likely to have had confirmed diagnosis in the UK than in Sweden; suggesting that diagnosis is difficult or not prioritised. Given the paucity of options to treat such a condition it perhaps not surprising that its diagnosis is not deemed important.

4.1 What is hiatus hernia?

Hiatus hernia is not a disease, it is a condition that allows reflux to occur.

The diaphragm is the thin but powerful muscle below the ribcage that divides the chest cavity – where the heart and lungs reside, from the stomach cavity. It is attached to the base of the sternum (breastbone) and follows the base of the ribcage and ends at the spine.

The aperture where the oesophagus passes through the diaphragm is called the Hiatus canal, here the diaphragm muscle grips around the oesophagus and ensures that mouth of the stomach cannot normally intrude upwards into the chest cavity. When the stomach intrudes at other times, in an uncontrolled and undesired way, stomach acids can be refluxed into the oesophagus. During the day, gravity aids the effect of holding the stomach down below the diaphragm, when lying down this effect is not present and is a factor in increased acidic reflux at night.

The valve at the top or mouth of the stomach is called the Lower Oesophageal Sphincter (LES), its job is to remain tightly closed except when swallowing and admitting food and drink into the stomach. An exception to this is when we need to belch, or when we are ill and need to vomit. In these cases, the neck of the stomach slides up through the diaphragm to allow the LES to open upwards to discharge gases or liquids. In its natural position below the diaphragm, it cannot do this. The LES is normally only able to flex open in a downward direction and permit one-way traffic into the stomach. The cause of this uncontrolled intrusion of the neck of the stomach is that the muscle gripping the oesophagus in the Hiatus canal is weakened or ruptured. When held in place below the diaphragm the LES cannot open upwards and allow stomach contents into the oesophagus. The underlying cause of reflux is therefore always a HH.

All babies are born with part of their stomach in the chest cavity; this is normal and usually does not cause a problem. Some, especially those who were born prematurely or in difficult circumstances, may exhibit the symptoms of reflux and projectile vomiting. They may also reject oral feeding; this is due to immaturity of the musculature in the digestive system. At the age of around 6 months the baby's oesophagus starts to grow and lengthen allowing the stomach to descend, and at around 12 months the stomach usually has achieved its correct position below the diaphragm.

5. The weakened diaphragm muscle can be trained like any other

If reflux is allowed by a HH, and this is only a muscle weakness, then why do we treat with medication or by surgical intervention?

If a patient presented with an arm that had atrophied because it had been in a plaster cast for three months, we would not hesitate to recommend a rehab programme based on weights and exercises – and we would not be surprised when it was 100% successful either.

However, there are key differences between the arm muscles and the muscles that need strengthening in the diaphragm.

The arm is made up of skeletally striated muscles that can be commanded by the individual to flex and can therefore be consciously exercised, whereas many of the muscles in the swallowing chain cannot.

Some muscles in the swallowing chain are smooth muscle which are controlled only by the autonomic system - through different command pathways to our voluntary systems.

So, the answer to our question why doctors do not get patients to train this muscle, is that they think that it cannot be done. A patient can be asked to do sit-ups, or lift weights, but not to shut his epiglottis tightly, make peristaltic waves down his oesophagus or squeeze the muscles around his Hiatal canal tightly. Yet it is just this last exercise which is required. The muscles that we need to exercise include these smooth muscles controlled by the body's autonomic system, not only the striated muscles that we can control voluntarily. But we can successfully exercise this musculature back to full strength if we can stimulate the brain stem to issue commands to these muscles. This is the basis of neuromuscular training: the physical exercise stimulates the brain to activate and strengthen the affected smooth muscle.

6. IQoro

IQoro (**Figure 2**) is a simple hand-held neuromuscular treatment device consisting of a curved plastic plate which is inserted pre-dentally by the patient – that is, inside the lips and in front of the teeth. The user grips the handle that protrudes out through his lips, seals his lips and then pulls forward strongly. The partial vacuum thus produced thus triggers the neurological and muscular effects described below. It exercises the muscles in the orofacial and swallowing processes

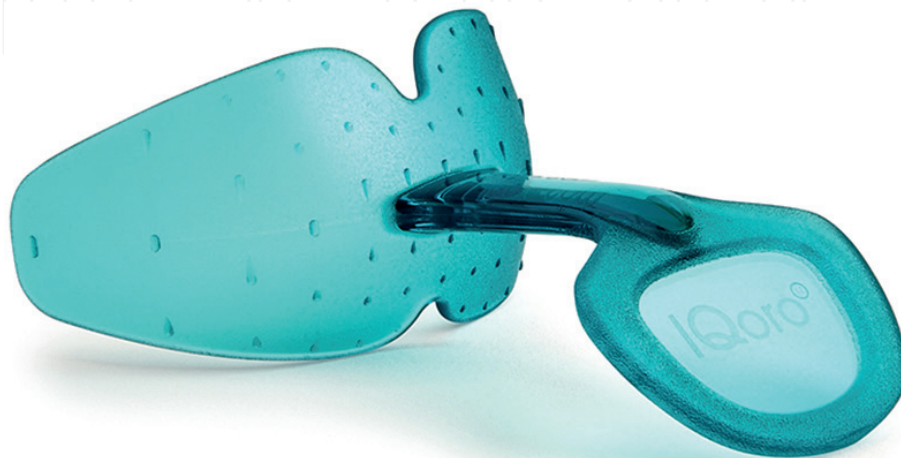


Figure 2.
The IQoro neuromuscular training device.

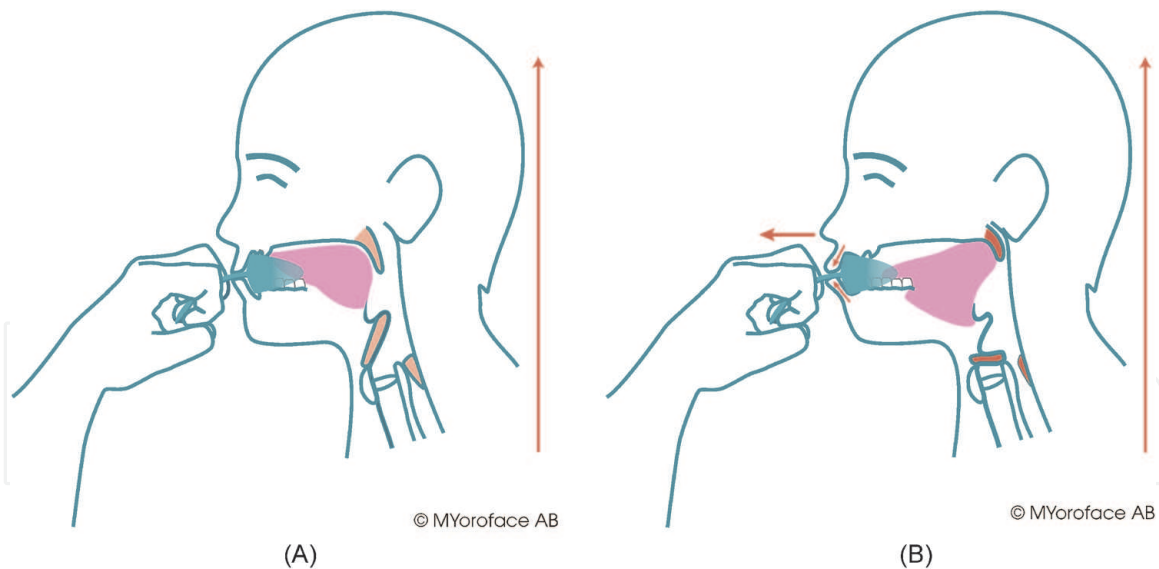


Figure 3.

(A, B). IQoro training regime. (A) the IQoro is inserted pre-dentally, behind closed lips. (B) the patient presses his lips firmly together whilst pulling straight forward strongly for 5–10 seconds, and does this 3 times with 3 seconds rest between each pull. These sessions are performed three times per day, preferably before mealtimes. **Video 1** [20].

from the face, lips, mouth, throat, airways and oesophagus down to the diaphragm and stomach.

By closing your lips tightly against the handle and pulling the device forward, a low-pressure is created in the oral cavity making the tongue rise and retract and seal against the anterior palatal arch and the soft palate. Further, the naso-pharyngeal and upper airways close, the larynx rises, the epiglottis shuts, and the Upper Oesophageal Sphincter (UES) opens. In other words, the exercise action provokes the mechanical components of a swallow. The UES is also known as the Posterior Oesophageal Sphincter (PES).

These physical movements alone are not enough to strengthen the weakened musculature in the diaphragm; indeed the muscles that need to be targeted to repair the hernia lie around and outside the oesophagus. No amount of low pressure flexing the oesophagus can have a direct effect on the muscles in the hiatal canal around the oesophagus.

Instead, they are exercised by proxy, the muscle and organ movements described above promote intense stimuli in the afferent Cranial Nerves to the brainstem. Here they provoke a sensory motoric reflex arc that causes messages to be issued through the efferent, motor nerves to the muscles in the swallowing chain. Crucially, this includes the smooth musculature that can only be commanded by the autonomic system.

In this way, for example, the long outer muscles that run down along the side of the oesophagus and fasten below the diaphragm, by the hiatal canal, are activated. As they flex, they pull on the weakened musculature around the hiatal canal and this musculature is exercised and strengthened.

The training regime (**Figure 3** A, B; **Video 1**) was developed during research studies; optimal training is three such pulls, each of 10 seconds' duration, and repeated three times per day, totally 90 seconds per day. Some positive effect on reflux symptoms is often noticed within the first month, and more than 60% of respondents reported improvement within 5 months [19, 20].

7. The neurology of the swallowing process

Understanding the neurology a little more deeply is therefore key for those who wish to understand neuromuscular training more fully.

The process of transmitting food and drink into the stomach is called the swallowing process, this also includes the process by which food and drink are held in the stomach and not refluxed. Hence a HH disrupts a normal swallowing process.

When food is to be eaten it is first processed using the voluntary muscles in the jaw, lips and tongue. As the bolus is pushed back to the pharynx by the action of the tongue base rising and retracting, the voluntary part of the process ends; the rest is reflexive.

Four sensory Cranial Nerves (CN) are primarily involved in the swallowing process. Stimulation of the CN (V) *Trigeminus* in the lips is the first step. In short order thereafter, the CN (IX) *Glossopharyngeus* and CN (X) *Vagus* nerves are also triggered, and then in turn the CN (V) *Trigeminus* and CN (VII) *Facialis* nerve too in the soft palate and anterior palate (**Figure 4**).

In the brain stem we find the *Nucleus Tractus Solitarius* (NTS), the afferent nucleus. The NTS is the core that gathers all incoming sensory signals from the lips, oral cavity and pharynx via the afferent nerve pathways, and transmits them either to the brain's cortex or directly to the network-like system in the brain stem called the *Formatio Reticularis* (FR). The FR not only controls the swallowing process, but also the respiratory and swallowing processes, cough reflex, orofacial and postural control, vomiting, bowel and bladder evacuation, these are all indivisibly interlinked at the neurological level, where the *Formatio Reticularis* plays a central role in governing all the muscles involved in these functions.

The three swallowing centres in the brain stem are triggered in the following sequence. The first swallowing centre interprets that something is to be swallowed, and this instruction is sent to the second swallowing centre.

The second swallowing centre transmits signals to the muscles via the motor nerves – the downward-transmitting efferent nerve pathways. Here, there is a pre-programmed 'go/no-go' decision: 'swallow' or 'do not swallow' - a so-called stereotypical muscle response. When something is to be swallowed the command is first sent to the *Nucleus Ambiguus* (NA) an efferent nucleus which, in its turn, sends the instruction to swallow to the major components of the swallowing musculature via the motor, efferent nerve pathways to the skeletally striated muscles. Concurrently, impulses are also sent to the third swallowing centre.

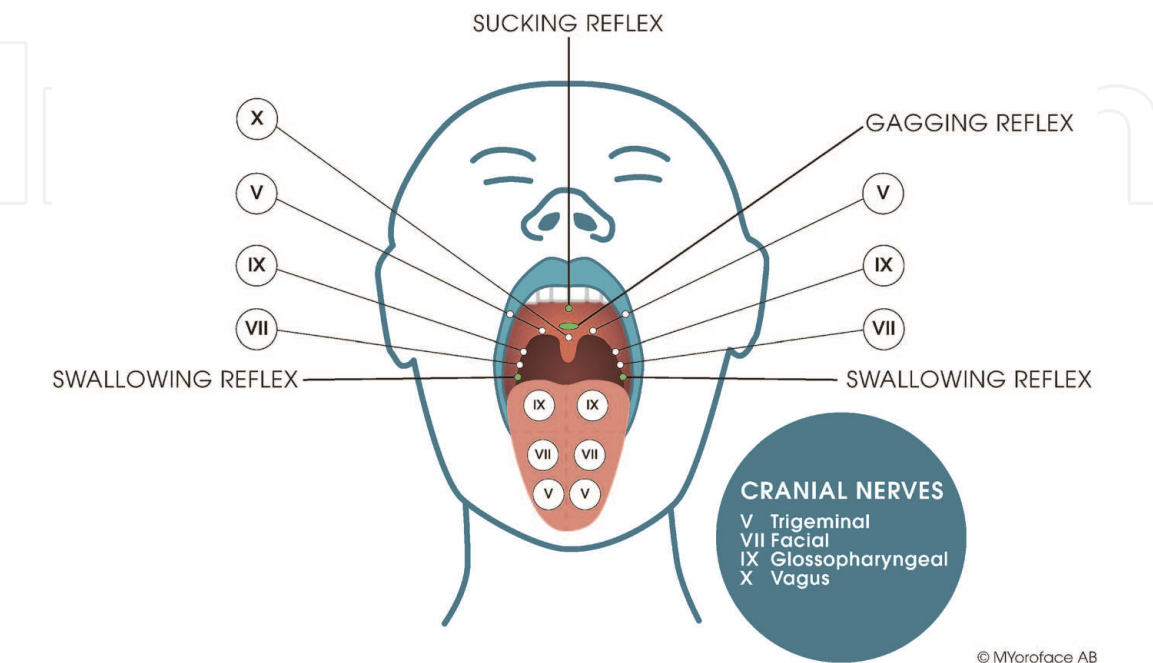


Figure 4.
Cranial nerves and reflex points in the oral cavity.

The five motor nerves that are important for swallowing are: *CN Trigeminus (V)*, *CN Facialis (VII)*, *CN Glossopharyngeus (IX)*, *CN Vagus (X)* and *CN Hypoglossus (XII)*. The first four are both sensory (afferent) and motor (efferent) nerve pathways.

The third swallowing centre transmits information to the *Nucleus Dorsalis Nervi Vagi* (NDNV) an efferent nucleus, and then onwards to the smooth muscles including those in the oesophagus (**Figures 5 and 6**).

The three swallowing centres' interactions - from brain stem to muscles.

These signals are transmitted via efferent nerves that can be thought of as cables containing various fibres, motor neurons, to the muscles and glands. There are three different kinds of motor neurons that are important in the swallowing process.

- The *General Somatic Efferent (GSE)* motor neurones are present in the *CN Hypoglossus (XII)* and *CN Oculomotorius (III)* which transmit signals onwards to the tongue's and the inner eyes' voluntary skeletal striated muscles musculature.
- The *Special Visceral Efferent (SVE)* motor neurons act through the *CN Trigeminus (V)*, *CN Facialis (VII)*, *CN Glossopharyngeus (IX)*, *CN Vagus (X)* and *CN Accessorius (XI)* which transmit signals to the voluntary musculature in

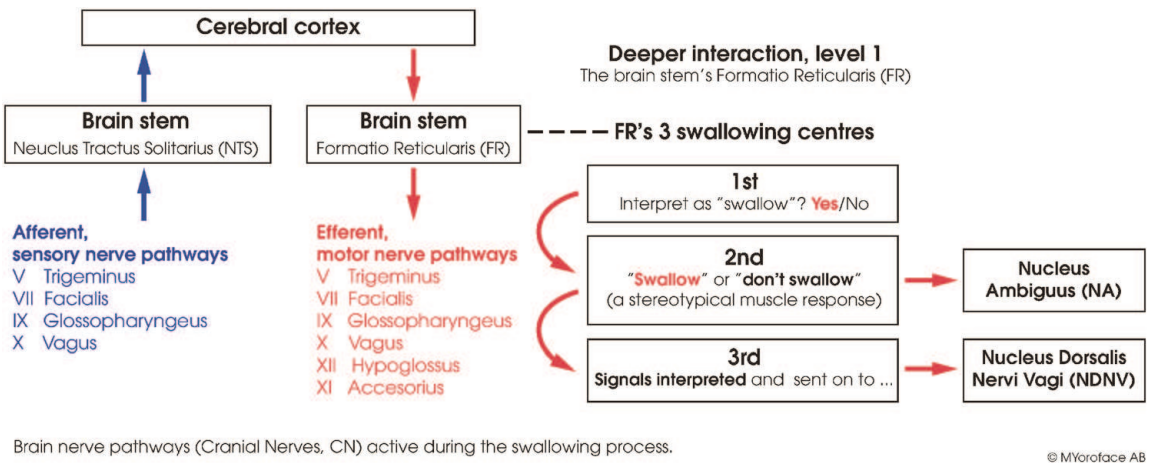


Figure 5.
The sensory-motor reflex arc (level 1). The three swallowing centres' interactions - from brain stem to muscles.

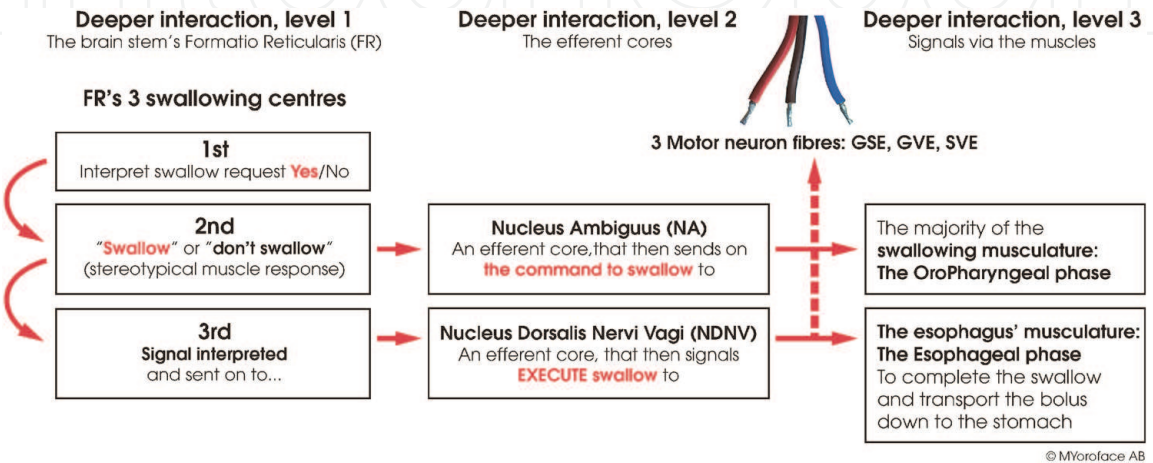


Figure 6.
The sensory-motor reflex arc (level 1-3). The three swallowing centres' interactions from: - the 2nd Centre to the striated muscles - the 3rd Centre to the smooth muscles.

the mouth, chewing muscles, facial musculature, pharynx, larynx, oesophagus and diaphragm.

- The *General Visceral Efferent (GVE)* motor neurons act via *CN Facialis (VII)* and *CN Glossopharyngeus (IX)* which transmit signals to the glands, blood vessels and smooth muscles in the pharynx, stomach and rectum.

The signal pathways from the above-named motor neurons are:

CN (V) Trigeminus – signals via the SVE.

CN (VII) Facialis – signals via the SVE and the GVE.

CN (IX) Glossopharyngeus – signals via the SVE and GVE.

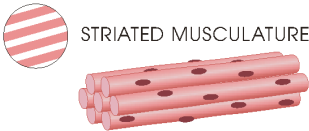
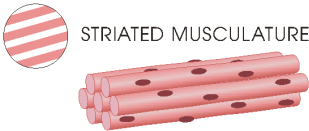
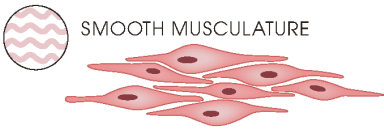
CN (X) Vagus – signals via the SVE.

CN (XII) Hypoglossus – signals via the GSE.

The sum of all the above signals initiates a pre-programmed cooperation between the 148 muscles that are involved in the transport of each food bite from the mouth down to the stomach. Controlled by these circuits and executed by these muscles. Breathing and postural control function are stimulated and strengthened, as are the tongue, soft palate and When using IQoro as a neuromuscular training device it triggers the sensory-motor reflex arc described earlier. This manifests itself in improvement in swallowing including the weakened diaphragm muscles that allow reflux, and then successively in other functions pharynx (**Figure 7**).

So, we have two effects of IQoro on the muscles. One is both neurological and physiological (the upper muscle chain from the lips to the upper part of the oesophagus) promoting movement, flexion and strengthening; and a second one, with only a neurological effect (the lower part of the oesophagus to the rectum).

The efferent nerves send signals to the muscles and glands through the following motor neurons:

Motor neuron fibres	Cranial nerves	Muscles and glands
General Somatic Efferent (GSE)  STRIATED MUSCULATURE	XII Hypoglossus III Oculomotorius	Tongue Eyes' inner muscles
Special Visceral Efferent (SVE)  STRIATED MUSCULATURE	V Trigeminus m. tensor tympani VII Facialis m. stapedius IX Glossopharyngeus X Vagus XI Accessorius	Face Oral cavity Chewing muscles Eyes' outer muscles Pharynx Larynx Esophagus Diaphragm
General Visceral Efferent (GVE)  SMOOTH MUSCULATURE	VII Facialis IX Glossopharyngeus	Glands Blood vessels Smooth musculature

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Figure 7.
The three motor neuron fibres, their nerves and effect organ connections.

8. Scientific evidence of the effectiveness of neuromuscular treatment

The effectiveness of neuromuscular training is supported by more than a dozen scientific studies conducted at university hospitals in Sweden. This section will present abstracts from three studies that are of particular relevance to HH and reflux.

In all three studies [16–18] quoted here the patients were long-term users of PPI medication before the studies began. In a Medtech Innovation Briefing [21] produced by the UK's National Institute for Health and Care Excellence in 2019 they quoted, “all patients continued with their PPI medication as advised. As symptoms reduced, patients ceased to medicate. Use or cessation of PPIs was under the control of the patients' doctors. At end-of-training in the 3 studies quoted 93%, 58% and 61% that they ceased all PPI medication, the remainder mostly reduced dose and intake frequency”. For this reason, medication can be excluded as the cause for improvement.

Overall, the studies showed success rates in the region of 98%, this is the same result reported by IQoro customers [19] in a survey conducted in 2020.

In these scientific studies of neuromuscular training there was particular focus on measurement methods. Patients were recruited as suffering from intermittent oesophageal dysphagia (IED) and reflux despite PPI medication from 1 year to many years and this was confirmed by a comprehensive test battery.

The test methodologies used were:

- Symptom Questionnaire [14]
- Visual Analogue Scale (VAS) [22] in which the patient records the ability to swallow food.
- Orofacial Motor Tests (OFMT) [23] and Orofacial Sensory Tests (OFST) [24] were carried out in order to exclude patients whose dysphagia were of central nervous origin. All tests showed normal brain function.
- Pharyngeal Sling Force (PSF) [25], measuring the resistance of the buccinator mechanism,
- Velopharyngeal Closure Test (VCT) [26] testing velum closure competence.
- Timed Water Swallow Test (TWST) [27] measuring swallowing competence and aspiration.
- PSF, VCT and TWST were used to confirm both normal oropharyngeal function and training compliance.
- High Resolution Manometry (HRM) [28] measuring pressure changes in the UES and the diaphragmatic hiatus.

In all cases tests were made in the recruiting process, at baseline, and at end-of-treatment; however, all patients were contacted by telephone or in the clinic two or three times to verify compliance before follow-up at end-of-treatment.

8.1 Oesophageal dysphagia and reflux symptoms before and after oral

IQoro® training. Hägg M, Tibbling L, Franzén T.
World J Gastroenterol 2015; 21(24): 7558–7562.
DOI: 10.3748 / wjg.v21.i24.7558 [16].

Study type

Peer reviewed, Prospective, Cohort pre- and post- study.

Aim

To examine whether training with an IQoro Neuromuscular Training (IQNT) improves oesophageal dysphagia and reflux symptoms.

Patients

43 patients (F = 22, M = 21) median age 57 years (range 22–85) with oesophageal dysphagia of a non-stenotic nature for a median period of 3 years (range: 1–15 years), of which:

- 21 patients with median age 52 years (range 19–85) with a confirmed Hiatal hernia,
- 22 patients with median age 57 years (range 22–85) exhibited Hiatal hernia symptoms but had no confirmed diagnosis.

All patients had been using PPI medication for more than one year.

Methods

IQoro training (**Figure 3 A, B; Video 1**), 3 x 10 seconds three times a day, totally 90 seconds per day, for a duration of 6 months. Outcome measurements were made at two time points: before training and at end of training.

Outcome measurements

Patients (*n* = 12), median age 53 years (range 22–68 years) with hiatal hernia were measured using:

- High Resolution Manometry during IQoro traction to record pressure in [28]:
 - the UES (normal restin pressure > 30 mmHg, **Table 1**).
 - the diaphragmatic pressure in the hiatus canal (normal resting pressure 10–35 mm HG, **Table 1**).

All patients were measured using:

- Symptom questionnaire (IED = intermittent oesophageal dysphagia a sensation of solid food retention in the chest at swallowing, acid chest symptoms and/or acid regurgitation), scored 0–3: 0 = no, 1 = slight, 2 = moderate, 3 = severe [14].
- Swallowing questionnaire (ability to swallow food), measured using
 - Visual Analogue Scale (VAS 0–100: 0 = normal, 100 = total inability) [22],.

Items	UES <i>n</i> = 12	Hiatus <i>n</i> = 12
Resting pressure	68 (40–110)	0 (0–0)
IQS traction	95 (80–130)	65 (20–100)

Data are mean (range) mmHg.

Table 1.
Oesophageal high resolution manometry pressures in the upper oesophageal sphincter (UES) and hiatus during rest and traction with an oral IQoro screen (IQS) in patients with hiatal hernia.

- Pharyngeal sling force (measured using Lip Force meter) [25],.
 - lower normal value ≥ 15 N
- Velopharyngeal Closure Test (VCT) [26],.
 - lower normal value ≥ 10 sec
- Orofacial motor tests [23],.
- Orofacial sensory tests (oral stereognosia and two-point discrimination) [24].

Results

All Orofacial motor tests and Orofacial sensory test scores were normal before treatment, indicating that there was no neurological cause to the patient's symptoms.

No significant difference in symptom frequency was found between the group with confirmed hiatus hernia, and those without a confirmed diagnosis, this was true both before and after training.

- Oesophageal dysphagia was present in all 43 patients at start of treatment, and 98% of patients showed improvement after IQoro neuromuscular training ($p < 0.001$).
- Reflux symptoms were reported before training in 86% of the patients, 100% of these showed improvement at end of training, ($p < 0.001$) and 58% were entirely symptom free and ceased PPI medication.
- VAS scores were classified as pathologic in all 43 patients, and 100% showed improvement after IQoro neuromuscular training ($p < 0.001$).
- Pharyngeal sling force test values ($p < 0.001$) were significantly higher after IQoro neuromuscular training.
- Velopharyngeal closure test values ($p < 0.001$) were significantly higher after IQoro neuromuscular training.
- High Resolution Manometry during IQoro traction showed an increase in mean pressure in the diaphragmatic hiatus region from 0 mm Hg at rest (range: 0–0 mm Hg) to 65 mm Hg (range: 20–100 mm Hg, **Table 1**).

Statistical significance of result

($p < 0.001$) oesophageal dysphagia.

($p < 0.001$) reflux symptoms.

($p < 0.001$) VAS values.

($p < 0.001$) pharyngeal sling force scores significantly higher.

($p < 0.001$) VCT scores significantly higher.

($p = \text{NS}$) No statistical difference between symptoms or outcomes between those with or without confirmed Hiatal hernia diagnosis - both before and after treatment.

Conclusion

IQoro neuromuscular training can relieve/improve oesophageal dysphagia and reflux symptoms in adults, likely due to improved hiatal competence. The similarity

of the results in the two groups suggest that many people suffer from Hiatus hernia despite this not having been confirmed by diagnosis.

8.2 Effect of IQoro® training in hiatal hernia patients with misdirected

swallowing and oesophageal retention symptoms. Hägg M, Tibbling L, Franzén T. *Acta Otolaryngol.* 2015 Jul;135 (7):635–639.

DOI: 10.3109/00016489.2015.1016185 [17].

Study type

Peer reviewed, Prospective, Cohort pre- and post-study.

Aim

To investigate whether muscle training with IQoro influences symptoms of misdirected swallowing and oesophageal retention in patients with hiatal hernia.

Patients

28 patients, F = 14, M = 14. Adult, Median age 59 years (range 22–85). All patients had hiatal hernia with misdirected swallowing and oesophageal retention symptoms for median 4 years (range 1–28).

Methods

IQoro training (**Figure 3 A, B; Video 1**) of duration 3 x 10 seconds three times per day for a duration of 6–8 months. Outcome measurements were made at two time points: before and at end of training.

Outcome measurements

12 patients in the study

- High Resolution Manometry (HRM) [28].

All patients in the study,

- Symptom Questionnaire typical for HH [14],.
- Visual Analogue Scale – VAS – self assessed scoring [22],.
- Pharyngeal sling force (using Lip Force meter) [25],.
 - lower normal value ≥ 15 N,
- Velopharyngeal Closure Test (VCT) [26],.
 - lower normal value ≥ 10 sec
- Swallowing ability (measured using Timed Water Swallow Test - TWST) [27],.
 - lower normal value for swallowing rate ≥ 10 ml / sec
- Orofacial Motor Test [23],.
- Orofacial Sensory Test (oral stereognosia and two-point discrimination) [24],.

Results

All Orofacial motor tests and Orofacial sensory test scores were normal before treatment, indicating that there was no neurological cause to the patient's symptoms.

- Reflux symptoms were reported before training in 100% of patients, 100% of these showed improvement at end of training, ($p < 0.001$) and 61% were entirely symptom free and ceased PPI medication.
- All hiatal hernia patients were improved after training ($p < 0.001$) with IQoro and showed significant improvements in
 - misdirected swallowing
 - cough,
 - hoarseness,
 - oesophageal retention
 - globus sensation,
 - VAS, Pharyngeal Sling Force (PSF = LFT), VCT and TWST = SCT.
- Traction during the training action with IQoro resulted in a 65 mm Hg increase in the mean pressure of the Diaphragmatic Hiatus as measured by high resolution manometry (**Table 1**).

Statistical significance of result

($p < 0.001$) improvements in misdirected swallowing, cough, hoarseness, oesophageal retention, globus sensation, VAS scores, pharyngeal sling force, velopharyngeal closure and swallowing ability.

Conclusion

IQoro training significantly improves all the symptoms of hiatus hernia, potentially through improved hiatal competence. All symptoms were significantly improved at end of training suggesting that lasting improved hiatal competence had been achieved.

8.3 Oral neuromuscular training relieves hernia-related dysphagia and

GERD symptoms as effectively in obese as in non-obese patients.

Franzén T., Tibblin L., Hägg M. Acta Oto-Laryngol.

Jan 2019;138 (11):1–5 DOI: 0.1080/00016489.2018.1503715 [18].

Study type

Peer reviewed, Prospective, Clinical Study, Cohort pre- and post- study.

Aim

To investigate whether Body Mass Index (BMI) has significance on IQoro neuromuscular training's effectiveness in treating Hiatal hernia (HH) related symptoms.

Patients

86 adult patients (F = 46, M = 40) with verified HH and long-standing Intermittent Oesophageal Disease (IED) and other Gastro Oesophageal Reflux Disease (GERD) symptoms.

Before entry into the study the patients were partitioned into three groups according to BMI (**Table 2**):

- Group A:
 - normal weight, BMI < 25

- (n = 37: 19 women of median age 68 yrs., 18 men, median 72 yrs.)
- GERD symptoms - median duration 5 yrs. (1–75).
- PPI medication history median 5 yrs.
- Group B:
 - moderately obese, BMI 25–29
 - (n = 28: 16 women of median age 59 yrs., 12 men of median age 56 yrs.)
 - GERD symptoms - median duration 6 yrs. (1–15).
 - PPI medication history median 6 yrs.
- Group C:
 - severely obese, BMI 30–37
 - (n = 21: 11 women of median age 52 yrs., 10 men of median age 70 yrs.)
 - GERD symptoms - median duration 3 yrs. (1–29).
 - PPI medication history median 3 yrs.

Methods

All patients received IQoro neuromuscular training 3 x 10 seconds, three times per day for a duration of 6 months.

All patients were measured before and after treatment.

Outcome measurements

Radiology or gastroscopy was used to confirm HH and to rule out oesophageal stenosis before inclusion.

An Orofacial Motor Test (OFMT) and an Orofacial Sensory Test (OST) were performed in order to exclude symptoms of any central nervous lesion. Patients with neurological diseases were excluded.

All patients were measured before and after treatment using:

- Symptom questionnaire regarding IED and GERD (reflux, heartburn, chest pain, dysphagia, globus sensation, non-productive cough, hoarseness, and misdirected swallowing) [14]

Items	Group A; n = 37	Group B; n = 28	Group C; n = 21
Median age	69 yrs. (20–85)	57 yrs. (22–85)	62 yrs. (44–87)
Gender	19 women, 18 men	16 women, 12 men	11 women, 10 men
GERD symptom duration	5 yrs. (1–75)	6 yrs. (1–15)	3 yrs. (1–29)
BMI before/after IQNT	23 (17–24) / 23 (20–25)	28 (26–29) / 27 (24–29)	33 (30–37) / 31 (27–38)

Ranges in parentheses. BMI and GERD: median values; IQNT: Neuromuscular training with an oral IQoro.

Table 2.
Age, gender, symptom duration, and BMI in groups a, B, and C.

- Swallowing ability (measured using Timed Water Swallow Test - TWST) [27]
 - lower normal value for swallowing rate ≥ 10 ml/sec
- Pharyngeal sling force (measured using Lip Force meter) [25]
 - lower normal value ≥ 15 N
- Swallowing questionnaire (ability to swallow food) [22]
 - measured using Visual Analogue Scale (VAS 0–100)

Results

- At entry into the study there were no significant differences between the three BMI groups in:
 - TWST = SCT, PSF = LFT or VAS values
 - IED and GERD symptom severity, except that:
 - a. heartburn and cough were significantly more common in Groups B (moderately obese) and C (severely obese), and that
 - b. misdirected swallowing was significantly more common in Group C (severely obese).
- After **IQoro** neuromuscular training the following was observed in all three BMI groups:
 - all IED and GERD symptom scores were significantly improved or reduced ($p < 0.001$).
 - median BMI was not significantly changed.
 - self-assessed GERD symptom improvement showed no significant difference across the groups, except for heartburn, cough and misdirected swallowing which were significantly ($p < 0.01$) more reduced in obese patients than in normal bodyweight patients.
 - TWST = SCT and pharyngeal sling force (LFT) and VAS score, showed significant improvement ($p < 0.001$) in median values, with no significant difference between the BMI groups except for:
 - a. TWST values, which were significantly ($p < 0.01$) more improved in Group C (severely obese) than in Group A (normal weight).
 - b. pharyngeal sling force (LFT), which was significantly ($p < 0.05$) more improved in Group B (moderately obese) than in Group A (normal weight).

Statistical significance of result

($p < 0.001$) all IED and GERD symptom scores were significantly improved or reduced.

($p < 0.01$) heartburn, cough and misdirected swallowing were significantly more reduced in obese patients than in normal bodyweight patients.
($p < 0.001$) VAS score, TWST, and pharyngeal sling force (LFT) improved.
($p < NS$) no significant difference between other results across the three groups.

Conclusion

IQoro neuromuscular training (IQNT), a non-surgical treatment for IED and other GERD symptoms in hiatal hernia patients, is equally successful in treating moderately- or severely obese patients as in treating sufferers of normal weight. Obesity in itself does not therefore seem to be a handicap in treating IED and other GERD symptoms by IQNT.

9. Importance of neuromuscular treatment

Orally administered neuromuscular treatment as described, deserves wider deployment and, where more evidence is deemed necessary, further research. Unlike medication it treats the root cause of reflux, and without the cost and inconvenience of surgical intervention. It is self-administered by the patient and instructions for use are clearly explained in the accompanying manual; in surveys 98% thought that instructions were clear, and 97% thought it was easy to start training [19]. PPI drugs should not be re-prescribed routinely but rather only after a medication review; these reviews are often planned twice per year and add a burden to primary care practices. The drugs themselves have a considerable cost over the course of a patient's lifetime. An IQoro sells singly at around €150.

The overall advantage is that it addresses and treats the underlying condition, not merely the symptoms.

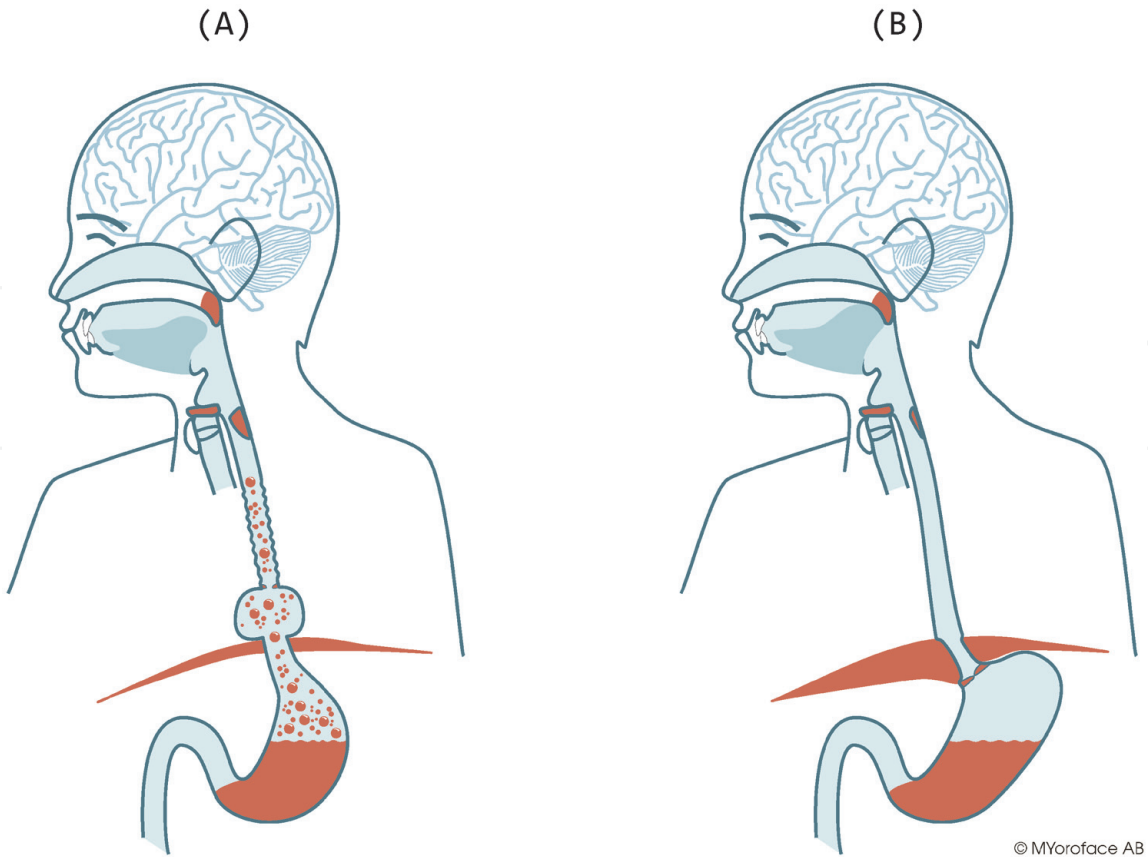


Figure 8.
(A) Sliding hiatal hernia; (B) functional anatomy (A) **sliding hiatal hernia**. The upper part of the stomach has slid up through the hiatal canal. This causes difficulties with opening the PES and allows gastroesophageal reflux. (B) **Normal anatomy**. The neck of the stomach is correctly held below the diaphragm promoting normal PES function and preventing reflux.

10. Conclusions

Esophagitis is a debilitating condition that is made worse by the effects of refluxed stomach acids. Reflux is caused by a Hiatus hernia, a weakening in the diaphragm muscles where the oesophagus passes through to join to the stomach (**Figure 8**). These weakened muscles can be compensated for by surgical intervention, or the amount and strength of the stomach acids produced can be reduced by medication. The most commonly prescribed drugs are Proton Pump Inhibitors, these carry proven unwanted side-effects.

Neuromuscular exercise is a safe, natural and simple treatment that can be carried out by the patient his or herself, and the underlying cause of the reflux is proven to be treated in 97% [16–18] of cases.

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Conflict of interest

IQoro® is patented and CE-marked by MYoroface AB. Mary Hägg is the inventor. Swedish patent SE 1350314–9, 2014 July 14. IQoro is a Class 1 Medical Device for therapeutic use. The authors, Mary Hägg and Thomas Franzén declare that they have no conflict of interest.

Notes/thanks/other declarations

The study was performed according to the Helsinki Declaration. Informed written and verbal consent was obtained from all the participants in the studies. All images are kindly provided by MYoroface AB.

A. Appendices

A.1. Appendix 1. Perceived symptom severity patient questionnaire

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References

- [1] Choueiri NE, Prather CM. Choueiri NE, et al. Barrett's esophagus: a pre-cancerous condition approach to diagnosis and management. *Mo Med*. 2009 Sep-Oct;106(5):339–42. PMID: 19902713
- [2] Yu HX, Han CS, Xue JR, et al. Esophageal hiatal hernia: risk, diagnosis and management. *Expert Rev Gastroenterol Hepatol*. 2018;12(4):319–29.
- [3] Siegal SR, Dolan JP, Hunter JG. Modern diagnosis and treatment of hiatal hernias. *Langenbecks Arch Surg*. 2017;402(8):1145–51.
- [4] Johansson KE, Ask P, Boeryd B, Fransson SG, Tibbling L. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. *Scand J Gastroenterol* 1986;21:837–847 [PMID: 3775250]
- [5] Stein E, Sloan J, Sonu I, et al. GERD for the nongastroenterologist: successful evaluation, management, and lifestyle-based symptom control. *Ann N Y Acad Sci*. 2020 Dec;1482(1):106–112. DOI: 10.1111/nyas.14496.
- [6] National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. (September 2014) (CG184). Available at: www.nice.org.uk/guidance/cg184/resources/gastrooesophageal-reflux-disease-and-dyspepsia-inadults-investigation-and-management-35109812699845
- [7] Bjornsson E, Abrahamsson H, Simren M et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: A double-blind, placebo-controlled trial. *Ailment Pharmacol Ther*. 2006; 24(6): 945–954
- [8] Saman Chubineh, John Birk. Proton pump inhibitors: the good, the bad, and the unwanted. *South Med J*. 2012 Nov; 105(11):613–618. DOI: 10.1097/SMJ.0b013e31826efbea.
- [9] NHS, Rotherham, Clinical Commissioning Group, Guidance to Review Proton Pump Inhibitors (PPIs) prescribing, Eloise Summerfield May 2019
- [10] All Wales Therapeutics and Toxicology Centre. All Wales Proton Pump Inhibitor and dyspepsia resource pack. Material to support appropriate prescribing of Proton Pump Inhibitors across Wales. April 2013 <http://www.awmsg.org/docs/awmsg/medman/All%20Wales%20Proton%20Pump%20Inhibitor%20and%20Dyspepsia%20Resource%20Pack.pdf>
- [11] Maret-Ouda J, Wahlin K, Artama M, et al. Risk of Esophageal Adenocarcinoma After Antireflux Surgery in Patients With Gastroesophageal Reflux Disease in the Nordic Countries. *JAMA Oncol*. Published online August 23, 2018. DOI: 10.1001/jamaoncol.2018.3054
- [12] Costing statement: Dyspepsia and gastro-oesophageal reflux disease. <https://www.nice.org.uk/guidance/cg184/resources/costing-statement-pdf-193164877>
- [13] D Mayo, A Darbyshire, S Mercer, et al. Technique and outcome of day case laparoscopic hiatus hernia surgery for small and large hernias: a five-year retrospective reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340(11):825–31. review from a high-volume UK centre. *Ann R Coll Surg Engl*. 2020 Oct;102(8):611–615. DOI: 10.1308/rcsann.2020.0151. Epub 2020 Jul 31.
- [14] Franzén T, Boström J, Tibbling Grahnl L, et al. Prospective study of symptoms and gastro-oesophageal reflux 10 years after posterior partial fundoplication. *Br J Surg*. 1999;86:956–

960. DOI: 10.1046/j.1365-2168.1999.01183.x.

[15] Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340(11):825–831.

[16] Hägg M, Tibbling L, Franzén T. Esophageal dysphagia and reflux symptoms before and after oral IQoro® training. *World J Gastroenterol* 2015;21(24):7558–7562. Open access: <http://www.wjgnet.com/1007-9327/full/v21/i24/7558.htm>

[17] Hägg M, Tibbling L, Franzén T. Effect of IQoro® training in hiatal hernia patients with misdirected swallowing and esophageal retention symptoms. *Acta Otolaryngol.* 2015;135(7):635–639.

[18] Franzén T., Tibbling L., Hägg M. Oral neuromuscular training relieves hernia- related dysphagia and GERD symptoms as effectively in obese as in non-obese patients. *Acta Otolaryngol.* 2018 Nov;138(11):1004–1008. DOI: 10.1080/00016489.2018.1503715. Epub 2019 Jan 10.

[19] PPT 1_Cust survey 2020 IQoro MYoroface, June 2020.

[20] Video 1_IQoro_This is how you exercise_EN_short version

[21] Medtech Innovation Briefing produced by the UK's National Institute for Health and Care Excellence in 2019. Available from: <https://www.nice.org.uk/advice/mib176>

[22] Joyce CR, Zutshi DW, Hrubes VF, et al. Comparison of fixed interval and visual analogue scales for rating chronic pain. *Eur J Clin Pharmacol.* 1975;8:415–420.

[23] Hägg M, Larsson B. Effects of motor and sensory stimulation in stroke

patients with long-lasting dysphagia. *Dysphagia* 2004; 19:219–230 [PMID: 15667056]

[24] Calhoun KH, Gibson B, Hartley L, Minton J, Hokanson JA. Age-related changes in oral sensation. *Laryngoscope* 1992; 102:109–116 [PMID: 1738279]

[25] Hägg M, Olgarsson M, Anniko M. Reliable lip force measurement in healthy controls and in patients with stroke: a methodologic study. *Dysphagia* 2008; 23: 291–296 [PMID: 18253790 DOI: 10.1007/s00455-007-9143-y]

[26] Netsell R, Hixon TJ. A noninvasive method for clinically estimating subglottal air pressure. *J Speech Hear Disord* 1978; 43: 326–330 [PMID: 692098]

[27] Nathadwarawala KM, Nicklin J, Wiles CM. A timed test of swallowing capacity for neurological patients. *J Neurol Neurosurg Psychiatry* 1992;55: 822–5.

[28] Tibbling L, Gezelius P, Franzén T. Factors influencing lower esophageal sphincter relaxation after deglutition. *World J Gastroenterol* 2011; 17: 2844–2847 [PMID: 21734792 DOI: 10.3748/wjg. v17.i23.2844]