Orbital decompression in Graves’ orbitopathy: state of the art and novel perspectives

Baldeschi, L.

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Chapter 1

Introduction

Part I:

General Introduction and Current Concepts on Decompression Surgery for Graves’ Orbitopathy

1. A MISNAMED DISEASE WHICH CONTINUES TO REQUIRE SURGICAL ATTENTION

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4. ORBITAL DECOMPRESSION IN GRAVES’ ORBITOPATHY: STATE OF THE ART


Part II:

Outline and aims of this thesis
1. A MISNAMED DISEASE WHICH CONTINUES TO REQUIRE SURGICAL ATTENTION

The multi-systemic disease which may include autoimmune thyroid disorders, goitre, exophthalmos, pretibial myxedema, and acropachy has been recognized as such for a very long time.

According to Jan-Gustaf Ljunggren 1, a Persian physician, Sayyid Ismail Al-Jurjani was the first to have noted the association of goitre and exophthalmos in the 12th century, and reported his observation in Thesaurus of the Shah of Khwarazm, the most famous of his five books, and the major medical dictionary of its period.

In more recent times, the Italian anatomist and surgeon Giuseppe Flajani in 1802 2, followed by another Italian physician Antonio Giuseppe Testa in 1810 3 described "exophthalmic goiter", though it was earlier recognized by Caleb Hillier Parry in 1786 and reported in his "unpublished medical writings" which appeared 3 years after his death in 1825. 4

Robert James Graves in 1835 5, and the German Karl Adolph von Basedow in 1840 6 independently reported the constellation of signs and symptoms which typifies the disease.

Long before any description of the association between exophthalmos and goitre appeared in the medical literature, a clear iconographic report of the disease was already available. In 2003, a painting in an Etruscan grave of the fourth century B.C., found in Sarteano, a small village in the Tuscan countryside of Siena depicts clearly these manifestations (Figure 1). 7

Figure 1. A painting in an Etruscan grave of the IV century B.C. in Sarteano, Siena, Italy. Charun the demoniac creature who transferred the defunct to the Ade, the Etruscan beyond, is depicted on his quadriga, as a patient with Graves' hyperthyroidism, and orbitopathy (left photo). The grave is named after this picture as "the grave of the infernal quadriga". An enlargement of the Charun's head and neck regions (right photo) clearly shows the presence of exophthalmos, lid retraction, frown, hyperaemic eyelids, cheek and lips. The presence of the goitre is further emphasized by the shadow behind the figure. (Photographs Civic Archeologic Museum of Sarteano; courtesy of Dr. Alessandra Minetti, reproduced with permission of the "Soprintendenza per i Beni Archeologici della Toscana").
Chapter 1

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As manifestation of the disease, orbital involvement has been given a multitude of names, including: thyroid eye disease, autoimmune orbitopathy, thyroid related or dysthyroid orbitopathy / ophthalmopathy, Basedow’s or Graves’ orbitopathy / ophthalmopathy. All of them are misnomers as they lack etiopathogenetic precision or eponymic priority. Until the pathogenesis of the disease is known and a more specific nosologic nomenclature is available, this bizarre orbital disorder should at least respect eponymic priority. For this reason, the adjective “Etruscan” should be mentioned when defining this orbitopathy and conversely the thyroid disease. This logical but regionalistic suggestion, however, might not sound appropriate to the international character of the two large consortia which at present are committed to research in the field of this disease, and which are both already named after it as European Group on Graves’ Orbitopathy (EUGOGO) and International Thyroid Eye Disease Society (ITEDS). Additionally, just for a coincidence..., it might appear parochially motivated by the Tuscan birth and Etruscan ancestry of the writer, together with the medieval but still strongly deep seated Ghibelline vicinity of Pisa, the author’s home town, to Siena.

By an astonishing twist of fate, and the serendipitous location of the Etruscan painting, Graves’ orbitopathy (GO), fulfils the writer’s proposal in part, that such a definition is maintained in this PhD thesis. This is also consistent with the writer being a member of EUGOGO.

The painting in the Sarteano grave in which Charun is depicted resembling a patient with Graves’ disease and GO (Figure 1) suggests that the somatic alterations and psychosis due to untreated hyperthyroidism might have already in that ancient culture been a source of prejudices resulting in social isolation for the affected patients.

Visible deformity, particularly involving the face, has always induced society’s aversion. Patients with facial disfigurement suffer from intrusions such as staring or comments. At the root of the patient’s distress lies a social pressure to conform to an idealized appearance. This obsession with appearance in our culture devalues those who do not match the perceived ideal and stigmatizes those with visible disfigurement.

Despite the long-lasting social implications and medical recognition of GO, its exact pathogenesis remains unknown. As a consequence a specific medical therapy is lacking,
and for many patients orbital surgery continues to represent an essential cornerstone in the treatment of their disabling and socially alienating disease.11

2. AN OVERVIEW OF GRAVES’ ORBITOPATHY AND ITS CURRENT MODALITIES OF TREATMENT: THE PLACE OF SURGERY

GO is an autoimmune disorder representing the most frequent and important extrathyroidal expression of Graves’ disease. It may also be found, although less frequently, in patients with no present or past history of hyperthyroidism (so-called euthyroid or ophthalmic Graves’ disease) or in patients who are hypothyroid due to chronic autoimmune (Hashimoto’s) thyroiditis.12, 13 In most affected individuals GO is mild and self-limiting, and only in 3-5% of cases, it is severe and potentially sight-threatening.12, 14

The exact pathogenesis of GO is unknown.15-18 It is, however, worth highlighting the clear-cut link between the orbit and the thyroid, because this has important clinical and therapeutic implications.19 In addition to endogenous (non-preventable) factors, such as genetics, age- and gender-related factors20, GO occurrence and progression are influenced by environmental (preventable) factors, such as cigarette smoking, thyroid dysfunction, and different treatments for hyperthyroidism.14, 21 This implies that control or correction of these risk factors is an integral part of GO management.

Independently of the complex association with thyroid dysfunction and its treatment, management of GO is difficult: decisions need to be made regarding the need for specific treatment or whether spontaneous regression is likely.

The natural history of GO is of gradual increase in severity followed by a plateau phase then gradual improvement.22 These are the active phases. The inactive phase follows with no change in severity. GO is thus self-limiting, although it often does not return to baseline. Treatment is aimed at accelerating recovery, preventing serious sequelae, and eventually functional and cosmetic rehabilitation.

Therapeutic options consist of medical therapy, radiotherapy, surgery, or frequently a combination of these. Consensus as to indications and timing of these options has been reached by the EUGOGO consortium (Figure 2).23, 24 More specifically the role of orbital decompressions in the state of the art rehabilitative surgery has been published in the
Figure 2. Management of Graves’ orbitopathy. Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. i.v. GCs, intravenous glucocorticoids; OR, orbital radiotherapy; DON, dysthyroid optic neuropathy.25, 26

second edition of the EUGOGO text book on GO25, 26, and the next two sections of this chapter describe these further.

3. Surgery for Graves’ Orbitopathy: The Place of Orbital Decompression

Graves’ orbitopathy (GO) is a debilitating disease which adversely interferes with the quality of life of affected patients.27 It is characterised by different degrees of disfigurement and alterations in vision, both of which contribute to loss of self-confidence, psychosocial stability and ability to function.

In GO, surgery, which may be necessary to protect visual function in the active phase of the disease or to correct the stable typical disfigurement and symptoms in the static post-inflammatory phase, should always be considered rehabilitative as it is aimed at restoring the individual integrity disrupted by the disease and ultimately the lost ability to function.

Commonly, however, surgery performed primarily to treat potentially sight threatening conditions such as optic neuropathy or exposure keratopathy is referred to as functional, while procedures primarily aimed at correcting disfigurement and symptoms are referred to as rehabilitative. For didactic purposes, we like to maintain this distinction between
functional and rehabilitative surgery, although it is necessary to admit that besides the above-listed semantic considerations, a clear-cut distinction between the two does not exist as surgery aimed primarily at restoring function also has positive effects on disfigurement and vice versa.

The definition *cosmetic surgery*, which does not stress the impact of the orbital disease in affected patients, appears inadequate and should be avoided. Surgery is in fact aimed at restoring a patient’s appearance as closely as possible to that preceding the onset of GO, and not at changing his or her somatic tracts to make them more beautiful. *Cosmetic/aesthetic rehabilitation* has often been used and can be considered an acceptable compromise when defining surgery mainly aimed at correcting disfigurement due to GO.

![Figure 3](image_url)

**Figure 3.** A patient affected by left, moderate severe, not-active GO with exophthalmos, mild restrictive esotropia and large angle restrictive hypotropia. An upper lid aponeurotic ptosis was also present left side. The general health condition of the patient and his scarce cooperation suggested to reduce as much as possible the number of surgical interventions. (a) Upon admittance for simultaneous orbital decompression and strabismus correction. (b) Five weeks after left deep lateral wall decompression through an upper skin crease approach followed by recession of the left inferior rectus muscle in the same surgical session. An adequate reduction of exophthalmos was achieved and the field of binocular single vision extended for more than 20° around primary position of gaze.
3.1. What Are the Steps and Timing of Rehabilitative Surgery?

During the post-inflammatory phase of GO, after a 6- to 8-month stable endocrinological and ophthalmic clinical picture, surgical rehabilitation can be performed if required. Depending on the severity of the disease, surgical rehabilitation can be more or less extensive, the full treatment consisting of decompression surgery, squint surgery, eyelid lengthening, blepharoplasty and eyebrow plasty.

The first rehabilitative step mainly consists of orbital bony decompression and early intervention soon after stabilisation has been advocated. Fibrosis due to long-lasting orbital disease or as a possible consequence of retrobulbar irradiation administrated in the early phase of GO has been questioned as a possible cause of poor distensibility and plasticity of the soft orbital tissues, resulting in scarce effectiveness of orbital expansion surgery. Recent studies, however, have demonstrated that long-lasting GO or preoperative radiotherapy do not adversely interfere with the results of orbital bony decompression; thus, when the stabilisation of Graves’ disease and orbitopathy has occurred, rehabilitative surgery can be started at any time and no adverse effects from common preceding treatments such as retrobulbar irradiation are to be expected.

Decompression surgery causes a reduction in exophthalmos as well as reduction in upper and lower eyelid displacement. It may positively influence extra-ocular muscle restriction, but displacement of the soft orbital tissues caused by decompression procedures may also cause strabismus. Possible squint surgery should therefore follow orbital decompressions, but considering that vertical tropias may influence eyelid position, squint surgery should precede possible correction of eyelid position. Finally, when necessary, the finishing touch can be given by eyebrow lift, forehead plasty and blepharoplasty.

In short, surgical rehabilitation needs to respect the given order since the preceding step may influence the necessity and the extent of the step that follows. When all the steps are necessary, the entire rehabilitation may require between 1.5 and 2 years. In particular cases, exceptions are possible and the rehabilitation can be favourably speeded-up by carrying out more than one procedure at the same time (Figure 3). The traditional management algorithm has not been respected in only a few series, and simultaneous decompression and strabismus surgery (in severe orbitopathy) or simultaneous decompression and correction of upper eyelid retraction (in mild to moderate, or in moderate to severe orbitopathy).
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3.2. How Should Patients Be Selected for Rehabilitative Surgery?

Patients should be selected on the basis of their motivation to undertake a long-lasting, potentially risky, and somewhat exhausting trail. Multiple interventions may also be necessary in cases where full treatment, starting with orbital decompression, is not required. Patients should be fully aware of the risks and benefits of each possible procedure and should accept the possibility of partial results or temporary worsening of their inability to function in the course of rehabilitation. Information provided by the physicians, although precise, may be inadequate to the patients, and potential candidates for surgery can better build up realistic expectancies by contact with patient associations. The psychological impact of GO on the affected patient is consistent, but should not itself be a reason to undertake a surgical treatment with potentially distressing effects in the same respect. It is up to the physician to understand when the patient has matured the adequate consciousness to be admitted to surgical rehabilitation, and the ophthalmologic controls necessary to assess disease stability should also be finalised according to this. Besides the patient’s determination to accept major surgeries, the possibility to aim for only partial results should always be weighed in the light of patients’ characteristics, such as age, general health conditions, profession, education and psychosocial environment. Often conservative surgery is of maximal benefit to the patient, in spite of modest final results that may be unattractive to the surgeon.
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4. ORBITAL DECOMPRESSION IN GRAVES’ ORBITOPATHY: STATE OF THE ART

4.1. What Is Orbital Decompression?
The autoimmune process at the basis of Graves’ orbitopathy (GO) induces swelling of the soft tissues contained within the boundary of the bony orbit, this causes impairment of the venous out flux towards the cavernous sinus and reverses the flux in direction of facial circulation. This positive feedback circle leads to an increase in the intraorbital pressure which is first responsible for the progression of GO and later for its typical signs and symptoms. Any surgical procedure aimed at decreasing the raised intraorbital pressure and its effects by means of enlargement of the bony orbit and/or removal of the orbital fat is defined as orbital decompression.

4.2. What Are the Aims of Orbital Decompression?
For one century decompression surgery has been used to treat GO. First it was used only to address sight-threatening conditions such as optic neuropathy refractory to medical therapy, or exposure keratopathy unresponsive to local measures, and/or minor eyelid surgeries. More recently, the indications of orbital decompression were extended to the treatment of disfiguring exophthalmos and symptoms. Eyeball subluxation (which may be a possible cause of acute optic neuropathy and exposure keratopathy), postural visual obscuration in patients with congestive inactive GO and choroidal folds due to eyeball indentation by enlarged extraocular muscles represent other more recently recognised functional indications for decompression surgery.

*Functional Aims*
According to a large retrospective study, decompression surgery can offer a rapid solution to dysthyroid optic neuropathy with an acceptable list of adverse effects (Figure 4).
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**Functional Aims**
According to a large retrospective study, decompression surgery can offer a rapid solution to dysthyroid optic neuropathy with an acceptable list of adverse effects (Figure 4). In GO exophthalmos, increased palpebral fissure width, blink rate alterations, lid lag, lagophthalmos, deficit of elevation and poor Bell’s phenomenon can all be potentially connected with drying of the ocular surface. In the course of active GO, ocular surface damage correlated significantly with a reduced tear secretion due to autoimmune lacrimal gland impairment, but not with increased ocular surface or impaired upgaze. Other studies had shown that in patients with a short duration of GO, tear secretion was not abnormal and exophthalmos, lid lag and lagophthalmos did not correlate with ocular surface damage, while the damage to the ocular surface depended principally on a widened...
palpebral fissure, which is the cause of increased ocular surface evaporation resulting in an elevated tear film osmolarity similar to that of sicca kerato-conjunctivitis. The influence of decompression rehabilitative surgery on increased eyelid aperture has recently been reported. A decrease in eyelid aperture based equally on decreased upper and lower lid displacement was found in about 50% of the patients presenting with preoperative increased eyelid aperture and decompressed by means of a 3-wall coronal approach which leaves the upper and lower lid retractors undisturbed. The effect of decompression surgery on severe corneal alteration had never been studied specifically, and although most of the studies on orbital decompression report a reduction in symptoms associated with exposure keratopathy, a case of severe corneal ulcer refractory to decompression surgery has also been published. Eyeball subluxation is a rare (0.1%) recurrent complication of GO that deserves urgent referral to a specialist centre as it represents a potential cause of visual loss. In light of the current literature, eyeball subluxation seems to occur in the type I, ‘lipogenic’ variant of GO as described by Nureny and never in the type II ‘myopathic’ variant. Globe subluxation in fact requires extensibility of the extraocular muscles. For this, it is conceivable that a definitive treatment of this sight-threatening condition can benefit either from bony and/or orbital fat decompression, but studies addressing this issue are lacking.

Among patients with inactive congestive orbitopathy there appear to be some with borderline optic nerve perfusion: a blood flow that is just able to maintain neural function. Such patients can present with recurrent visual obscuration associated with transient postural hypotension; diabetics appear particularly susceptible to this phenomenon. The vascular embarrassment of the optic nerve depending on elevated intraorbital pressure is very effectively relieved by orbital decompression and leads to an immediate cessation of postural visual obscuration.

Organised choroidal folds consecutive to eyeball indentation by enlarged extraocular muscles had been thought to be refractory to orbital decompression until recently when a positive response of this complication to bony decompression surgery has been reported.
Rehabilitative Symptomatic Aims

In GO, severe functional complications due to increased intraocular pressure are rare, different degrees of venous congestion, strabismus, eyelid puffiness and retraction, exophthalmos, and symptoms such as retroocular pressure and/or grittiness due to chronic corneal exposure are more frequent. Decompression surgery is the mainstay method to treat stable disfiguring alterations and/or symptoms that can typify the inactive post-inflammatory phase of the disease (Figure 5). Decompression surgery is not necessarily required only when exophthalmos exceeds the normal reference range. Patients with a flat forehead, scarce browbossing, and scarce anterior projection of the zygomatic eminence or patients with deep-set eyes before GO may be or feel disfigured at normal exophthalmometric values (Figure 6). Evaluation of pre-GO facial photographs may help the surgeon to restore a patient’s appearance as close as possible to how it was before the onset of orbital disease. Most of the studies dealing with orbital decompressions have indicated that this type of surgery is associated with lessening of the subjective perception of retro-ocular tension. In the early 1990s, Khan et al.\textsuperscript{53}, using the McGill pain questionnaire and visual analogue scales, specifically addressed this issue, and, although their study was not free of biases, it seemed to confirm that orbital discomfort significantly responded to orbital decompression.

4.3. Which Surgical Technique Should Be Preferred?
The raised intraorbital pressure and its consequences can be surgically addressed by expansion of the bony orbital boundary and/or by means of fat removal. For about one century, the two possibilities developed through parallel routes; only recently did it become clear that they should no longer be considered alternatives but complementary approaches concurring in tailoring the most adequate treatment to the specific patient’s needs (Figures 7, 8).\textsuperscript{54-56} Through the years, there have been many proposed techniques and variations. This has been largely due to the multifaceted nature of the disease, the different indications for decompression surgery, surgeon preferences and expertise, variations in orbital osteology, and patients’ expectations and attitude towards intervention. Furthermore, the constant attempt to implement the beneficial effects of this type of surgery while simultaneously decreasing the aesthetic impact of surgical scars, convalescence periods and
Figure 5. A patient with moderately severe non-active GO. (a) The patient upon admittance for orbital decompression. (b) The patient at the end of the surgical rehabilitation which included bilateral transinferior conjunctival fornix inferomedial orbital decompression, upper lid lengthening by means of transconjunctival Mullerectomy, and upper lid blepharoplasty.

Figure 6. A patient affected with GO, and presenting a flat forehead, and a scarce anterior projection of the zygomatic eminence. The patient appears disfigured by exophthalmos although her exophthalmometric value is only 18 mm.

risks for iatrogenic complications in general, and consecutive strabismus in particular, has further extended the case scenario (Figures 8-12).

Every type of fat removal or osteotomy has been hypothesized to cause critical relief of pressure at the apex, which can be beneficial for optic nerve dysfunction. The current
Figure 7. Bone removal in course of transinferior conjunctival fornix inferomedial orbital decompression.

Figure 8. Orbital fat removal. Lipectomies can be performed alone or may precede or follow osteotomies in the course of the same intervention. Preventive fat removal can be sufficient to adequately reduce exophthalmos and can aid bone exposure, thus easing the possible osteotomies that may follow. Fat removal following bone decompressions aids to increase the reduction in exophthalmos. (a) Removal of fat from the inferior lateral orbital quadrant as part of a combined transinferior conjunctival fornix inferomedial bone/inferior lateral fat decompression procedure. (b) Removal of fat from the inferior medial orbital quadrant during an extensive three-wall/fat decompression procedure performed through a combined transinferior conjunctival fornix and coronal approach.

trend is, however, to directly relieve the apical pressure as much as possible by increasing the apical volume of the bony orbit. This is obtained by removing the medial orbital wall (Figure 10b). In particularly severe cases, preventive removal of the lateral wall including its rim can prove convenient (Figure 10 a). Forces exerted by retractors in an attempt to
achieve apex decompression along the medial orbital wall can increase the already high retro-bulbar pressure up to critical levels for optic nerve fibres and vasculature. The preventive removal of the lateral orbital wall permits surgeons to address the deepest orbit more smoothly, reducing the risk of adding an iatrogenic component to the pathologically high orbital pressure at the basis of the neuropathy. There are several possible options to remove the medial orbital wall, but transconjunctival routes (either transcaruncular or transinferior fornix), which leave no visible scars are currently preferred. The endoscopic transnasal approach, described first and relatively recently by Kennedy et al., addressing the orbital apex without any substantial increase in the intraorbital pressure can also be a valid alternative that can even be performed under local anesthesia.

During the last three decades, when the number of rehabilitative orbital decompressions started to rise, it became of primary importance to balance a given technique in terms of not only effectiveness in reducing exophthalmos, but also (and mostly) in terms of safety. In the early 1980s, the antral-ethmoidal decompression by a transantral approach, as described by Walsh and Ogura in 1957, was the mainstay technique. The major disadvantage reported with transantral surgery was a subsequent motility imbalance as high as 52%, and therefore alternative procedures were sought in an attempt to decrease the risk of decompression-induced diplopia. In cases of mild exophthalmos, trans-lid antral-ethmoidal decompression appeared to be a valid alternative, with a risk of iatrogenic diplopia in only 4.6% of patients. For more severe exophthalmos, infero-medial decompression was used in combination with lateral decompression. Such procedures were also related with a low incidence of consecutive diplopia. In 1989, Leone et al., in an attempt to further reduce post-decompression strabismus, proposed balancing the decompression by removing the medial and lateral orbital walls while sparing the floor. This technique, which theoretically should have minimised the risk of iatrogenic diplopia, later appeared to be associated with a higher risk of such a complication compared with removal of the lateral orbital wall alone, or with inferomedial and three-wall surgeries.

At present the medial wall, the orbital floor and the lateral wall continue to be addressed during bony decompression surgery (Figure 10), while orbital roof removal has been abandoned due to the fact that its contribution to orbital expansion is minimal and associated with potential complications and side effects. Although orbital floor removal in
the course of orbital decompression is currently not favoured in North America, a recent prospective survey of the European Group on Graves’ Orbitopathy (EUGOGO) showed that inferomedial bone decompression is still a widely used procedure in Europe.\textsuperscript{71}

Depending on the severity of exophthalmos, the effect of inferomedial decompression can be implemented by adding lateral wall decompression and/or removal of the fat, usually of the inferior lateral orbital quadrant (Figures 8, 11). In view of reducing postoperative diplopia, an opposite sequence which involves firstly the removal of the lateral wall, associated or not to fat excision, and secondly, if necessary, the removal of the medial and inferior walls has been suggested.\textsuperscript{54} This strategy represents a significant conceptual departure from the traditional approach, which began with inferomedial decompression, and suggests regarding the lateral orbital wall and in particular its deep portion as being the region of first choice for orbital decompression in the case of rehabilitative surgery (Figure 10a). Removal of the lateral orbital wall - which appears to be connected with a low risk of consecutive diplopia or severe complications, such as cerebrospinal fluid leak - perfectly fits the needs of the increasingly demanding patient population.\textsuperscript{54-56} It was recently reported that removal of the deep lateral wall as part of a rehabilitative coronal-approach 3-wall decompression gives a 32\% enhancement in exophthalmos reduction without increasing the risk of consecutive diplopia as compared with traditional more conservative 3-wall decompression.\textsuperscript{72} The same study, however, confirmed the known high interindividual variability in the volume of the deep lateral wall. In light of this, the deep lateral wall is to be considered an effective although not always available zone of possible orbital volume expansion when dealing with rehabilitative decompression surgery.\textsuperscript{72} The effect of pure lateral wall decompression on exophthalmos reduction may be modest if not associated with medial wall removal, but in this case the risk of consecutive diplopia arises, while the result of lateral wall decompression can be augmented by intraconal fat removal without substantially increasing the risk of iatrogenic strabismus. On the contrary, removal of the lateral orbital wall and intraconal fat was beneficial in reducing preoperative primary gaze diplopia.\textsuperscript{36}
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Figure 9. Common surgical incisions for orbital decompression: (1) coronal; (2) ‘Lynch’; (3) upper skin crease; (4) lateral canthus; (5) sub-ciliary; (6) inferior fornix; (7) direct translower lid; (8) transcaruncular; (9) transnasal; (10) transoral; (4+6) swinging eyelid.

Figure 10. Common zones of bone removal for orbital decompression. (a) Axial projection of an orbital CT scan which highlights possible lateral wall osteotomies: conservative anterior (red), deep (green), extended (red + green), total (blue). (b) Coronal projection of an orbital CT scan which highlights possible osteotomies: inferior (yellow), medial (red), inferomedial (yellow + red).
Figure 11. Schematic representation of sites for orbital lipectomies reachable (yellow) or not (blue) through hidden transconjunctival incisions (red line) superimposed on a periorbital region photograph of a patient with GO (a) and on a coronal projection of an orbital magnetic resonance scan taken at the level of the middle orbit in a patient with GO (b). The fat compartment of the superior lateral quadrant (blue) can be exposed only through transcutaneous incisions; however, it is not used as an elective site for lipectomy because it hosts delicate structures and its removal gives a minimal contribution to fat decompression surgery.

Figure 12. A patient with moderate non-active GO and documentation of his intervention. (a) The patient upon admission for orbital decompression. Exophthalmos, hypoglobus, and lower lid displacement right side were present. (b) The patient 3 months after superomedial transcutaneous-septal fat decompression performed through an upper skin crease approach. Exophthalmos, hypoglobus, and lower lid displacement were adequately treated. (c) Surgical site. The skin and the orbicularis oculi muscle are retracted. An aperture through the orbital septum (white arrow heads), which is kept open with a cotton tip applicator following partial removal of the superomedial extraconal fat, shows (from left to right): medial margin of the levator palpebrae superioris muscle aponeurosis (blue arrow), anterior margin of the superior oblique muscle tendon (white arrow), intraconal fat (yellow arrow), and belly of the medial rectus muscle (red arrow). (d) Fat removed from the superomedial orbital quadrant at the end of surgery.
Rehabilitative decompression surgery aimed at addressing the tiresome retroocular tension that may characterise the postinflammatory stage of GO\textsuperscript{53} can be performed with minimally invasive techniques leading to minimal, if any, impact on extraocular motility or complications in general.\textsuperscript{74}

Pure orbital fat decompression was first described by Moore in 1920.\textsuperscript{75} From the 1980s, Olivari has used and popularized fat decompression.\textsuperscript{39, 76-78} After a publication (in German) reporting on a small series of 9 patients\textsuperscript{76}, he presented a larger series of 75 patients (147 orbits) and reported a mean exophthalmos reduction of 5.9 mm, an improvement in all the operated patients presenting with preoperative diplopia, and a complete resolution of diplopia in 55%.\textsuperscript{77} In such a series, new-onset permanent strabismus was observed in 14.3%, and an additional 57% of patients not presenting with pre-decompression diplopia experienced transient double vision up to 6 months after surgery.\textsuperscript{77} The same results have not been fully confirmed by other authors. With fat removal orbital decompression, Trokel \textit{et al.}\textsuperscript{79} (in a series of 81 patients, 158 orbits) did not have any cases of permanent induced diplopia and on average restrictions in extraocular eye motility ameliorated; however, only a modest reduction in exophthalmos could be attained. It was on the order of 1.8 mm, and rose to 3.3 mm only in patients with preoperative Hertel measurements of $\geq$25 mm.\textsuperscript{79} In terms of exophthalmos reduction, better results than those were reported by Adenis \textit{et al.}\textsuperscript{80} who obtained an average reduction in exophthalmos of 4.7 mm, with complications limited to extraocular eye motility disturbances, but the incidence of new-onset diplopia of this series rose to 22.2%. In 2003, the same author\textsuperscript{81} found even a higher incidence of new-onset diplopia (32%), in a study specifically aimed at evaluating the occurrence of such a complication after fat removal orbital decompression performed by using a similar technique to the one proposed by Olivari. Based on such results, Adenis \textit{et al.}\textsuperscript{81} concluded that the risk of new-onset diplopia after fat removal orbital decompression was similar to the average risk reported for bone decompression surgery.

A more recent series of 222 Asian orbits treated by means of fat removal orbital decompression through a swinging eyelid approach, however, showed promising results in terms of effect on extraocular eye motility with an incidence of new-onset diplopia of only 2% and cure of double vision in 20% of the patients affected by that before surgery.\textsuperscript{82} The authors explained these results and a lower mean exophthalmos reduction (3.6 mm), as
compared with the series of Adenies et al., on the basis of differences in surgical techniques used and in anatomy between the Asian and Caucasian orbits. Simultaneously with the Asian series, the group of Olivari reported on their 20-year experience with trans-palpebral fat decompression by presenting a monumental series of 2,697 operations. Although the mean exophthalmos reduction remained similar to the earliest study of the mentor of this group, persistent new-onset diplopia requiring surgical or prismatic correction later than 6 months after surgery rose to 22.2%. Despite the discrepancy in the amount of exophthalmos reduction and effects on extraocular eye motility, overall fat removal orbital decompression has proven to be a safe procedure through the years, and its positive effects also include improvement in visual function and reduction in intraocular tension when elevated secondary to raised intraorbital pressure. It appears to be an effective procedure mostly indicated in moderate-to-severe cases of lipogenic exophthalmos and periocular disfigurement due to fat prolapse and venous congestion, although it has also been used as a standard approach to any type of functional or rehabilitative orbital decompression (Figures 12, 13).

During recent years, the combination of bone decompression associated with fat removal (Figure 8) has been gaining popularity in view of its reported safety and increased effectiveness as compared with bone or fat decompression alone. Beveled osteotomies and onlay alloplastic periorbital implants - although sporadically used to camouflage more than to reduce exophthalmos - remain of uncertain effectiveness, and their edges, not infrequently visible, may devalue the final rehabilitative cosmetic result.

Most of the techniques currently used seem to be effective either in restoring impaired vision, and eye position or reversing congestive symptomatology and disfigurement of the periorbital region. An unbiased analysis of the current literature in terms of effectiveness versus safety, however, is extremely difficult because of the great heterogeneity of the patients included in the published studies; differences in definitions and methodologies used to study patients before decompression and to assess results after surgery; variations applied to surgical techniques that while falling under the same general definition may be completely different concerning surgical route, modality, location, and amount of removed bone or fat. Furthermore, it should be noted that the evidence of the literature concerning...
rehabilitative decompression surgery is modest, and mostly based on retrospective case series.\(^8\)7

As a result, most of the current speculations regarding the reliability and effectiveness of different techniques for decompression surgery are lacking conclusive proof. In an attempt to estimate the effectiveness of various surgical techniques, a prospective comparison of different treatment modalities along with different decompression surgeries - using a powerful tool, such as the Graves’ orbitopathy quality of life questionnaire (GO-QoL)\(^8\)8 - was advocated\(^7\)4, and recently carried out by the EUGOGO consortium.\(^7\)1 The study showed that, except in rare cases where a tailored approach was offered to the patients, the choice of surgical technique continues to be based on the surgeon’s personal experience and local tradition.\(^7\)1 With such an attitude, exophthalmos reduction, complications, side effects, and patient satisfaction were largely comparable, and independent of the chosen technique.\(^7\)1 In light of this, if one technique fits all, and the surgeon’s experience and local tradition are the factors which regulate the choice of technique in decompression surgery, there is no doubt that minimally invasive approaches are to be preferred.\(^8\)9

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**Figure 13.** A patient affected by moderate non-active GO with exophthalmos, eyelid puffiness and retro-ocular tension. (a) Upon admission for orbital decompression. (b) One month after inferior medial and inferior lateral, orbital fat decompression performed through a sutureless transinferior conjunctival fornix approach. Signs and symptoms were adequately cured.
Although the average results may be largely comparable regardless of the surgical technique used, forcing patients into standardised surgical frames is suboptimal as a standardised approach may produce unsuitable results for the single patient. Ideally, the planning of decompression surgery should comply with the patient’s expectations and needs, and should be matched to the patient’s anatomical and pathological substrates and possible previous surgeries. In clinical practice, this desirable approach to orbital decompression, which may involve the use of several different surgical techniques, is possible only in centres where adequate referral and a long-lasting tradition in orbital surgery favour transmission of expertise and warrant adequate back-up, whilst offering the possibility to develop new techniques or to master ongoing variations of others. As this cannot be the case in most of the centres dealing with GO, the use of a standardised versatile approach is to be regarded as an acceptable although suboptimal alternative.

The swinging eyelid approach described first by McCord in the early 1980s - with the conjunctival incision that can be extended medially as much as necessary, offering an adequate access to the bony orbit and to the orbital fat compartments - is a versatile technique that can be used for the majority of patients needing decompression surgery. As an alternative, inferior and medial conjunctival fornix and upper skin crease incisions can be used separately or in combination (Figures 9-12).

In 2003, Cruz and Leme questioned whether the coronal approach continues to have a role in orbital decompression and concluded that there is little, if any, need for this technique. Although the study design and the results of their paper could not offer strong support to their conclusions, it is easy to share their doubts about using an invasive approach, such as the coronal incision, as a standard route for orbital decompression.

Minimally invasive approaches and hidden periorbital incisions are currently preferred (Figures 5, 9, 11-13); nevertheless, the coronal incision is not to be abandoned as it can be an additional tool in surgeons’ hands when dealing with patients who can benefit more from a tailored approach than a standardised one. There are many circumstances in which this may happen. These include the presence of remarkable periorbital swelling or conjunctival chemosis, the necessity of minimising the number of periorbital incisions, or the necessity of extensive manipulation of the lateral wall (including its rim). Through
a coronal incision, brow lift, and correction of frontal/glabellar rhytids, which are often necessary in patients with GO, can be performed simultaneously with orbital decompression; thus, favourably speeding-up the timing of rehabilitative surgery.\textsuperscript{89, 92}

4.4. What Are the Possible Complications of Orbital Decompression?

Orbital fat decompression has never reached the popularity of bone decompression due to the theoretical (more than real) complications that may potentially be connected with this approach and which encompass damages to oculomotor ciliary and lacrimal nerves, orbital vasculature, extraocular eye muscles, optic nerve and the eyeball itself.\textsuperscript{80} Also, in the case of bone orbital decompression, in spite of theoretical expectations, severe complications are rare in clinical practice. Common complications of this surgical approach are consecutive strabismus, infraorbital hypoesthesia and sinusitis,\textsuperscript{93} lower lid entropion,\textsuperscript{94} and eyeball dystopia,\textsuperscript{95} while leakage of cerebrospinal fluid, infections involving the central nervous system, damage to the eye and optic nerve or their vasculature, cerebral vasospasm, ischaemia and infarction are severe but rare events.\textsuperscript{42, 96} Reactivation of GO after rehabilitative bony orbital decompression is another rare complication very recently described in 3 of 239 patients not treated with perioperative glucocorticoids. The phenomenon consisted of the onset of typical signs and symptoms of active GO with radiologic evidence of extraocular muscle enlargement a few weeks after surgery and following a normal convalescence period. Based on its clinical characteristics, the observation was named delayed decompression-related reactivation (DDRR). The incidence of DDRR appeared to be in the order of 1.3% and could be controlled with systemic immunosuppression or retrobulbar irradiation.\textsuperscript{97}

In addition to complications common to orbital decompressions in general, different surgical approaches and routes may carry the risk of specific complications. The second branch of the trigeminal nerve may be damaged in the course of orbital floor removal decompression. This may potentially induce the formation of traumatic or amputation neuromas. Such lesions, although rare, should be included in the potential complications of decompressions when counselling patients about to undergo this type of surgery, as they are difficult to treat and may cause persistent and disabling pain.\textsuperscript{98}
into the nasal cavity and scarring of the nasal mucosa with meatal and sinus obstruction, mucocele and sinusitis can occur with endoscopic endonasal approaches.\textsuperscript{99, 100}

The coronal approach leaving the eyelid undisturbed is less likely than periorbital incisions to create complications which may potentially be harmful to the eye. Periorbital scarring with iatrogenic lid retraction and cicatricial lagophthalmos, eyelid margin malpositions and ptosis (although rare) are more likely to occur with periorbital incisions. On the other hand, temporal bossing, damage to the frontalis nerve, scarring and alopecia at the site of the scalp incision, or effects upon ischemic areas of the frontal flap after healing by secondary intention may complicate the coronal approach.\textsuperscript{89}

The coronal approach should not be considered a more hazardous technique as compared with the less invasive periorbital incisions. The more serious complications connected with the coronal approach have been reported in small series where less than 3 patients per year were operated upon.\textsuperscript{90, 101}

4.5. Can Complications Be Predicted or Prevented?

Most of the possible complications cannot be predicted and their prevention is based on recommendations which are not specific in nature, and which include careful manipulation of the orbital content, accurate dissection of the orbital fat, and avoidance of expandable haemostatic agents and/or extensive use of diathermy within the orbit.

Other complications with known pathogenesis such as sinusitis can be simply prevented by taking care to create an adequate sinus aeration as a part of the surgical procedure at the time of bone decompression.

The occurrence of other complications, namely infraorbital hypoesthesia or pain, eyeball dystopia leakage of cerebrospinal fluid and possible consecutive infectious involvement of the central nervous system, can be reduced by means of accurate evaluation of preoperative imaging, adequate planning of surgical intervention and the use of prophylactic antibiotics.

Strict observance of this methodology helps detecting patients at an increased risk of possible complications. A low lamina cribrosa for instance should be regarded as a possible source of cerebrospinal fluid leakage for those patients planned for medial wall decompression. Late-onset enophthalmos and hypoglossus can be prevented simply by avoiding inferomedial decompression when dealing with patients recognised to be at higher risk due to their anatomical substrate. The complication had in fact been described as
dependent on prolapse of orbital fat into the ethmoidal infundibulum in the presence of a predisposing anatomy which includes septal deviation to the affected side and eventual abnormal middle turbinate whose inferior part, directed laterally, also crowds the maxillary infundibulum.95

Diplopia has a considerable impact on the quality of life of patients with GO, and is a feared complication that often prevents patients and physicians from undertaking decompression rehabilitative surgery. In light of the current literature, strabismus subsequent to decompression surgery has been linked to mechanical and neurological implications connected with the ‘lipogenic or myopathic’ types of GO50, the surgical route, the extension and location of the osteotomy, and the preservation of structures such as the maxillary ethmoidal strut or the anterior periorbit. Differing types of motor and/or sensory capacities for compensation of induced muscle imbalances may also play a role.33 A better understanding of all of the possible factors involved in the pathogenesis of diplopia consecutive to decompression surgery may help its prevention.

Outline and Aims of this Thesis

In 1999 the European Group on Graves Orbitopathy (EUGOGO) 7 was established in Amsterdam in an attempt to contribute to a better understanding of the immunopathogenesis of Graves' orbitopathy and to improve the frequently unsatisfactory outcomes in patients affected by this disease. This was followed by years of preparation and extensive internal discussions before any multicentric clinical studies could be started. Since the beginning, as ophthalmic delegate from one of the involved centres (University of Amsterdam) and founding member of the Group, I had the privilege to participate in the debates. The limitations in methodology and the scarce evidence of the available literature concerning the ophthalmic surgical management emerged frequently during that period, and were later confirmed in published reviews on the subject. 23, 24, 87

"Time honoured axioms" and misleading statements also appeared in this same literature. The studies which are included in this thesis were designed and conducted with the purpose of highlighting and possibly amending some limitations, flaws, or unproven concepts in the accepted literature within the field of decompression surgery (chapters 2-4); to critically evaluate and review its current trends regarding osteotomies and approaches (chapters 5, 6); to analyse the abnormal "situations" affecting GO patients about to undergo or who have undergone decompression surgery and whose investigations might have contributed to a better understanding (chapters 7, 8) and management (chapters 9-10) of this debilitating orbital disease.

This latter purpose was specifically included into the present thesis to show that the value of orbital surgery can go beyond its practical results and most importantly as a tribute to the far-sightedness of Professor Leo Koornneef, the mentor of Dutch orbital surgery, to whom this thesis is dedicated. Long ago, he recognised the value of multidisciplinarity, which continues to inspire the work of the EUGOGO consortium and to motivate initiatives such as the Amsterdam declaration. 102-104 In his words: "The pathogenesis of Graves' orbitopathy is still poorly understood. Through research into the normal and abnormal situations, approached by different disciplines, might elucidate the problems and enable better management to prevent this disfiguring disease."
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Chapter 2 discusses the effect of early versus late intervention on the outcomes of rehabilitative decompression surgery. The study aimed at investigating whether a group of patients with long standing disease and possible subsequent fibrosis of the soft orbital tissues had different surgical outcomes as compared with a group of patients decompressed by means of the same surgical technique and with similar baseline characteristics except for having received earlier decompression surgery.

Chapter 3 is concerned with the effect of pre-decompression administered orbital radiotherapy on the outcome of rehabilitative decompression surgery. The study aimed at investigating whether a group of patients who received pre-decompression radiotherapy (which could have been a possible cause of subsequent fibrosis of the soft orbital tissues) had different surgical outcomes as compared with two other groups of patients decompressed by the same surgical technique and with similar baseline characteristics except for having received systemic glucocorticoids or a combination of orbital radiotherapy and systemic glucocorticoids in the active phase of the disease preceding rehabilitative decompression surgery.

In chapter 4, a prospective observational case series is presented regarding a novel evaluation for the outcome of a graded bone removal of the infero-medial orbital wall in patients with GO. Outcomes of the novel appraisal were also compared with the results which could have been detected in the same cohort using a traditional methodology. The novel evaluation method consisted in scoring whether the targets (amount of desired exophthalmos reduction, improvement of retroocular tension, reduction of peri-orbital swelling / oedema, resolution of lagophthalmos) established before surgery were indeed achieved; in characterizing the cohort of included orbits and patients, and their sub-groups with indices which could readily identify: a) invasiveness of surgery to which they were exposed, b) score in target achievement, c) influence of surgery on central binocular vision; in performing comparisons after stratification of the included orbits for amount of desired exophthalmos reduction and invasiveness of surgery.

Traditional methodology examined the entire series as a single homogeneous cohort which underwent rehabilitative surgery with infero-medial decompression independently of the different invasiveness of surgery.
In chapter 1, a case control study is presented on the contribution of the popular deep lateral wall orbital osteotomy on rehabilitative exophthalmos reduction in GO and the influence of such a procedure on the onset of consecutive diplopia.

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In chapter 5, a case control study is presented on the contribution of the popular deep lateral wall orbital osteotomy on rehabilitative exophthalmos reduction in GO and the influence of such a procedure on the onset of consecutive diplopia.

In chapter 6, a review is presented on the indications, advantages, disadvantages, reported complications and their possible causes, of small versus coronal incisions in orbital decompression surgery. Practical implications associated with the choice of a standardized surgical approach as opposed to customized one are also discussed.

In chapter 7, an observational case series and retrospective follow-up study is presented on the incidence, clinical presentation, clinical course and treatment of previously unreported decompression induced reactivation of GO. Eventual pathogenetic hypothesis of this phenomenon are discussed and correlated to those of GO.

In chapter 8, the case of a patient who was a possible candidate for orbital decompression is presented. He was affected by X-linked childhood cerebral adrenoleukodystrophy and developed Graves’ hyperthyroidism and GO after a whole bone marrow transplantation from his sister. She was not affected by Graves’ hyperthyroidism at the time of bone marrow transplantation, but developed the condition thereafter. As in the preceding chapter, pathogenetic hypotheses are discussed and correlated to those of GO.

In chapter 9, the case of a patient affected by GO, and presenting with a CT and biopsy proven presence of a supernumerary extraocular muscle enlarged because of the orbitopathy and co-determinant of restrictive strabismus, is presented underscoring the importance of an accurate preoperative assessment to avoid diagnostic and surgical mistakes.

In chapter 10, the case of a patient affected by GO who developed a traumatic neuroma of the infraorbital nerve subsequent to inferomedial orbital decompression is presented. The causative mechanism of traumatic neuromas are discussed and, the relevance to mention
Chapter 1

this previously unreported cause of trigeminal neuralgia when counselling patients about to undergo inferomedial decompression is stressed.

In chapter 11, a historical perspective, associated with an overview on the most recent technical innovations in the field of orbital decompressions, and an analysis of the current possibilities of implementation for this type of surgery, are used as a framework for the discussion of the previous chapters. Their contribution to patient care, research and new perspectives in the field of orbital decompression surgery, along with their input towards a basic science approach to GO are critically reviewed.
Chapter 1

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Chapter 1


