Volumetric measurements in Graves’ orbitopathy
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Chapter 1

Introduction
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1. Graves’ Orbitopathy

1.1 Pathogenesis

Graves’ Orbitopathy (GO), also known as Graves’ Ophthalmopathy, Thyroid Associated Ophthalmopathy (TAO), Thyroid Eye Disease (TED) or Thyroid-Related Orbitopathy (TRO) is a disorder of the soft tissues of the orbit, frequently resulting in upper eyelid retraction with or without exophthalmos. The combination of goiter, palpitations and exophthalmos was first described in the 19th century by Baron Von Basedow. On the European continent, the disease became known as “Morbus Basedow” and in the Anglo-Saxon literature as “Graves’ Disease”. 1,2

GO is closely related to Graves’ hyperthyroidism, which is caused by auto-antibodies against the TSH Receptor (TSH-R). 3,4 Orbital fibroblasts, which also show TSH-R expression, are likely to be the target of the autoimmune attack in GO. 4 The annual incidence of GO in women is approximately 16 in 100,000 and in men 3 in 100,000. 5 Although most patients with GO experience only mild ocular discomfort, approximately 5% have severe orbitopathy with symptoms of excessive chemosis, proptosis or even loss of vision. 6

The pathogenesis of GO is thought to be of autoimmune origin and consists of infiltration of T-lymphocytes and macrophages in orbital tissues.4 Influenced by cytokines and other immunomodulatory molecules, fibroblasts proliferate and differentiate and glycosaminoglycan (GAG) production is stimulated. These GAG’s are hydrophilic in nature and cause edema by attraction of water. This leads to swelling of orbital tissues, both muscle and fat, and produces the clinical manifestations. 7-9

Environmental factors are important triggers for the development of Graves’ disease. Smoking is proven to be, and stressful life events are possibly, related to the development of Graves’ disease.10 There is also a genetic predisposition, since Graves’ disease runs in families and about 70% of the likelihood of developing Graves’ disease is attributable to genetic factors and 30% to environmental factors. 10,11 The best known risk factor for the development of GO is smoking. 12-17 The proportion of smokers among Graves’ patients is much higher than in the general population or in patients with Graves’ hyperthyroidism without GO. Prummel et al. found an Odds Ratio of 7.7 (95% C.I. 4.3-13.7) for smokers to develop GO.13 In addition, patients who continue smoking benefit less from treatment of their eye disease than patients who do not smoke. 16,17

1.2 Clinical presentation and pathophysiology

There is a large variability in the clinical presentation of patients with GO. Some patients merely complain about photophobia or a gritty sensation in the eyes, whereas others have complaints of severe facial disfigurement due to protruding globes, swelling of the eye lids, eyelid retraction and/or visible squint. Other complaints consist of double vision or disturbed visual acuity and retrobulbar pain at rest and/or with eye movements.
Patients with GO usually suffer from Graves’ hyperthyroidism as well, although about 10% of these patients are euthyroid and 5% are diagnosed with primary hypothyroidism. On the other hand, at least 40% of patients with Graves’ hyperthyroidism show signs and symptoms of GO. The symptoms and signs of GO can be explained mechanically by the discrepancy between the increased volume of the swollen orbital tissues and the fixed volume of the bony orbit. The expanded orbital tissues displace the globe forward and impede venous outflow from the orbit. These changes result in pain, proptosis, periorbital oedema, conjunctival injection, and chemosis.

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The eye changes of GO and their severity can be scored by using the NO SPECS classification (No signs and symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement and Sight loss). The activity of the disease can be described using the Clinical Activity Score (CAS) as proposed by Mourits et al. The CAS is based on the classical signs of inflammation: pain, redness, swelling and impaired function.

What is the prevalence of eye symptoms? Most studies agree that the prevalence of eyelid retraction is about 75%, of proptosis ≥ 23 mm 38%, of diplopia 49%, whereas 16% have corneal- and 5% optic nerve involvement. Corneal involvement is the result of exophthalmos, eyelid retraction, reduced blinking, impaired Bell’s phenomenon and altered tear composition.

An impaired apposition of the upper eyelid may also play a role. We noticed that in at least 40% of patients there was an air bubble visible on CT-scans in the upper fornix. In the majority of patients, this bubble was located opposite the insertion of the superior rectus. This air bubble may prevent an equal spread of the tear film over the cornea during blinking and can thus be the cause of a gritty sensation, blurred vision and intolerance to contact lenses, which is difficult to control with eye drops only. This condition may lead to painful punctate keratopathy and, when not treated properly, to corneal infiltration and ulceration. Sight loss caused by corneal involvement can be recognized early and should not be confounded with sight loss due to optic nerve involvement.

Optic neuropathy is due to compression of the optic nerve caused by swelling of the extraocular muscles in the apex of the orbit, seen as ‘apical crowding’ on CT- or MRI-scans. These swollen muscles are thought to compress the optic nerve in a direct way. Another possible mechanism is a high intraorbital pressure that is not relieved by developing exophthalmus. This is confirmed by Otto et al., who showed, that the intraorbital pressure just before decompressive surgery in patients with optic neuropathy ranged from 12 – 40 mm Hg (mean 29 mm Hg) and was reduced by 8 – 12 mm Hg after surgery. In contrast, the intraorbital pressure in patients decompressed for rehabilitative reasons (marked exophthalmus without optic neuropathy) was 9 – 11 mm Hg, and did not change after surgery. Riemann et al measured the intraorbital pressure of patients just before a subtenon injection prior to cataract surgery. The intraorbital pressure was 4.4 ± 2.2 mm Hg (Mean ± SD) in normal orbits, 7.8 ± 3.5 mm Hg in GO patients without and 12.4 ± 4.9 in patients with optic neuropathy. So even in the absence of neuropathy
the intraorbital pressure is higher than in normal individuals.\textsuperscript{28,29} Patients, who suffer from optic neuropathy do not necessarily have significant proptosis. In contrast, they may have relatively low Hertel readings. Obviously, these patients do not develop marked proptosis (which can be considered to be nature’s own decompression), but develop a high intraorbital pressure with circulatory disturbances.\textsuperscript{30,31} Impaired venous outflow can lead to a cascade of events mimicking the changes seen in GO.\textsuperscript{32} Koornneef suggested that a relatively firm connective tissue system attributes to the development of optic neuropathy.\textsuperscript{33} Sight loss caused by optic neuropathy is often accompanied by visual field defects, impaired color vision and a delayed latency on visual evoked potential. Papillary edema and disk pallor can be seen.

1.3 Natural history
Although the aetiology of GO is still not clarified, the natural course of the disease has been described in detail. The concept of disease activity originates from observations on the natural course of GO in patients who were not treated for their eye disease, and from a few histological studies performed on orbital tissues from patients with variable eye disease duration.\textsuperscript{34,35} Rundle followed 12 GO patients and found that the eye disease starts with a dynamic phase which is characterized by aggravations and remissions, followed by a static phase.\textsuperscript{36} The disease could still be severe when the static stage was reached. The concept of Rundle’s curve is supported by histological studies by Naffziger and Brain.\textsuperscript{37,38} During the active phase there usually is edema, a lymphocytic infiltrate and activation of fibroblasts. In the end-stages there is only muscle fibrosis. This concept implies that interference with immunosuppressive therapy is only useful in the “active” inflammatory phase and rehabilitative surgery mainly in the inactive end stages of GO.\textsuperscript{20} Rundle’s curve is generally accepted, even though the time axis varies widely between patients and may read anywhere between some months and several years. It was noted that while the disease tends towards spontaneous regression, a return to the normal, pre-disease state was seldom reached. These observations were later confirmed.\textsuperscript{39} Perros et al. found that spontaneous improvement occurred in 64% of 59 GO patients during a median follow-up of 12 months, while the disease remained stable in 22% and progressed in 14% of cases. These results were biased, because it concerned a group of selected GO patients in whom the treatment was not warranted. The observed improvement rate was probably overestimated. Regardless of the fact that the majority of patients seem to improve to some point, most patients feel that their eyes never return to normal.\textsuperscript{40} The last decades there have been case reports of patients with a revival of their orbital disease after decompression in spite of years of static phase.\textsuperscript{41}
2. Volumetry

2.1. Orbital anatomy

Knowledge of the anatomy is imperative for understanding how orbital volumes can best be calculated from CT or MRI scans. The orbits are pyramid-shaped bony compartments with their apices directed posteriorly and their bases directed anteriorly. The orbits contain the globes, extra ocular muscles (EOM), nerves, blood vessels, the lacrimal glands and the orbital fat. The four walls of the orbit separate the intraorbital contents from the surrounding brain and facial structures. Two major fissures, the superior orbital fissure (SOF) and the inferior orbital fissure (IOF) are in the lateral wall. The SOF transmits the superior and inferior divisions of N III, N.IV, the lacrimal, frontal and nasociliary branches of N.V, N.VI, the superior ophthalmic vein and sympathetic nerve fibers. The IOF transmits the infraorbital artery, the infraorbital nerve and the venous connection between the inferior ophthalmic vein and the pterygoid venous plexus. The orbital fascia forms the periosteum of the orbit and is called periorbit. It is continuous posterior with the dura mater and the sheath of the optic nerve and anterior with the periosteum that attaches to the anterior margin. The orbital septum is a thin fibrous sheath that extends superiorly to the aponeurosis of the levator palpebrae in the upper lid and to the tarsal plate of the lower eyelid. The orbital fat is limited anterior by the orbital septum.

Six EOM control the eye movements. The four rectus muscles originate from the (tendinous) annulus of Zinn in the apex. They extend forward to insert in the sclera and the orbita wall through pulleys. The superior orbital vein runs in the apex outside the muscle cone. The superior oblique muscle originates from the annulus of Zinn and courses forward medially from the rectus superior. The tendon passes through the trochlea, then turns laterally to insert to the postero-lateral aspect of the eye ball beneath the superior rectus muscle. The inferior oblique muscle originates from a depression in the upper surface of the maxilla, passes inferior to the inferior rectus to insert postero-lateral in the globe.
2.2. Volumetry of orbit and orbital soft tissues

Volumetry can be performed with the aid of Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), radiological imaging modalities whereby the body, or part of the body, is imaged in a cross-sectional fashion. A CT image shows a two-dimensional representation of a “slice” of the human body. The image is constructed from a matrix of numbers which are based on the local linear X-ray attenuation coefficient. Each matrix element containing one number is called a “pixel” (picture element). Given the thickness of the slice of tissue represented by the CT-image, one can also state that each two dimensional pixel in the image represents a three dimensional volume element (called: “voxel”) in the patient.

The elementary volume of the voxel is equal to the square of the pixel size times the slice thickness (figure 2). Any volume in the patient can now be calculated given the number of voxels it contains.\textsuperscript{45}

Figure 2. Definition of a ‘pixel’ and a ‘voxel’

The linear attenuation coefficient is represented in the image matrix as a CT-number, which ranges between -1000 and +3095. These CT numbers are called Hounsfield Units (HU) and the range is called Hounsfield scale. On this scale, the CT number of water is zero and each unit represents 0.1% of the linear attenuation coefficient of water.\textsuperscript{46} The HU were named in honor of Sir Godfrey Newbold Hounsfield (Nobel prize for Medicine in 1980) who invented the principle of CT scanning in the late 1960s and early 1970s.\textsuperscript{47-49} CT distinguishes normal and abnormal structures of different tissue density on the basis of this X-ray attenuation.
Volume measurements using CT scans were first based on manually drawn contours on X-ray film or on the display screen. This resulted in an accuracy range between 7 and 10%. The use of thresholding and region growing resulted in an accuracy of about 3% if the correct thresholds are applied. Tissue segmentation of for instance muscle is performed by having the computer select all pixels with HU known to include muscle (Forbes et al.0 to +135 HU 1985 and Zonneveld et al.1991 -30 to +160 HU). 2.2.1 Extraocular muscle volumes

Different observers have used different methods of segmentation for calculating volumes of extra ocular muscles (EOM). A nice overview is given by Bijlsma et al. Even with improved imaging techniques, the superior rectus muscle, the superior ophthalmic vein and the levator palpebrae muscle cannot be distinguished easily, because of their close relationship. Most researchers, therefore measure these structures together as the levator/superior rectus complex, which is probably the reason for a slightly larger muscle volume than in reality for the superior rectus alone. Nevertheless, reported orbital volumes cannot be compared easily. Other investigators choose to exclude these muscles. Excluding too many muscles will result in less information on muscle volumes; it seems preferable, as in the guidelines from Bijlsma et al., to measure the levator /superior rectus complex as a single entity. In coronal views the rectus muscles tend to become inseparable as they approach the orbital apex. Especially in GO when the muscles are enlarged, it is difficult to separate the muscles. More anteriorly in the orbit, the muscles transit to a tendon before insertion on the globe. Volume measurement should stop at the transition, but it is hard to pinpoint the exact location of this transition. It thus appears almost impossible to measure the exact full muscle volume. However, using manual or automated segmentation on CT images, the muscle volumes can be approximated well.

2.2.2. Orbital fat volumes

Reports on fat volume calculations are mostly found in the maxillo-facial surgical literature dealing with blowout fractures. The contralateral, noninjured orbit is used as a control. But, as with EOM, the method of calculation varies. Orbital fat absorbs less X-ray energy than water and more than air. When the HU were introduced for the CT numbers, the CT numbers for fat were converted to a range from – 100 till – 50 HU. Although most studies on GO focused on the increase of extraocular muscle volume, it has been recognized that an increase of the orbital fat volume can also occur in GO. Zonneveld et al. tried to determine both the intra- and the extra-orbital fat volume as did Peyster et al. By doing this, they hoped to unravel the possible mechanism of the bulging of orbital fat through the orbital septum, which reduces both the exophthalmos as well as the intraorbital pressure. More recently Darcy et al. found that in the normal aging process, the orbital fat will bulge in the lower eyelid without disrupting the orbital septum. The orbital fat was thought to fill out the space between the other orbital structures. Koornneef already showed in 1977, that the orbital fat has a shape of its own. Since then software has
been developed that could calculate “three-dimensional” (3-D) reconstructions displayed in a 3-D image. Actually they are two-dimensional projections of a volume and show only their third dimension when rotated or with the use of “surface shading”.73;74 Only a few volume measurements of the total orbital fat using CT have been reported in GO.52;53;55;61

3. Purpose of this thesis

Many observers report an increase in muscle volume and/or fat volume in GO as prominent features, but most do not respect influences of gender, race and age and used a variety of methods for calculating orbital volumes .58 The relative frequency and the determinants of muscle and fat enlargement in GO patients have received little scientific attention.

The aims of this study were:

1. to find commercially available software for calculating orbital soft tissue volumes and to validate the chosen technique.
2. to establish reference values for orbital fat- and muscle volumes in relation to age, gender and race.
3. to study the clinical characteristics in consecutive patients with GO subdivided in four groups according to their fat- and muscle volumes.
4. to compare densities of orbital fat and EOM between controls and GO patients, since the increase of fat volume in our GO patients was less than expected and the 3D images differed between the four subgroups.
5. to study the influence of smoking on orbital soft tissue volumes in GO patients, because smoking seems the most important environmental factor that influences GO.
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