CALCULATION OF EXTRAOCULAR MUSCLE VOLUME IN PATIENTS WITH GRAVES' OPHTHALMOPATHY AND THE CORRELATION WITH DISEASE SEVERITY AND CLINICAL ACTIVITY OF THE GRAVES' DISEASE

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ABSTRACT

INTRODUCTION

Graves' disease (GD) is an autoimmune disease affecting the thyroid gland, orbital soft tissues and subcutaneous tissues of the extremities. Ophthalmic signs are clinically evident in 25-50% of patients with GD and 3-10% of cases develop severe disease.

This study discusses the current understanding of the pathophysiology of GD and the associated ophthalmopathy. It summarises the clinical features of the condition and examines the numerous scoring systems used to measure and monitor the ophthalmic features of the disease.

The three main radiological techniques used to image the orbit, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are discussed.

Although CT is regarded as the radiological investigation of choice for imaging orbit details subtle changes related to Graves' ophthalmopathy (GO) can be missed. To accurately calculate extraocular muscle volume we have developed a computer software package, the Volume Estimation Tool. This software allows outlining of structures from a CT image and then calculates the volume of the structure.

The aim of this study is to determine if extraocular muscle volume and orbital volume estimates from CT imaging correlate with clinical signs and scores of disease activity or severity.

METHODS

Study Design

This is a retrospective study comparing the orbital CT scan findings in patients with GD with their clinical activity, as close as possible to the time of the scan, and their disease severity.

The initial hope had been to use high definition 3 dimensional ultrasound to calculate muscle volume. This proved inaccurate and non-reproducible for calculating muscle volumes.

We therefore, worked in conjunction with the Christchurch Hospital Medical Physics department to develop a computer programme to estimate muscle volume from coronal slices of CT scans. This volume estimation tool was used to calculate the volume of muscles and soft tissue orbits in a series of patients with clinical evidence of GO. The same muscle and orbital volumes were calculated for a set of matched controls without GO.

In addition, methods of measuring disease state in patients with GO were compared. Disease activity and severity were calculated from the clinical records of the patients with GD as close as possible to time of the CT scan. The activity of the GO and the severity of the disease were then correlated with the muscle and orbital volumes to see what relationships there are. The clinical symptoms and signs of GO were then related to muscle volume to determine which have the greatest impact on clinical activity and disease severity.

Participants

A record of all patients with thyroid eye disease was compiled by correlating records of patients seen in both the thyroid clinic, Nuclear Medicine Department

and the ophthalmology clinic at Christchurch Hospital. From this cohort, we used radiology department records to obtain a subset of patients for whom head/neck CT scans had been ordered. A control group of patients with no history of GD and CT scans with normal radiology reports from the same period were selected.

Outcome Measures

Clinical activity and disease severity were calculated by different methods and compared. The activity and severity were also compared to the estimated muscle and orbital volumes to determine any possible relationships.

RESULTS

In patients with GO muscle volume may be a more sensitive indicator of muscle enlargement than subjective viewing of the CT images looking for enlargement of muscle bellies. Muscle volume for patients with GO was significantly higher than for patients with no GO ($p<0.0001$). Patients with GO also have larger orbital volumes than patients without GO ($p=0.003$).

Muscle volume in patients with GO also correlates positively with clinical activity ($p<0.0001$) and disease severity ($p<0.0001$).

When individual clinical features are examined there is a weak correlation between muscle volume and proptosis ($p=0.05$), but no association with lid retraction and muscle volume ($p=0.12$). Neither is there a correlation between horizontal or vertical muscle restriction and muscle volume ($p=0.56$ and $p=0.44$ respectively).

CONCLUSIONS

The results show that accurate calculation of extraocular muscle volume using this software package is possible. We confirm that calculating extraocular muscle volume in patients with GO gives additional useful information for assessing and managing patients with GO.

Muscle volume correlates positively with clinical activity and disease severity. Patients with more active and more severe disease have greater changes in muscle volume than those without.

For 2 patients with optic nerve compromise there was a high percentage of orbital volume taken up by muscle. This suggests this ratio, rather than muscle volume alone, may predict risk of optic nerve damage.

However, patients with very active disease or severe residual disease do not have an increased risk of restrictive eye movements despite having larger total muscle volumes.

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TABLE OF CONTENTS

		Page No
Abstract		ii
Acknowledgements		v
Contents		vi
List of Tables		viii
List of Figures		ix
List of Abbreviations		xi
Section 1	**Description of Current Understanding of Pathogenesis of Graves' Disease**	
1:1	Introduction	2
1:2	History	4
1:3	Pathophysiology of GO	6
1:4	Histology	15
1:5	Risks of GO	16
Section 2	**Diagnosing and Classifying GO**	
2:1	Clinical Features of GO	20
2:2	Making the Diagnosis of GO	27
2:3	Classification and Activity	29
Section 3	**Imaging in GO**	
3:1	Imaging Techniques	41
3:2	Differential Diagnosis from Imaging	42
3:3	Ultrasound in Ophthalmology	42
3:4	Computed Tomography	48
3:5	Magnetic Resonance Imaging	51
Section 4	**Methods**	
4:1	Ethics Committee	53
4:2	Patient Selection	53
4:3	Assessing the Patients	55
4:4	Computer Software	57
4:5	Statistics	60
4:6	Changes in Process Due to the Study	
Section 5	**Results**	
5:1	Demographics	63
5:2	Reason for Scan	63

5:3	Disease Severity and Clinical Activity	66
5:4	Muscle Volume Calculations	67
5:5	Orbital Volume	73
5:6	Analysis of Clinical Features	78
5:7	Summary of Clinical Findings	89
Section 6	**Discussion**	
6:1	Study Outline	92
6:2	Muscle Volume in "Normal" CT Scans	93
6:3	Muscle Volume Calculations	94
6:4	Orbital Volume Calculations	97
6:5	Optic Nerve Involvement	98
6:6	Criteria for Assessing Extent of GO	100
6:7	Reproducibility	101
6:8	Alternatives to Total Volume	102
6:9	Limitations of this Study	104
Section 7	**Conclusions**	
7:1	The Technique	107
7:2	Extraocular Muscle Volume	108
7:3	Clinical Activity and Disease Severity	108
7:4	Restrictive Eye Disease	109
7:5	Orbital Volume	109
7:6	Risk of Optic Neuropathy	109
7:7	Role for Muscle Volume Calculation	110
Section 8	**References**	112
Section 9	**Appendices**	
Appendix 1	Information Sheet for Participants in Study on Thyroid Eye Disease	118
Appendix 2	Consent Form for the Study Examining Patients with Thyroid Eye Disease	122

LIST OF TABLES

Number	Title	Page
Chapter 2		
Table 2:1	NOSPECS classification for grading severity of GO	30
Table 2:2	Clinical activity score as described by Mourits *et al*	35
Table 2:3	Disease Severity Score as Described by Feldon and Unsold	37
Chapter 5		
Table 5:1	Demographic data for cases with GO with information about CT scan	64
Table 5:2	Demographic data for age and sex matched controls and the reason the CT scan was ordered	65
Table 5:3	Muscle volume for left and right eyes in cases with GO with clinical activity and disease severity scores	68
Table 5:4	Muscle volume for left and right eyes in control patients with no evidence of GO	69
Table 5:5	Orbital volume for left and right eyes in patients with GO and the Clinical Activity and Disease Severity Scores	74
Table 5:6	Orbital volume for left and right eyes in control patients with no evidence of GO	75
Table 5:7	Value for the specific clinical factors measured for each patient with GO	79
Table 5:8	Summary of findings related to muscle volume, orbital volume and disease status	89
Table 5:9	Summary of correlation coefficient (r) and p values for each of the clinical criteria compared to muscle volume, Disease Severity Score (DSS) and Clinical Activity Score (CAS)	90

LIST OF FIGURES

Number	Title	Page
Chapter 1		
Figure 1:1	Robert James Graves (1976-1853)	4
Figure 1:2	Summary of the pathogenesis of GO	14
Chapter 2		
Figure 2:1	Eyelid retraction in thyroid-associated ophthalmopathy	21
Figure 2:2	Soft tissue involvement in thyroid-associated ophthalmopathy	23
Figure 2:3	Eye muscle involvement in thyroid-associated ophthalmopathy.	24
Figure 2:4	Photograph showing use of exophthalmometer to measure degree of exophthalmos	25
Figure 2:5	Optic neuropathy in patient with thyroid-associated ophthalmopathy.	26
Figure 2:6	Hypothetical Relationship between disease activity and severity in the natural history of GO	29
Figure 2:7	The activity and severity of thyroid eye disease	33
Figure 2:8	VISA Classification; Vision, Inflammation, Strabismus, Appearance.	39
Chapter 3		
Figure 3:1	20Hz B scan ultrasound image of normal eye showing lens, retina and optic nerve shadow.	44
Figure 3:2	B-scan USS with 20Hz probe showing increased detail when focused on the anterior chamber	44
Figure 3:3	Axial and coronal CT images of a patient with GO showing enlarged extra-ocular muscles.	50
Chapter 4		
Figure 4:1	Image from the VET showing the coronal CT scan and outlines of the 4 muscle regions and the orbit	58

Chapter 5

Figure 5:1	Scatter plot comparing Clinical Activity Score and Disease Severity Score	66
Figure 5:2	Scatter plot comparing total muscle volume between left and right eyes	70
Figure 5:3	Scatter plot comparing total muscle volume to clinical activity score	71
Figure 5:4	Scatter plot comparing total muscle volume to disease severity score	72
Figure 5:5	Scatter plot comparing % of total orbital volume made up by muscle with Clinical Activity Score.	77
Figure 5:6	Scatter Plot comparing % of total orbital volume made up by muscle with Disease Severity	77
Figure 5:7	Scatter plot comparing proptosis and Clinical Activity Score	80
Figure 5:8	Scatter plot comparing proptosis and disease severity	81
Figure 5:9	Scatter plot comparing proptosis and muscle volume	81
Figure 5:10	Scatter plot comparing lid retraction with Clinical Activity Score	82
Figure 5:11	Scatter plot comparing lid retraction and disease severity	83
Figure 5:12	Scatter plot comparing lid retraction and muscle volume	83
Figure 5:13	Scatter plot of horizontal restriction with Clinical Activity Score	84
Figure 5:14	Scatter plot of horizontal restriction and disease severity	85
Figure 5:15	Scatter plot of horizontal restriction versus muscle volume	85
Figure 5:16	Scatter plot of vertical restriction versus Clinical Activity Score	86
Figure 5:17	Scatter plot of vertical restriction versus disease severity	87
Figure 5:18	Scatter plot of vertical restriction versus muscle volume	87

LIST OF ABBREVIATIONS

Abbreviation	Full Description
GD	Graves Disease
GO	Graves Ophthalmopathy
CT	Computed tomography
MRI	Magnetic resonance imaging
TSH	Thyroid stimulating hormone
LATS	Long acting thyroid stimulator
IgG	Immunoglobulin
HLA	Human leukocyte antigen
TSH-R	Thyroid stimulating hormone receptor
TPO	Thyroid Peroxidase
T3	Triiodothyronine
T4	Thyroxine
GAG	Glycosaminoglycans
mRNA	Messenger ribonucleic acid
RAI	Radioactive iodine
ATA	American Thyroid Association
CAS	Clinical Activity Score
DSS	Disease Severity Score
VISA	Vision, Inflammation, Strabismus, Appearance
EUGOGO	European Group on Graves' Orbitopathy
3D	Three dimensional
VET	Volume Estimation Tool
DICOM	Digital imaging and Communications in Medicine
PACS	Picture archiving and communications system

SECTION 1

DESCRIPTION OF CURRENT UNDERSTANDING OF PATHOGENESIS OF GRAVES' DISEASE

1:1 INTRODUCTION

The aim of this study is to determine if extraocular muscle volume and orbital volume estimates from CT imaging correlate with clinical signs and scores of clinical activity or disease severity.

Graves' disease (GD) is an autoimmune disease affecting the thyroid gland, orbital soft tissues and, infrequently, the subcutaneous tissues of the extremities. Many labels have been attached to the eye disorder including thyroid associated orbitopathy, endocrine exophthalmos, dysthyroid orbitopathy and thyroid eye disease. Graves' disease and Graves' ophthalmopathy (GO), the terminology used in this paper, are the eponymous names after one of the early observers of the clinical syndrome, Robert J Graves.

GO is the most common orbital disorder and the most common cause of exophthalmos in adults.[1] GO is the underlying cause in 15% to 28% of cases of unilateral exophthalmos and 80% of cases of bilateral exophthalmos.[1]

GO has an estimated prevalence of 1.85% in the United Kingdom, and 0.5% in the USA.[2] No data could be found giving accurate prevalence or incidence figures for Australia or NZ.

Ophthalmic signs are clinically evident in 25-50% of patients with GD and 3-10% of cases develop severe disease.[2 3].

The pathogenesis for the exophthalmos in GD is multifactorial and the following factors have all been implicated: enlargement of extraocular muscles, increased orbital fat volume and venous stasis caused by increased orbital pressure from the

enlarged extraocular muscles. These findings have been clearly demonstrated radiographically with CT scans show that most patients with GD have enlargement of the extraocular muscles, orbital fat, or both. [4]

It is currently believed that the localized connective tissue manifestation of GD and the ophthalmopathy, are not a direct consequence of thyroid function abnormalities, but reflect an underlying autoimmune process, in which stimulatory antibodies bind to TSH receptors in the thyroid gland and orbit. [2]

The clinical symptoms and signs of GO can be explained mechanically by the discrepancy between the increased volume of swollen orbital tissues and the fixed volume of the bony orbit. [4] The expanded orbital tissues displace the globe forward and impede venous outflow from the orbit. There may also be impedance of the lymphatic drainage from the orbit. These changes, combined with the local production of cytokines and other mediators of inflammation, result in the ocular manifestations of the disease; pain, gritty eyes, photophobia, chemosis, diplopia, and proptosis.[4] Compression of the optic nerve by orbital soft tissues can lead to visual loss and blindness, in extreme cases.

1:2 HISTORY

Thyroid eye disease or Graves' disease is named after Robert J. Graves, MD. Graves was the first physician to formally describe the exophthalmic goitre, now called Graves' disease.[1] In 1834, Graves delivered a series of lectures in Dublin that were later published in the London Medical and Surgical Journal and the London Medical Gazette. He described in detail three patients with 'palpitations and enlargement of thyreoidea'. One of the patients had eye symptoms: 'the eyeballs were visibly enlarged, to such a degree the eyelids were unable to shut during sleep and when trying to close the eye. When the eyes were open the white of the eyes could be seen in the breadth of several lines around all of cornea.' The constellation of goitre, palpitations and exophthalmoses is now known as Graves disease.[5]

Figure 1:1 Robert James Graves (1796-1853)
From the Wellcome Institute of the History of Medicine

Karl Adolf von Basedow, a German physician, also described the triad of exophthalmos, goitre and exophthalmos around 1840.[6] Because of this association, in some parts of the world Graves' disease is referred to as Basedow's disease.

The earliest recorded case of TAO may be from Bodhidharma, also known as Daruma, who, in the sixth century, was the founder of Zen Buddhism and Kung Fu. [6]

The discovery of an abnormal thyroid stimulating factor, that was not thyrotropin, (TSH) in the serum of patients with Graves hyperthyroidism was made in the 1960s by Adams and Purves *et a.* [7] This factor was known as long acting thyroid stimulator (LATS) because of it's prolonged action on bioassay compared to that of TSH. These investigators were working in Dunedin, New Zealand at the time of this major discovery in the pathogenesis of GD.

The subsequent identification of this stimulator as an IgG (Immunoglobulin G) antibody took a further 10 years of research. [8] It is now clear that GD is caused by these thyroid stimulating antibodies, which bind to and activate the thyrotropin receptor on thyroid cells, although the exact pathogenesis still remains elusive.

The main alteration of the orbit in GO is the enlargement of the extraocular muscles and this was first observed by Rundle and Pochin in cadavers.[9]

1:3 PATHOPHYSIOLOGY OF GD AND GO

GD is accompanied by a number of symptoms directly referable to thyroid hormone excess including palpitations, anxiety, tremor, and weight loss. In addition, some patients with GD develop manifestations in other systems including ophthalmopathy and dermopathy. It is believed that the connective tissue manifestations of the disease are not a direct consequence of alterations in thyroid function, but reflect the underlying autoimmune disease process. [2]

The exact aetiology of GO is unknown, although it is widely accepted to be an autoimmune disease. An unidentified pathogen or its mediator may induce lymphocytic infiltration, swelling and later fibrosis in the orbital tissues. Both humoral and cell-mediated immune mechanisms have been implicated.[10]

1:3:1 HYPERTHYROIDISM

Thyrotoxicosis refers to the clinical syndrome that results when tissues are exposed to high levels of circulating thyroid hormone.[11] In most cases, thyrotoxicosis is due to hyperactivity of the thyroid gland, or hyperthyroidism. Occasionally thyrotoxicosis may be due to other causes such as excessive ingestion of iodide or thyroid hormone from ectopic sites. [11]

Of the thyrotoxic patients, only those with GD develop the ophthalmic features discussed in this thesis. The other causes of thyrotoxicosis do not have associated ophthalmic features. Although rare patients with hypothyroidism have been reported to develop ophthalmic features consistent with GD,[12] these patients are not included in this review.

The Thyroid Clinic at our Institution have audited their patients and found, of 1000 sequential thyrotoxic patients, 70% had GD, 18% had multinodular toxic goiter, 4% had toxic nodules and the remainder other conditions such drug or iodide related. Less than 5% of patients with GD develop severe ophthalmic signs.

The ophthalmic features tend to follow the thyroid hormone abnormalities and in most cases occur within 12 months of diagnosis.[13] However, cases of GO have been reported in patients prior to development of any hormone imbalance and some patients develop ophthalmic signs many years after diagnosis. The dermopathy is most often a late finding and is a marker of more severe GD.

1:3:2 THE IMMUNE SYSTEM

The physiologic role of the immune system is to differentiate native from foreign or altered macromolecules. This occurs through interaction between specific immune mechanisms, antibody systems and cell-mediated immunity, and non-specific mechanisms such as the complement cascade and inflammatory cells. [14]

Autoimmunity results when there is a loss of recognition of self. This may be explained by a defect in immune regulation in which there is a failure of suppressor lymphocytes, permitting survival of a clone of helper T-lymphocytes establishing a localised cell-mediated immunity and development of directed against self antigens by B-lymphocytes.[15,16] A second theory of autoimmunity is a shift in antigenicity, so that an antigen is not recognised as self, resulting in antibodies or cell-mediated immunity directed at the altered antigen[17].

The immune system has been implicated in the pathogenesis of thyroid diseases for more than 50 years[16,17]. Other diseases characterised by an autoimmune process may be associated with thyroid disease, such as pernicious anaemia, Addison's disease, myasthenia gravis and type I diabetes. [18] The most common association is with pernicious anaemia[19], and this is proposed to be related to the close embryological association between the thyroid gland and the gastrointestinal system.[20]

In GD, antibodies are directed to the cell membrane of the thyroid cell and the antibody is capable of combining with the thyrotropin (TSH) receptor and stimulating that receptor. This causes increased release of thyroid hormones.

1:3:3 AUTOANTIBODIES

The aetiology and mechanics of the autoimmune cellular and antibody responses are by no means fully elucidated. They involve a combination of human leukocyte antigen (HLA) linkage, genetics and environmental factors to determine the initial and subsequent stages of the development of autoimmune thyroid disease.[21]

There are 3 important antigens currently thought to be involved in thyroid autoimmunity: thyroglobulin, the thyroid stimulating hormone receptor (TSH-R), and thyroid peroxidase (TPO). [21] TPO was originally described as thyroid microsomal antigen in 1985. [22] There are other less well-described antigens, like the recently cloned sodium iodide symporter, which may play a role in the pathogenesis of GD.

Thyroglobulin

Thyroglobulin is a 670kDa protein with 2 polypeptide chains, from which the thyroid hormones triiodothyronine (T3) and thyroxine (T4) are produced. [21] Iodination of thyroglobulin produces multiple antigen configurations which are functionally active but immunologically distinct. Several of these thyroglobulin polymorphisms are capable of inducing a T-cell response which contributes to triggering autoimmune thyroid disease. [21]

Antibodies to thyroglobulin are very common in GD, but the major drawback with their clinical application is their lack of specificity, with 11% of the general population having detectable antibodies. [21]

TSH Receptor Antibodies

The original description of the serum element, which was able to stimulate mouse thyroid receptors was named long acting thyroid stimulator (LATS), but this term is no longer favoured and now TSH receptor stimulatory antibodies is the accepted terminology.[21] The auto-antibodies directed to the TSH receptor can either mimic or block the effects of TSH. [21]

Circulating stimulatory TSH receptor autoantibodies simulate the effect of TSH resulting in hypersecretion of thyroid hormones and the resulting symptoms of GD are related to the effect of increased circulating thyroid hormones.[2]

The TSH receptor is a 2 subunit glycoprotein; the extracellular A subunit is recognized by thyroid stimulating antibodies, while those antibodies recognising the B subunit appear to function as blocking antigens. In addition, because these antibodies can react with multiple epitopes on the TSH receptor molecule, antibodies which block and mimic the effect of TSH can be present in the same patient. [21] Unfortunately it is difficult for laboratories to measure these subtypes of

antibodies to determine if they block or stimulate, meaning that clinical implications of the subtype of antibody are still not routinely detectable. [21]

TPO

TPO is present on the apical surface of the thyroid follicular cells and is the antigen involved in cell-mediated toxicity. Multiple B-cell reactive epitopes are present on human TPO, each giving rise to different antibodies. These epitopes may be genetically determined and are believed to be stable within each patient. [21]

1:3:4 GRAVES OPHTHALMOPATHY

Some patients with Graves' disease also develop changes in the orbit, skin and nails. The mechanisms behind this are becoming clearer. The most popular theory for the association between GD and development of ophthalmopathy is immunological cross-reactivity of sensitized T-lymphocytes and/or autoantibodies against antigens common to the thyroid and orbit. [23]

Although the target antigen still remains unidentified, the TSH receptor is the main candidate. Concentrations of TSH receptor antibodies have been shown to correlate directly with clinical features of thyroid eye disease. TSH receptors have been found in orbital tissue and in affected skin in patients with thyroid associated dermopathy. [24] Although these findings have led support to the theory that the TSH receptor is the shared antigen connecting the affected organs in thyroid eye disease, the hypothesis remains unproved.[24]

Fibroblasts

The extraocular muscle fibres are intact in early active stages of the disease, suggesting they themselves are not the target of the autoimmune attack. Rather,

the enlargement of the muscle bodies results from an accumulation of glycosaminoglycans (GAG), especially hyaluronic acid, with attendant edema. [4] In later stages of the disease, the resolving inflammatory process within the muscles, and deposition of collagen, may leave them fibrotic. [4]

The oedema is due to the hydrophilic action of glycosaminoglycans secreted by fibroblasts. [8] Fibroblasts have been shown to increase their production of GAG under stimulation from certain cytokines (IL-1β, TNFα, IL-8, IL-10 and γ interferon)[25] The inflammation is due to infiltration of the extra-ocular muscles and orbital connective tissue by lymphocytes and fibroblasts.[8] The increase in the volume of retrobulbar tissue is responsible for most of the clinical manifestations of the ophthalmopathy.

The orbital fibroblast appears to be the target cell in Graves ophthalmopathy [4] Orbital fibroblasts have been shown to express TSH receptors. [23] The sensitized T-cells circulate to the orbit and bind to and stimulate the TSH receptors on orbital fibroblasts.[23] Involvement of T cells and activation of fibroblasts occur early in the disease process. [25]

Orbital fibroblasts exhibit remarkable phenotypic heterogeneity.[4] When stimulated, one sub-population can produce hyaluronic acid and inflammatory prostanoids; other cells (pre-adipocytes) can differentiate into mature adipocytes. [25] The former sub-population is found in connective tissues investing the extra-ocular muscles, and the latter is found primarily in the orbital fat compartment. It is proposed that selective activation of these sub-populations explains why some patients have predominant eye muscle disease and others expansion of the retro-orbital adipose tissue compartment as the major disease factor.[26]

Fibroblasts also possess a wide array of tissue-specific phenotypes, which likely affect the apparently selective involvement of the skin of the anterior lower legs, termed pretibial dermopathy. [4] The presence of pretibial dermopathy is a clinical marker of severe ophthalmopathy. [27] It is present in 15% of GD patients with severe ophthalmopathy and is much less common in GD overall (<5%). [4] The dermopathy often appears many years after the hyperthyroidism and the ophthalmopathy.[28] The histological change in dermopathy appears to be similar to ophthalmopathy within the orbit without the increase in adipose tissue volume. [27]

The TSH receptor

The close relationship between Graves' hyperthyroidism and ophthalmopathy suggests that both result from an autoimmune response to one or more antigens in the thyroid and orbit. The currently favoured antigen is the TSH receptor, which is proposed to be expressed by the orbital adipose tissue[4] and fibroblasts. [8]

A pre-requisite for involvement of the TSH receptor as an autoantigen in GO is that this protein be expressed in affected orbital tissue. [4] Multiple studies from many laboratories have demonstrated the presence of TSH receptor mRNA (messenger ribonucleic acid) and protein in orbital adipose tissue specimens from patients with and without graves ophthalmopathy. [4]

Additional studies have shown that levels of TSH receptor are higher in patients with ophthalmopathy than those without suggesting that increased TSH receptor expression in the orbit may be responsible for disease development. [29]

Similarly, TSH receptor appears to be more abundant in pretibial dermopathy than in normal pretibial skin.[30] In tissue excised during orbital decompression surgery, correlation was found with patients disease activity score and the level of TSH receptor mRNA.[4] The findings suggest that adipogenesis is enhanced in the

orbits of patients with GO and that increased expression of TSH receptors is a consequence of this process.

IgG

IgG from patients with thyroid eye disease can cause orbital fibroblasts from patients with thyroid eye disease (but not those without) to produce T lymphocyte chemo-attractants (ICAm-1 and interleukin 16) which would be expected to promote thyroid eye disease. [18] However there are no proven cases of neonatal thyroid eye disease (in neonates born to mothers with active hyperthyroidism or with treated GD and positive antibodies). If IgG has a pathogenic role in thyroid eye disease, IgG alone transferred across the placenta is not sufficient for disease expression.[18]

Recent studies by Pritchard and associates [31] further investigated the role IgG in thyroid ophthalmopathy. They demonstrated that fibroblasts from patients with GD are activated by IgG from these same donors to synthesise molecules that stimulate the infiltration of activated T ells into areas of inflammation. This process is mediated by the insulin-like growth factor receptor, which suggests patients with Graves have auto-antibodies against this receptor. The IgG activation of this receptor is not restricted to the fibroblasts from the orbit and pre-tibial skin and suggest the receptor may have a role in lymphocyte trafficking. [4]

1:3:5 ANATOMY

Unique anatomical features of the orbit and lower extremities appear to be clinically important in Graves disease[30] The unyielding bony orbit predisposes to compression of low-pressure venous channels increasing retrobulbar pressure and causing periorbital oedema. The role of orbital lymphatics in normal and diseased

orbits is yet to be fully elucidated. While vestigal lymphatic structures have been demonstrated in the lacrimal gland and optic nerve sheath, most authorities regard the orbit to be devoid of true lymphatics. Without effective lymphatic drainage, orbital oedema may persist longer.

Similarly, prolonged standing contributes to compromise of the channels in the lower extremities, contributing to the dependent oedema seen in pretibial dermopathy, [30]although dermopathy can occur in other body sites such as the upper extremities and trunk.

Moreover, individual anatomic variations in venous or lymphatic vessels may place some individuals with GD at special risk for the development of severe ophthalmopathy or dermopathy.

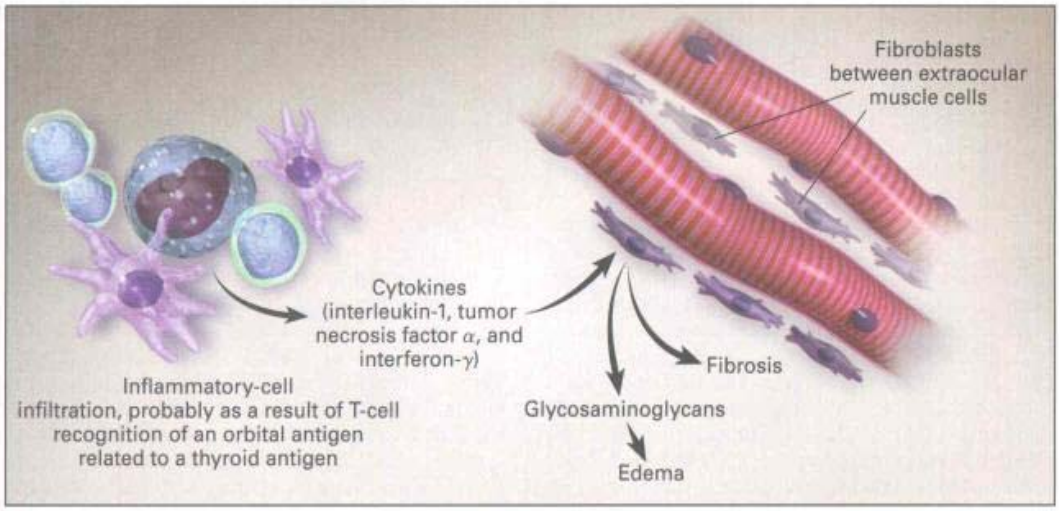


Figure 1:2 Summary of the pathogenesis of GO taken from Weetman, NEJM. [8]

An inflammatory infiltrate composed of activate T lymphocytes localises in the extra-ocular muscles and orbital connective tissue. This may be through recognition by T cells of an orbital antigen that cross-reacts with a thyroid antigen, such as the thyrotropin receptor expressed in fibroblasts. Cytokines produced by the infiltrate activate fibroblasts and stimulate production of GAG leading to oedema and later fibrosis.

1:4 HISTOLOGY

GO is characterized by inflammation, congestion, hypertrophy, and fibrosis of orbital fat and muscles leading to enlargement of tissue. [1]

Histological examination of the extra-ocular muscles shows the muscle fibres are preserved and the increase in muscle bulk reflects changes in connective tissue. [32] Within the connective tissue fibroblasts are numerous, which produce mucopolysaccharides, specifically hyaluronic acid, a form of glycosaminoglycans. [33] An inflammatory infiltrate characteristic of an immunological disturbance is seen. [17] The inflammatory cells are composed of lymphocytes, plasma cells, mast cells and macrophages[33] All of these changes lead to ingress of extracellular fluid and the development of interstitial oedema. [32] The lymphocytes are predominantly CD4+ T lymphocytes. [34]

Although the inflammatory reaction is predominantly seen in the muscle, it can also occur in the tendons.[33] Biopsies of orbital fat from affected patients have had the same lymphocytic inflammatory infiltrate as that seen in the extraocular muscle compartments.[33]

In the later stages there is fibrosis and fatty infiltration of the muscles resulting in a restrictive myopathy. [33]

The preferential involvement of certain muscles, notably the medial and inferior recti, is possibly related to their innervation and fibre size. [33]

1:5 RISKS OF GD

1:5:1 SEX

It is well known that auto-immune diseases are more prevalent in females than males. This is true for GD as well., and the disease is 5 [24] to 8 [2] times more common in females. The molecular mechanism that underlies the gender preference still needs to be elucidated.[2]

1:5:2 SMOKING

Once a patient has GD the major clinical risk for developing thyroid eye disease is smoking [10]. Patients with thyroid eye disease are 4 times more likely to be smokers or former smokers than never smokers. [10] The greater the number of cigarettes smoked per day, the greater the risk of developing thyroid eye disease. Giving up smoking seems to reduce the severity of the eye signs.[8] The association may be due to an increase in orbital glycosaminoglycans in response to relative hypoxia. [2]

1:5:3 AGE

Thyroid eye disease most often occurs between 30 and 50 years of age, suggesting that as yet unidentified age factors or hormonal changes contribute to enhanced disease susceptibility[2]

1:5:4 RADIOIODINE

There is controversy over the association between radioactive iodine and GO. Some researchers have shown an increased risk of developing eye signs after radioactive iodine (RAI) compared to surgical or medical treatment of the hyperthyroidism. [35] [36]

The first study[35] showed 33% of patients treated with RAI developed eye signs de novo or had worsening of pre-existing eye signs, compared to 16% having surgery and 10% of patients receiving methimazole.

In the second study[36], 15% of patients receiving RAI developed ophthalmopathy or worsening of pre-existing eye disease and only 3% of those receiving methimazole.

Critics of these studies have argued that the RAI groups had a larger proportion of smokers and that post radioactive hypothyroidism was not corrected, as well as questioning the statistical methods used to compare the groups. [23]

Because of these studies, many endocrinologists favour antithyroid medications over RAI as first line therapy of GD, especially when ophthalmopathy is present. [23] In our institution, any sign of active ophthalmopathy means radioiodine is not offered as a treatment option. The endocrinologists we work with consider the risk of developing ophthalmopathy after radioiodine is increased if patients become hypothyroid after treatment. They are therefore carefully monitored and any elevation in TSH promptly treated.

1:5:5 GENES

Increased incidence of the disease among family members indicates that genetic factors play an important role in the susceptibility to GD.[2] No single gene has been identified. It is likely that multiple genes interact with multiple environmental factors to cause thyroid eye disease. [24]

Twin studies indicate a higher concordance further suggesting a genetic predisposition to the disease[2]. Other studies have shown that patients with GD more often express human leukocyte antigen (HLA) B8 than controls [37]. There is conflicting evidence in the literature about genetic susceptibility to GD and a recent review summarized the findings and concluded that multiple genetic factors contribute to the risk of developing GD and the penetrance of the disease is about 30%.[38]

1:5:6 ENVIRONMENT

As with many other autoimmune diseases an environmental factor has long been suspected in GD. [2] Although no such factor has been identified, bacteria or viruses are proposed to initiate an autoimmune response to a specific self-antigen. [2] This may occur through activation of the inflammatory response leading to pro-inflammatory cytokines that cause aberrant expression of major histocompatability complexes and costimulatory molecules, allowing activation of antigen specific T-cells. [2] Microbial infections may also cause over-expression or altered expression of certain self-proteins which are then perceived as foreign. [2]

SECTION 2

DIAGNOSING AND CLASSIFYING GRAVES DISEASE

2:1 CLINICAL FEATURES OF GO

Signs and symptoms of GD, including GO, are varied and involve different organ systems. Hyperthyroidism often involves changes in energy levels, weight, sleep, bowels, heart rate and rhythm.

The inflammatory reaction in the orbit can lead to a wide variety of signs and symptoms. They may occur in isolation or in conjunction with one another. The frequency of the various symptoms and signs varies considerably from study to study.[39]

2:1:1 OPHTHALMIC SYMPTOMS

Pain is a common symptom in patients with GD. In an incidence cohort of 120 patients with GO, Bartley *et al* found pain to be the most frequent presenting symptom, occurring in about 30% of patients. [40] It may be caused by an inflammatory reaction in the eye muscles, especially when the presence or magnitude of pain is dependent on direction of gaze.[41] Increased intraorbital pressure is also likely to play a role in the initiation of pain.

Diplopia due to involvement of the eye muscles is the second most common complaint (17% of patients) at the diagnosis of GO.[40]

Soft tissue symptoms, including photophobia and epiphora, are common, with approximately 15% of patients suffering each of these.[40]

Bartley *et al* described blurred vision in 6% of study patients. In two of the 120 patients studied, visual loss was due to optic nerve dysfunction. However,

changes in refraction, superficial keratitis or epiphora are more common explanations for blurred vision in TAO.[40]

2:2:2 OPHTHALMIC SIGNS

Lid Retraction

Retraction of the upper lids producing the characteristic staring and frightened expression was fully described by William White Cooper (1849) but is usually known as Dalrymple's sign. The retraction is usually bilateral but may occur in one eye only. [1] The retraction of the upper lid may be spasmodically increased on attentively fixating on an object, Kocher's sign. The normal position of the upper eyelid is 1-2mm below the superior corneoscleral limbus.

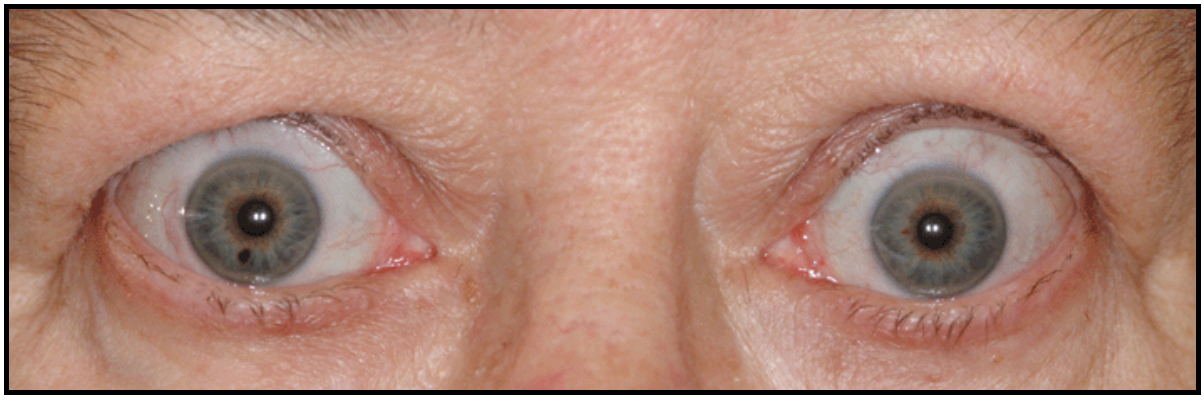


Figure 2:1 Eyelid retraction in thyroid-associated ophthalmopathy.

Lid Lag

In Von-Grafe's sign of lid-lag, (1864) when one's gaze is directed downwards there is a failure of the upper lid to maintain its relative position with respect to the globe resulting in an immobility or lagging of the lid. The downward movement of the lid may be jerky and uneven, so that is doesn't correspond to that of the eye, Boston's sign.

Lagging of the lid in upward gaze has also been described, Griffith's sign (1886). On gentle closure a trembling may be visible, Rosenbach's sign. An infrequency and incompleteness of the blinking reflex is called Stellwag's sign (1869). Fullness of the eyelids due to a puffy oedema is known as Enroth's sign. [1]

Incomplete closure of the lids, lagophthalmos can lead to further complications such as corneal exposure, infection and rarely perforation. In addition, patients may complain of symptoms of excessive lacrimation, gritty sensation, and photophobia.

Chemosis and Injection

A deep injection of the conjunctiva, particularly over the horizontal recti muscles may be seen. Oedema of the conjunctiva or chemosis may also develop. [1] A swelling of the caruncle is reported and is one of the features of activity proposed by Mourits. [42]

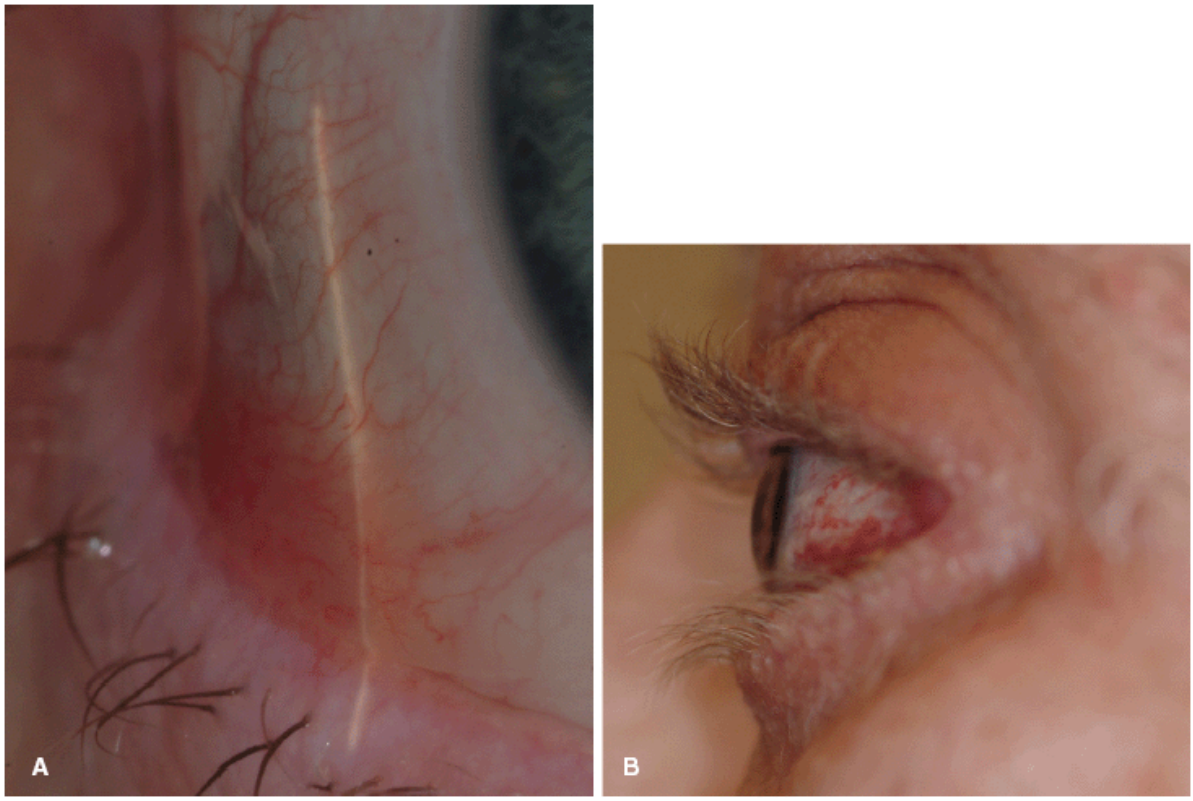


Figure 2:2 Soft tissue involvement in thyroid-associated ophthalmopathy includes conjunctival hyperaemia chemosis (A) and lid oedema (B).

Motility Defects

All variations in defective motility may be seen, although limitation is the most common finding.[1] The most common finding is limitation in elevation, followed by limitation of horizontal eye movement. [33]The motility disturbances are usually associated with diplopia in the corresponding fields of gaze. [33]

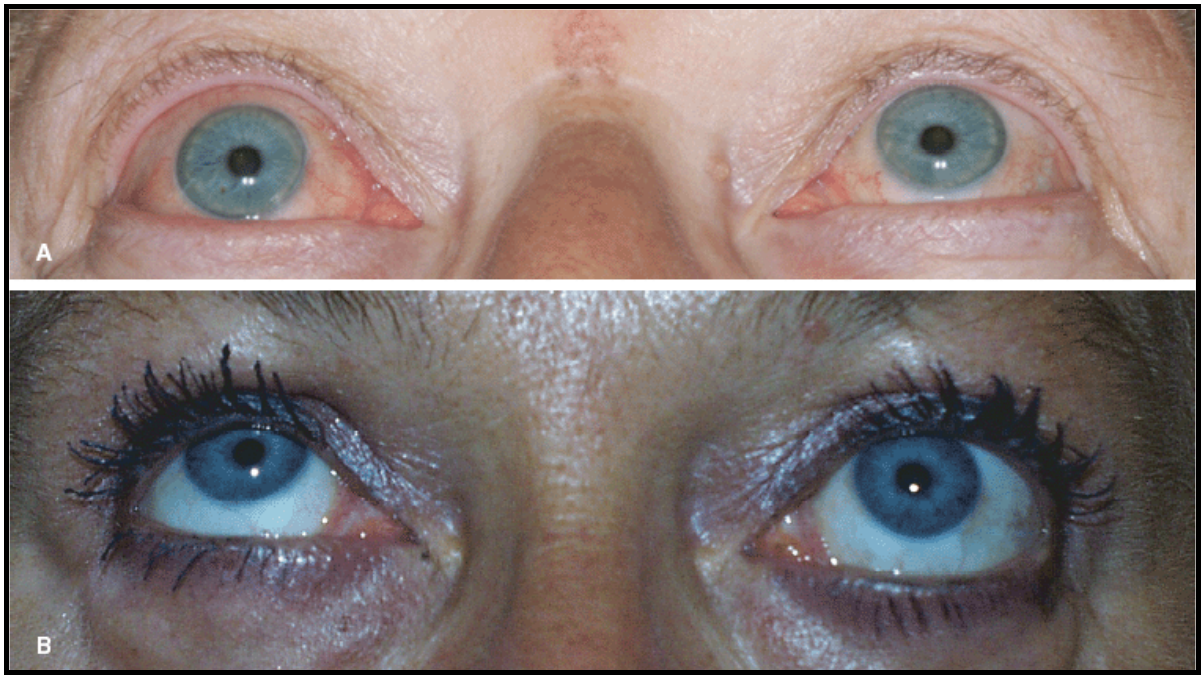


Figure 2:3 Eye muscle involvement in thyroid-associated ophthalmopathy. (A) Mild restriction of upward gaze due to inflammatory reaction in the right inferior rectus muscle. (B) Moderate restriction of upward gaze due to fibrosis in the left inferior rectus muscle in inactive stage

Exophthalmos

Exophthalmos is the classical feature of the disease. It is encountered in 34% to 93% of patients. [1] The onset of exophthalmos is usual insidious and gradual in its progression.[33] Most patients have mild exophthalmos in the range of 3mm, although slight asymmetry is common.[33]

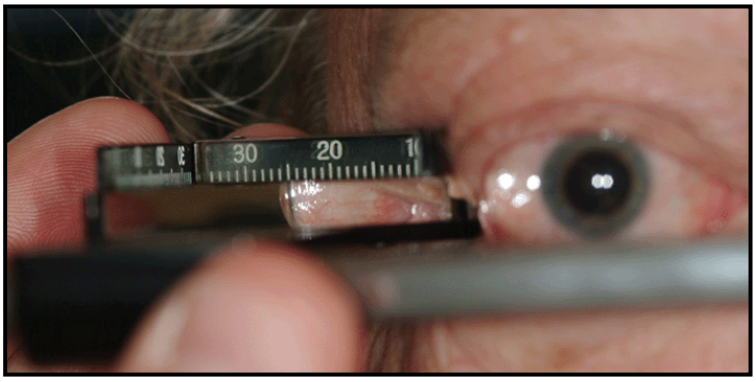
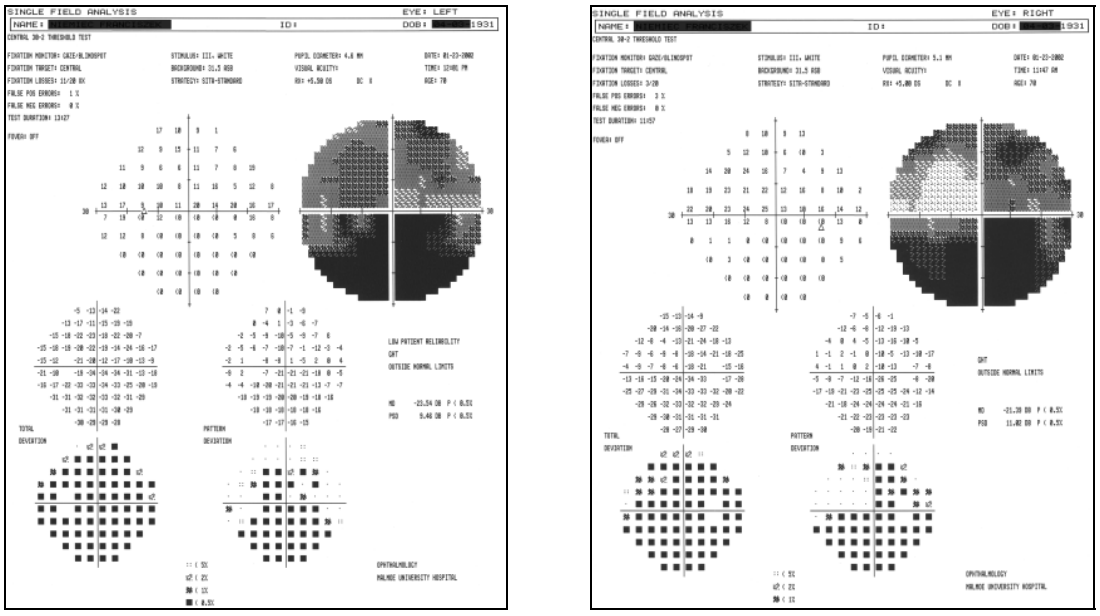


Figure 2:4 Photograph showing use of exophthalmometer to measure degree of exophthalmos in patient with moderate GO (26 mm)

Visual Loss

The ocular complications of exophthalmos can lead to visual complications, exposure keratitis can lead to ulceration of the cornea, perforation and infection and raised intra-orbital pressure can cause optic nerve compression, leading to optic nerve atrophy and visual loss. [1]



A **B**

Figure 2:5 Optic neuropathy in patient with thyroid-associated ophthalmopathy. Deep inferior visual field defects in the left (A) and right (B) eyes

2:2 MAKING THE DIAGNOSIS OF GD

2:2:1 TESTS OF THYROID FUNCTION

The function of the thyroid gland can be tested in many ways: tests of thyroid hormones in the blood, evaluation of the hypothalamic-pituitary-thyroid axis, assessment of iodine metabolism, estimation of gland size, thyroid biopsy, observation of the effects of thyroid hormones on peripheral tissues and measurement of thyroid auto-antibodies. Some of these methods are further elaborated below.

Thyroid Hormones in Blood

Baseline thyroid function testing is the radioimmunoassay of total serum T3 (tri-iodothyronine) and total and free levels of T4 (thyroxine). It is the free hormone level that determines the biological activity. [11]

The Hypothalamic-Pituitary-Thyroid Axis

A sensitive test has been developed to measure circulating TSH (thyroid stimulating hormone) using monoclonal antibodies against human TSH. [11] Early radioimmunoassays of TSH were adequate for detecting elevated TSH in hypothyroidism, but could not detect suppressed levels in hyperthyroidism. Third generation "supersensitive assays" are sensitive enough to detect about 0.01μU/mL allowing detection of TSH well below the normal range of 0.5-5μU/mL. [11]

Thyroid Antibodies

Additional helpful tests include detection of the thyroid autoantibodies, antithyroid peroxidase (TPO), anti-thyroglobulin, and thyroid stimulating receptor antibodies.[33] The TSH receptor antibody is characteristic for GD and is positive in 90% of patients with the condition.[11] It is most useful in patients with euthyroid ophthalmopathy or in predicting neonatal GD in the newborn of a mother with past or active GD. [11]

As in most clinical laboratories, the assay used by our institution to detect TSHR antibodies does not distinguish between stimulatory and inhibitory antibodies. The NZ laboratory performing this assay is in Hamilton. Audit from the Thyroid Clinic, Christchurch Hospital shows 87% of patients with GD have positive TSH receptor antibodies in line with reported figures. [11]

2:2:2 RADIOLOGY

Although the diagnosis of GD and GO is often established by clinical means, radiological examination may help if the diagnosis is uncertain. [33] Orbital CT or MRI can confirm whether soft tissue or extra-ocular muscles are affected, but the findings of these radiological investigations need to be interpreted in light of the clinical findings. [24,33]

In research laboratories radioactively labeled markers and scintography are used to look for uptake of affected extraocular muscles in patients with GD.

2:3 CLASSIFICATION AND ACTIVITY

The majority of patients with GO have a mild and non-progressive ocular involvement that does not require any specific intervention, but in severe forms of the disease aggressive measures may be needed. [34] The assessment of a patient with GO relies on two different features, the severity and the activity of the disease. [34]

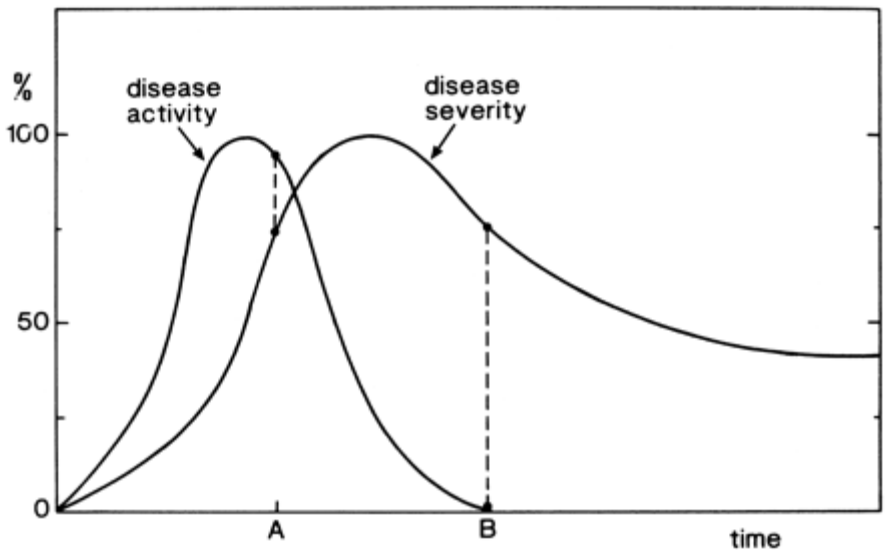


Figure 2:6 Hypothetical relationship between disease activity and severity in the natural history of GO based on the initial concepts by Rundle [43]

2:3:1 NOSPECS

In the late 1960s, Dr Sidney C. Werner proposed a formal and systematic arrangement of the categories of the signs of what he called "the eye changes of GD." This formal classification was approved by the American Thyroid Association (ATA) in 1969.[44] The first classification had 2 forms: a detailed and an abridged form.

The abridged form summarized the 6 classes which had been devised, the first letter of each class forming the acronym "NO SPECS." The detailed classification provided specific criteria for grading within each of the 6 classes and also designated the activity of the orbital process with modifiers, "active, static or inactive." The abridged NOSPECS version is widely used to determine disease severity and is shown in the table below.

Class	Definition
0	**N**o signs or symptoms
I	**O**nly signs, no symptoms (limited to upper lid retraction and stare, with or without lid lag and proptosis)
II	**S**oft tissue involvement (symptoms and signs)
III	**P**roptosis
IV	**E**xtraocular muscle involvement
V	**C**orneal Involvement
VI	**S**ight loss (optic nerve involvement)

Table 2:1 NOSPECS classification for grading severity of GO

Modifications

In 1977 some modifications were made to the NOSPECS grading system in an attempt to make it more reproducible. This included specifying the degree of proptosis to be greater than 23mm and allowing for myopia and racial differences in orbital depth. The original nomenclature and classes were retained.[45]

These classifications continue to be used to the present day, but there was no way of determining whether patients are in the active or quiescent stage of the disease with the NOSPECS system. As it became clearer that patients responded to treatment better if they were in the active phase of the disease further methods of disease classification were developed. [41]

2:3:2 Clinical Activity and Disease Severity

Severity and activity of GO are not synonymous, but both are important in determining whether a patient needs treatment, and what that treatment might be. If the ophthalmopathy is non-severe, no interventional treatment is required; if the ocular involvement is severe assessing the degree of activity is important: severe active disease is likely to respond to medical treatment and/or radiotherapy, whereas severe inactive disease most likely requires surgical intervention. [34] Discussion of treatment options and outcomes of GO are not the focus of this paper.

2:3:3 RUNDLE'S CONCEPT OF DISEASE ACTIVITY

The concepts of disease activity for GO originated from the observations of Rundle and his coworkers. [46] Although the natural history of GO is not completely understood, Rundle's initial observations appear correct. There is an initial active phase of progressive exacerbation of the ophthalmopathy, followed by subsequent partial regression, leaving a static, inactive phase where the residual manifestations of the disease are unlikely to substantially alter.[34]

Rundle noted that in the stage of active inflammation the eyes are red and painful, and the quiescent stage in which the eyes are white and unchanging with a painless motility deficit. Intervening during the active phase to prevent fibrosis developing is the aim of treatment of GO. The intention is to reduce the peak of "Rundles curve" (shown below) to leave less severe manifestations of the disease in the inactive phase.

This theory is attractive because it may explain why as many as one-third of patients with severe disease do not respond to immunosuppressive treatment. Those in the inactive phase of the disease are less likely to respond to corticosteroids or radiotherapy and failure to distinguish between patients in the active and inactive phases may explain the lack of treatment response. [47]

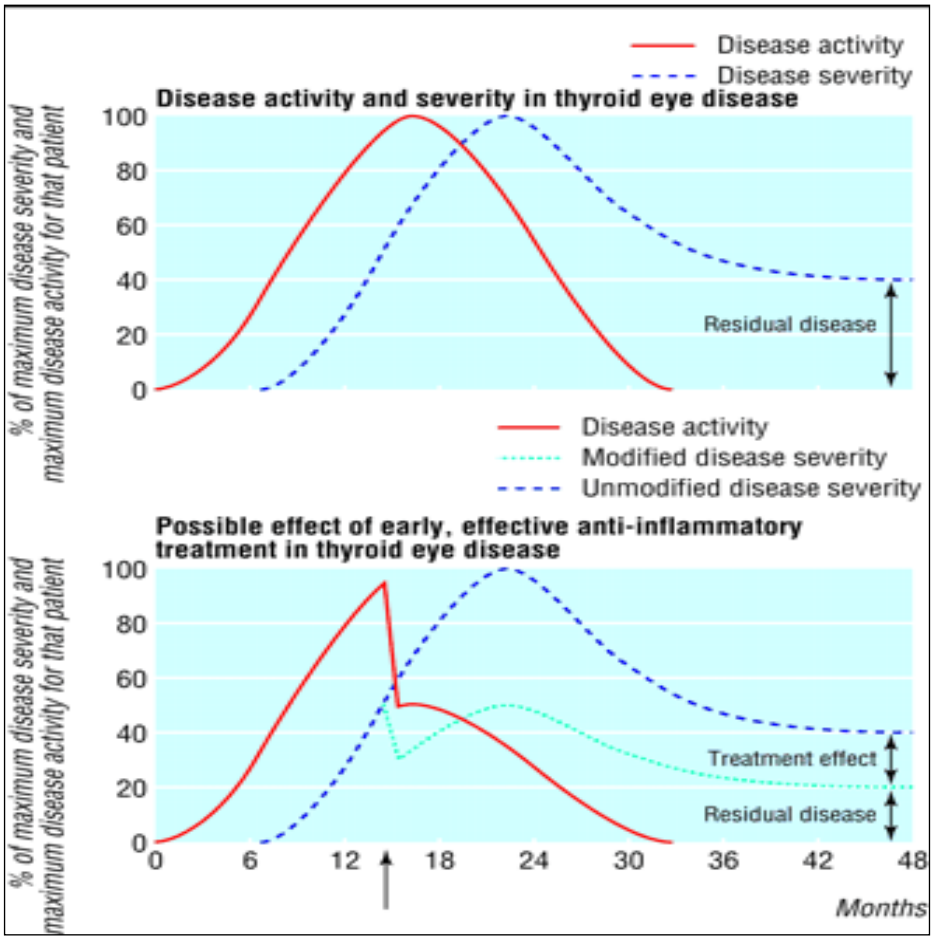


Figure 2:7 The activity and severity of thyroid eye disease, reproduced from Wiersinga 2002[43].Adapted from Rundle[9,46]
The lower panel shows the possible outcome of treatment (indicated by the single arrow) which has 50% efficacy, given at 50% of maximal disease severity, and 95% disease activity. Treatment given later, when the disease is less active, is likely to have much less effect on disease severity

2:3:4 CLINICAL ACTIVITY SCORE

The most widely used method for assessing disease activity, at the present time, is the clinical activity score proposed by Mourits [42] and its derivations [48] This classification attempted to grade disease severity by rate of progression of the symptoms rather than severity of the symptoms, as the NOSPECS classification did.[42]

Its aim was to determine whether patients were in the active or quiescent phase of the disease and is based on well known signs of acute inflammation: pain (Latin: dolor), redness (rubor), swelling (tumor), and impaired function (function lasea), defined by Celsus and Galen centuries ago. [42] This system was entirely clinical and did not rely on use of special instruments. [42] Clinical activity of the disease could be measured after 2 clinical assessments only a few months apart. [42]

A score of 1 is given for each clinical feature present (as seen in the table below). The sum of the points defines the clinical activity score.[42] Patients with an activity score of 3 or more were proposed to benefit from medical treatment and those with a score of 0 were to be spared radiotherapy or steroids. These patients could then be managed surgically if necessary for correction of persisting proptosis, eye muscle restriction or lid retraction.[42]

Pain	Painful oppressive feeling on or behind globe during last 4 weeks
	Pain on attempted up, side or down gaze
Redness	Redness of the eyelid(s)
	Diffuse redness of the conjunctiva
Swelling	Chemosis
	Oedema of the eyelid(s)
	Swollen caruncle
	Increase of 2mm or more in proptosis during last 1-3 months
Impaired function	Decrease in eye movements of 5 degrees or more in last 1-3 months
	Decrease in visual acuity (1 line or more on Snellen chart, using pinhole) last 1-3 months

Table 2:2 Clinical Activity Score (CAS) as described by Mourits *et al.*[42]
Score 1 point for each criteria present to maximum of 10.
Score >3 consider medical therapy or radiation.
Score 0 consider surgical correction of cosmetic defects

2:3:5 DISEASE SEVERITY SCORE

In 1982 Feldon and Unsold [49] designed a classification for GO based on clinical signs. The clinical severity of GO was determined by evaluating the following signs: proptosis, lid retraction, lid lag, horizontal oculomotor dysfunction, vertical oculomotor dysfunction, optic nerve involvement, and periorbital oedema. Each sign was judged as mild, moderate or severe based on strict semiquantitive criteria. The criteria for severity are given in the table below. We have referred to the score from this system as the Disease Severity Score (DSS). A small modification was made to this system, for use in this study, and this is discussed in the methods section later in the Thesis. The modification was to allow comparison between CAS and DSS.

	Mild	Moderate	Severe
Proptosis Exophthalmometry Or Asymmetry	 22-24mm 2-4mm	 24-27mm 4-6mm	 >27mm >6mm
Lid retraction Height of lid margin above limbus	 0-2mm	 2-3mm	 >3mm
Lid lag Increase in down gaze	 <2mm	 2-4mm	 >4mm
Horizontal muscle dysfunction Phoria or Tropia Or limitation of ductions	 <12PD <20%	 12-30PD <50%	 >30PD >50%
Vertical muscle dysfunction Phoria or tropia Or limitation of ductions	 <6PD <20%	 6-15PD 20-50%	 >15PD >50%
Optic nerve involvement And Visual Acuity	NFL defects or hyperaemia >20/30	Mild disc pallor or nerve edema and venous engorgement >20/60	Obvious disc pallor or well developed swelling <20/60
Periorbital edema Thickening of upper lid	 <1mm	 1-3mm	 >3mm

Table 2:3 Disease Severity Score as described by Feldon and Unsold[49]

Class 1: No severe signs and no more than 1 moderate sign
Class 2: One severe sign or 2 moderate criteria
Class 3: At least 2 severe criteria

2:3:6 OTHER SCORES USED TO RATE AND MONITOR GO

Many other scales have been suggested and used by investigators, but the majority seem to be based on the clinical activity score with additional features to look at severity of disease.

As recently as October of this year 2 further groups have published their grading scales for GO. Dolman and Rootman [50] use the VISA classification, an acronym for the 4 disease end points vision, inflammation, strabismus and appearance. The vision section is designed to look for features of optic neuropathy. The inflammation section is based on the clinical activity score validated by Mourits and discussed above. Strabismus scores are calculated from the limitation of ductions and the appearance section related to lid retraction and exposure. [50] The features assessed are the same as those we have used in this paper.

The VISA classification has been presented on a 1 page form (which is reproduced below) which also includes an assessment of change in disease state from prior clinic appointments. The form provides a useful checklist to ensure consistency between clinicians as to the features assessed at each visit.

The European Group on Graves' Orbitopathy (EUGOGO) was established to promote better clinical care of patients with Graves' orbitopathy. [51] In a recent paper they have reproduced a list of recommendations which they suggest should be used in routine clinical assessment of patients with GO. [51] Again their features are based on the clinical activity score and severity measures and cover the same features we have looked at in this study.

VISA FOLLOW-UP FORM

Date: Visit #:

Patient Label:

Date of birth: Age:
Gender:

ORBITOPATHY
Symptoms:

Progress:

Therapy:

THYROID
Symptoms:

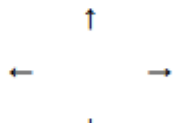
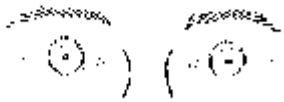
Status:

Therapy:

GENERAL
Smoking:

Meds:

QOL: ☹ - - - - - - - - - - ☺

SUBJECTIVE	OBJECTIVE	OD	OS	
VISION				**Refractions** Wearing _____ + _____ X _____ _____ + _____ X _____ Manifest _____ + _____ X _____ _____ + _____ X _____
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	
	with manifest	20/___	20/___	
Color vis: n / abn	Color vision plates (HRR) / 14			
	Pupils (afferent defect)	y / n	y / n	
	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
Progress: s / b / w	Macular/ lens pathology	y / n	y / n	
INFLAMM^N/ CONGESTION				**Inflammatory Index (worst eye/eyelid)**
	Caruncular edema (0-1)			Caruncular edema (0-1):
	Chemosis (0-2)			Chemosis (0-2):
Retrobulbar ache	Conjunctival redness (0-1)			Conj redness (0-1):
At rest (0-1)	Lid redness (0-1)			Lid redness (0-1):
With gaze (0-1)	Lid edema Upper (0-2)			Lid edema (0-2):
Lid swelling: y / n	Lower (0-2)			Retrobulbar ache (0-2):
Diurnal variation: (0-1)				Diurnal Variation (0-1):
Progress: s / b / w				Total: (10):
STRABISMUS/ MOTILITY				Prism Measure:
Diplopia:	Ductions (degrees):			
None (0)				
With gaze (1)				
Intermittent (2)				
Constant (3)	Restriction > 45°	0	0	
Head turn/ tilt: y / n	30-45°	1	1	
	15-30°	2	2	
Progress: s / b / w	< 15°	3	3	
APPEARANCE/EXPOSURE				Fat prolapse and eyelid position:
	Upper lid position: MRD	mm	mm	
Lid stare y / n	Scleral show (upper)	mm	mm	
	(lower)	mm	mm	
	Levator function	mm	mm	
Light sensitivity y / n	Lagophthalmos	mm	mm	
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
Ocular irritation y / n	Corneal ulcers	y / n	y / n	
	IOP -straight	mmHg	mmHg	
Progress: s / b / w	-up	mmHg	mmHg	

DISEASE GRADE			Grade	Progress / Response	DISEASE ACTIVTY
V	(optic neuropathy)	y / n	/ 1	s / b / w	
I	(inflammation/congestion)	0-10	/ 10	s / b / w	Active
S	(diplopia)	0-3	/ 3	s / b / w	
	(restriction)	0-3	/ 3	s / b / w	Quiescent
A	(appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT **FOLLOW-UP INTERVAL:**

Figure 2:8 VISA classification; Vision, Inflammation, Strabismus, Appearance. Form designed by Dolman and Rootman to grade and monitor patients with GO. [50]

SECTION 3

IMAGING IN GO

3:1 IMAGING TECHNIQUES

Imaging with CT, MRI and ultrasound all provide important information in the diagnosis of GO. Imaging of the extraocular muscles and orbital soft tissue in GO provides valuable information for both diagnosis and treatment decisions.

A reliable laboratory parameter correlating with disease activity in GO is missing and scoring of disease activity currently rests with largely subjective testing. Thickening and edema of the extraocular muscles may be present before the onset of symptoms and complaints and we are still looking for ways to better identify these changes to help us make treatment decisions. [52]

It is widely agreed that to date, assessment of the activity of the autoimmune disease process is difficult from radiological examination.[32]

Experimentally, orbital scintigraphy with radioactively labeled somatostatin analogues as tracers has been used to assess the activity of the orbital disease in patients with GD with some success.[53] This nuclear medicine technique with a variety of labeled tracers is not widely available clinically and has been used mostly as a research tool.[53]

3:2 DIFFERENTIAL DIAGNOSIS FROM IMAGING

Differential diagnosis of GO includes pseudotumour, lymphoma, metastases, tumours of the nasal cavity or sinuses, amyloid, acromegaly, cysticerosis, trichinosis and fistula of the carotid cavernous sinus.[33] The major differential of TED is myositis, a local form of orbital pseudotumour. [32] This non-specific, inflammatory condition may involve every orbital structure to a different extent. Enlargement of the muscle, including the tendon, is characteristic for this inflammation.

3:3 ULTRASOUND IN OPTHALMOLOGY

Ultrasound was first used as a diagnostic tool in ophthalmology by Mundt and Hughes in 1956 [54]. They used an industrial ultrasound to examine enucleated normal eyes and eyes with intraocular tumours. The first use of A-scan ultrasound was for ocular measurement in 1957 by Osaka[54]. Ultrasound is now a standard modality for measuring ocular dimensions, monitoring ocular disease and providing information about orbital disease.

Ultrasound is an acoustic wave comprising compressions and rarefactions that propagate within fluid and solid substances [54]. Ultrasound waves differ from sound waves because they resonate at a higher frequency rendering them inaudible. Because it is a wave ultrasound can be directed, focused and reflected in the same way other wave, forms such as light, can be.

Ultrasound examinations of soft tissues use reflective systems analogous to those used in radar and sonar. This technique allows examination of a thin slice through

these soft tissues. A piezoelectric transducer acts as the ultrasound transmitter and receiver. It generates a short burst of ultrasound energy that propagates through the eye and is partially reflected at tissue boundaries where there are different mechanical characteristics. [54] The reflections, or echoes, return to the transducer where they are electronically detected. Because the tissues in the eye exhibit similar mechanical characteristics, much of the wave is transmitted and only a small part is reflected at each interface. The major reflective surfaces in an eye are the cornea, lens and posterior sclera. The time interval between echo pulses is used to determine the thickness of the corresponding tissue segment.

3:3:1 TYPES OF ULTRASOUND

A and B scan methods are used to image the eye and orbit. A-mode systems graphically display the echoes generated as a function of time on a video monitor. These are used primarily in ophthalmology to determine the axial length of the eye and for calculations related to intraocular lenses. B-mode systems generate cross-sectional grey scale images, recreating the ocular anatomy and are used to visualize ocular and orbital structures, particularly when there is media opacity affecting the quality of the view. A 20Hz ocular image of a normal eye and the 20Hz image of the same eyes anterior chamber are shown below.

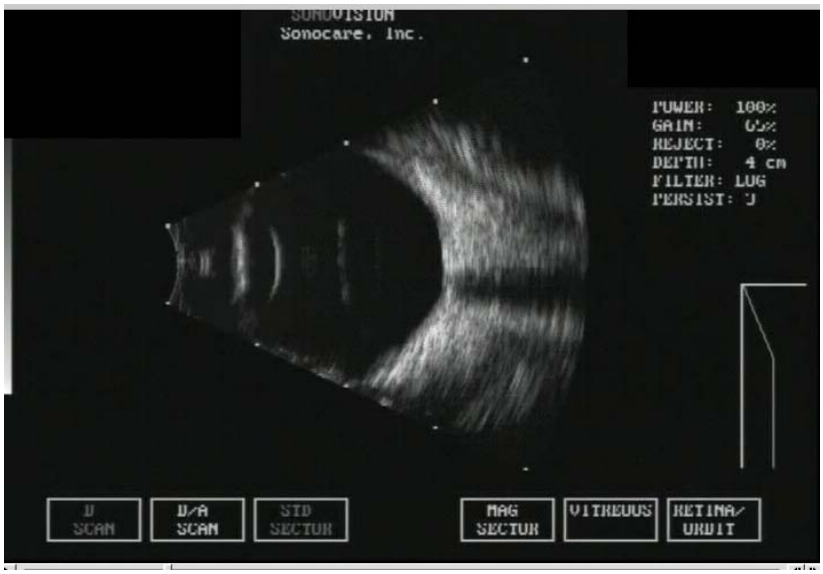


Figure 3:1 20Hz B-scan ultrasound image of normal eye showing lens, retina and optic nerve shadow.

Figure 3:2 B-scan USS with 20Hz probe showing increased detail when focused on the anterior chamber

3:3:2 CREATING AN US IMAGE

As an ultrasound wave propagates through any medium, its energy is progressively attenuated through scattering and absorption. Scattering redirects incident energy reducing levels that reach distal tissues. It occurs from many tissues, such as small blood vessels, cellular aggregates, calcify deposits and connective tissue septae. Scattering results in development of complex echo voltages which reduce the quality and hinder the interpretation of the ultrasound image. Absorption converts acoustic energy to heat. In biologic media absorption arises from complex cellular and molecular phenomena that are not completely characterized. The attenuation of ultrasound owing to absorption and scattering is important because it significantly reduces echo amplitudes at deep tissue sites. It therefore constrains the maximum tissue depth that can be examined and limits the frequency that can be used. These factors are largely responsible for the poor resolution often achieved of structures posterior to the globe.

3:3:3 QUALITY OF THE ULTRASOUND IMAGE

The quality of the ultrasound image is also reduced by electronic noise. Noise consists of small, random voltage variations that arise because of statistical fluctuations of electrons in system components. These signals obscure the low amplitude echoes and effect interpretation of the ultrasound images. Other electronic and acoustic artifacts can influence the quality of the B-mode ultrasound image.

Digital storage of B-mode images confers great advantages and allows post-processing enhancement. Modalities such as contrast, brightness and zoom can be altered on most units. Storing images digitally also allows for 3-dimensional (3D)

construction of images. This requires capturing a series of images in all dimensions which are then merged using computer software. The 3D renderings can be rotated, translated, zoomed and sectioned, allowing additional information to be extracted from the data. The quality of the images is still limited by the resolution of the B-scan images captured.

3:3:4 ULTRASOUND AND THE ORBIT IN THIS PROJECT

The primary method of imaging the orbit is CT, MRI and plain X-ray. In the hands of a skilled technician ultrasound can provide most of the information of the other modalities. [54] In fact it has advantages over other modalities in cost effectiveness, repeatability and safety. It does require a skilled technician to perform the test for useful information to be gathered.

Although other investigators advocate ultrasound as a diagnostic tool for orbital pathology,[52] they follow this imaging with MRI or CT for complete radiological work-up. This indicates ultrasound of the orbit is not considered investigation of choice for these conditions.

Demands on resources mean access to facilities such as CT are increasingly difficult. A departmental ultrasound machine would provide an inexpensive, non-invasive resource which could increase speed of diagnosis and limit patient exposure to potentially harmful X-rays.

All imaging techniques continue to improve with increasing computer power, particularly in ultrasound, where higher frequency systems and digital analytic techniques permit increased resolution of posterior orbital structures such as the optic nerve and extraocular muscles.

These advances led to our interest in capturing images of the extraocular muscles for diagnosis and monitoring of patients with thyroid eye disease. Our aim was to use an ultrasound probe focused in the orbit to capture a series of images of the extraocular muscles. Computer software would then be used to reconstruct the series of images in a 3-dimensional form.

Practical use of Ultrasound to create images of extraocular muscles

An Aviso Ultrasound Unit from Quantel Medical (France) was used. B-mode ultrasound was used to capture images of the orbit and extra-ocular muscles. Even immersion ultrasonography, through a water bath, to increase penetration of ultrasound waves failed to produce high resolution images. We used a variety of USS probes from 2 to 20Hz and altered the focal point of the scan, but were unable to recreate images of sufficient quality to perform quantitative analysis of the extraocular muscles.

We then preceded to trial the ultrasound machine used in the radiology department of our institution. Again, even with immersion techniques and trials with a variety of probe frequencies (from 2Hz to 20Hz), the quality of images we were able to capture were not sufficient to allow further reconstruction or computerized modifications.

Due to the surprisingly poor quality images ultrasound was able to provide of the orbital structures a change of direction for this project was necessary.

3:4 COMPUTED TOMOGRAPHY (CT)

CT can distinguish normal and abnormal structures of different tissue density on the basis of differential X-ray absorption. Orbital fat absorbs X-rays to a lesser degree than water; it is imaged in CT as a black low density area that contrasts with the higher-density images of the extraocular muscles and optic nerve. [32]

Orbital CT scans are routinely performed using 1-2mm thick sections at 2-mm intervals in the axial plane. Individual volume elements obtained from these axial slices can be reformatted to produce coronal, sagittal, paraxial or parasagittal oblique images. [32] In contrast to direct coronal scans, sagittal and coronal reformations avoid high spatial artifacts from dental appliances or other metal implants. [32]

3:4:1 CT FEATURES IN GO

In GO the imaging pattern from CT is quite characteristic: the extraocular muscles appear to be the site of primary involvement, but some suggest fat and muscle volume are both increased[32,55] Unlike orbital pseudotumour, evidence of muscle involvement on CT of GO is usually limited to the non-tendinous portion of the muscle. [32] Although it has been reported that tendons may also be enlarged in GO. [33,56]Often several muscle bellies are enlarged, especially at the orbital apex. [32]

The inferior rectus is the most commonly enlarged muscle belly, followed by medial rectus and then superior rectus. [33] This has been confirmed in a number of studies; in a series of 116 patients with GO, definite enlargement of the extraocular muscles was seen in 85% of cases. [57] The inferior rectus was enlarged in 77%, the superior rectus in 51%, the lateral rectus in 80%. In a Japanese CT scan study on

349 patients with TED [5] the inferior rectus was enlarged in 43%, the medial rectus in 38%, the superior in 29% and the lateral in 16% of cases. One muscle was enlarged in 31%, 2 muscles in 25%, 3 muscles in 24% and all 4 recti in 21% of patients with ocular involvement.

Extraocular muscle enlargement may be asymmetric in as many as 30% of cases of GO. [32] However, in patients with unilateral eye findings, 50-70% have bilateral orbital involvement on CT scans.[32]

It is essential to evaluate coronal sections on CT as single muscle enlargement, particularly of the inferior and superior rectus muscles, is easily missed on axial slices. [33]

The second most common finding in GO is expansion of the orbital fat.[33] This is difficult to quantify on CT, but is suspected in patients with moderate to severe exophthalmos. Fatty expansion leads to considerable stretching and straightening of the optic nerve.[33] Normally the nerve is undulated when the globe is in a normal position. Occasionally there are mottled densities within the orbital fat and the lacrimal gland enlargement is commonly encountered in patients with GO.[33] Stretching of the optic nerve and intracranial fat prolapse are other reported features seen on CT in patients affected with GO. [58]

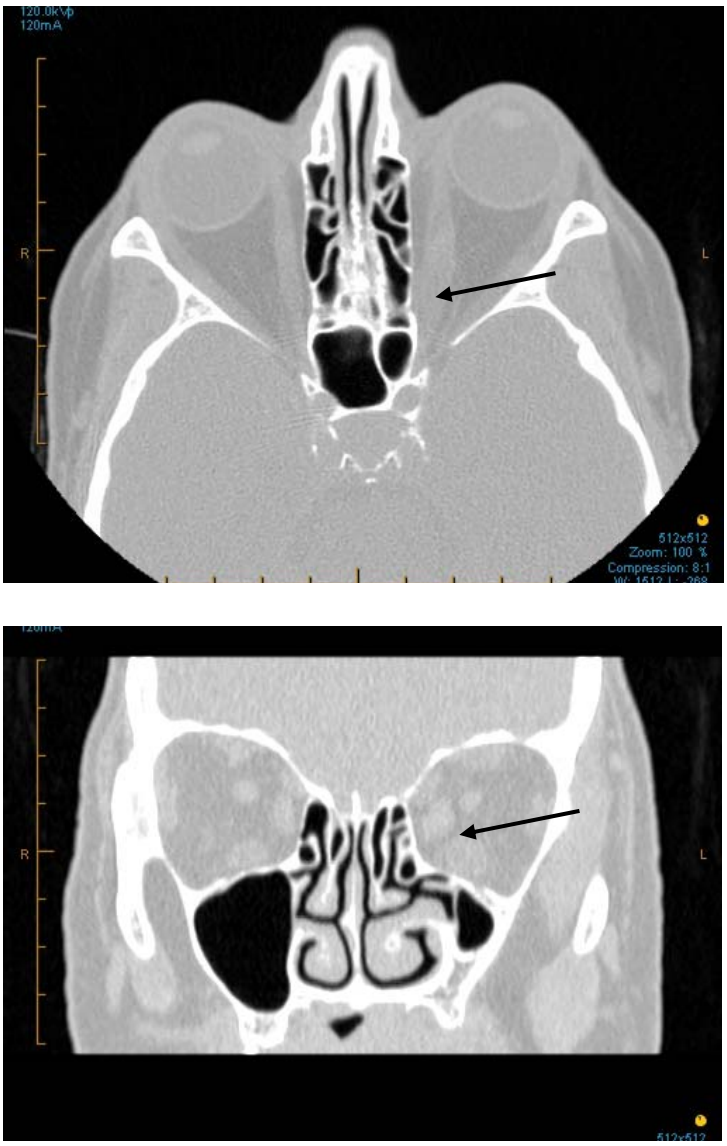


Figure 3:3 Axial (above) and coronal (below) CT images of a patient with GO showing enlarged extra-ocular muscles. Black arrow indicates enlarged medial rectus muscle.

3:5 MAGNETIC RESONANCE IMAGING (MRI)

Hydrogen nuclei with an odd number of nucleons (protons and neutrons) behave as small magnets or dipoles. Protons are ubiquitous, and their resonance is the basis of MRI techniques. [32] Imaging with MRI represents free moving protons of a given tissue, producing energy (as read signals) while returning to their primary position in a high magnetic field after deflection by a high energy pulse. [32] When the orbit is placed in a magnetic field there is an alignment of protons. When exposed to radio-frequency excitation there is a reversal of polarity of these hydrogen nuclei, and they are raised to a higher energy level. When the radio-frequency is terminated, the protons return to the baseline polarity, and the emitted energy can be measured. [32]

Of all the modalities MRI is the best at estimating disease activity in patients with GO. [32] However the cost and availability of this modality limit its clinical application, particularly in our institution.

MRI is able to estimate disease activity in the T2 sequences, where water content of tissues is best estimated. [32] Normal T2 might indicate burned out fibrotic or quiescent disease with low water content, whereas prolonged T2 might suggest ongoing tissue inflammation with tissue oedema. [32] In a study comparing extraocular muscle signal in GO patients and controls, a high T2 signal was consistent with increased clinical activity. [59]

MRI of the optic nerves also demonstrates compression better than CT, and delineation of compressive optic neuropathy is better on MRI than CT. [60]

SECTION 4

METHODS

4:1 ETHICS COMMITTEE

Approval for this study was granted by the Upper South A Ethics Committee, in Canterbury NZ. Information sheets and consent forms were produced to give to patients enrolled in the study. These are enclosed as Appendix 1 and 2 respectively.

All data collected from the study was kept in a locked filing cabinet by the investigator. No information which could lead to the identity of the cases or controls is kept to protect patient confidentiality.

Verbal consent was given by all patients for clinical photographs to be taken and used for research and teaching purposes.

Patients were asked to consent to an OCT scan as part of this study. This information was not analysed or used as part of this current thesis. Further investigation into correlations between optic neuropathy and OCT changes and orbital volume changes and OCT thicknesses may be part of future work. We had anticipated that the information we obtained might lead to creating a new grading system, but again this might form the basis of future research. We were hoping the information we collated may help us detect damage from GD earlier or predict risk factors that may enable us to advise monitoring at risk groups more. The data and small sample sizes have not enabled us to do this.

4:2 STUDY DESIGN

This is a retrospective cohort study. Retrospective comparison is made of the orbital CT scan findings in patients with GD with their clinical activity and disease severity. The matched control group was selected from patients with no GD and normal CT scans taken over the same period.

4:3 PATIENT SELECTION

A record of all patients with thyroid eye disease was compiled by the investigator and a subset of these patients formed the basis of this Thesis.

The Thyroid Clinic, Nuclear Medicine Department reviews all thyroid function test results performed at our Institution. Most patients with abnormal hormone levels or antibodies are reviewed in their department and a Thyroid Clinic database of personal details and diagnosis is recorded of all patients. All patients seen between June 2000 and June 2006 were included in this first list.

This master list of all thyroid patients was then cross-correlated with all patients seen in the Eye Department. This enabled compilation of a list of all patients with thyroid disease who had had, or were waiting for, an ophthalmic assessment.

A complete list of all head CT scans ordered by the ophthalmology department between June 200 and June 2006 was obtained from the radiology department. It was necessary to compare the patients with GO to a list of all head and neck scans and there is not a separate code for patients having an orbital CT scan. There were 213 Head/neck CT scans requested by the ophthalmology department between June 2000 and 2006.

By correlating the patients with GO with this list we were able to obtain a complete subset of all patients, in our institution, for whom CT scans were performed to aid in the diagnosis or management of their GO over the 6 year period. Thirty five patients with GO had orbital CT scans performed to assist in diagnosis or management of their condition.

4:3:1 THE CT SCANS

CT scans had been taken in the Radiology Department on 2 different machines. From 2000-2005 scans were performed on the GE CTI single slice CT scanner (General Electrical, Milwaukee, USA). Slice thickness was mostly 3mm for scans analysed during this period. From July 2005 all scans were performed on the GE VCT 64 slice CT scanner (General Electrical Milwaukee, USA). Slices on the VCT scanner were reformatted at 1mm thickness for the coronal views.
Slice thickness could be adjusted for by the computer software used to analyse the volumes of the orbital structures.

Only CT scans with coronal sections where the equator of the globe and the orbital apex could be visualised were analysed. This reduced the number of films we analysed with the Volume Estimation Tool from 35 to 21 (42 eyes). Seven controls (14 orbits) were analysed.

4:3:2 THE CONTROL GROUP

Seven age and sex matched controls for the 21 patients were selected. These were patients with no history or findings to suggest GD who had CT scans which were reported as normal over the same June 2000 to June 2006 period.

4:4 ASSESSING THE PATIENTS

All patients in this study were reviewed by the investigator (RRS). They had a complete clinical examination in the ophthalmology department. Examination comprised best corrected visual acuity, monocular colour vision with 15 Ishihara colour plates, RAPD check, intra-ocular pressure check by applanation tonometry, measurement of palpebral aperture and clinical drawing of external eye with upper and lower lid position documented and note of periobrital and external eye swelling, chemosis and injection, exophthalmometry with Oculus exophthalmometer, corneal examination with fluroscein dye to check tear film and tear break up time, fundus examination to assess the optic nerve and macula particulary for choroidal folds. Confrontation visual fields were examined and if there was any clinical suggestion of optic nerve dysfunction an automated Humphrey visual field 24/2 was completed. Extra-ocular motility and strabismus examination was done at each visit by the same orthoptist and Hess charts were completed if clinically indicated. Motility was also assessed by the investigator and documented.

Five patients with GO in whom scans had been performed were no longer patients of the Ophthalmology Department. These patients were contacted and asked to present for reassessment with a full explanation of the study and the nature of their reassessment. All 5 patients agreed and were fully examined and assessed. A full summary of their condition at the time of the CT scan was collated from the clinical records.

4:4:1 CLINICAL ACTIVITY

Disease severity and clinical activity were determined by 2 methods. A clinical activity score (CAS) was determined at each visit according to the Mourits' classification. [42] The severity of disease was also graded with a score from a modified version of the classification designed by Feldon and Unsold and is referred to as the disease severity score (DSS) [49]

The original classification by Feldon and Unsold involved classifying patients into class I, II and III depending on the number of mild, moderate and severe criteria they had. The details are given previously in this paper. The modification made was to give one point for every mild criteria, 2 points for a moderate criteria, 3 points for a severe criteria and 0 if the criteria was not present. This gave a range of 0 to 21 points. The reason for this modification was to make the DSS more comparable to the CAS.

A score was calculated for each of the patients with TED in whom a CT was analysed. Where possible this was done by the investigator in person as close to the time of the scan as possible. When this was not possible, as some historical scans were analysed, a CAS and DSS were calculated from the details recorded in the clinical notes, as close to the time of the scan being performed. All patients included in the study had sufficient clinical details to enable accurate scores to be calculated.

4:5 COMPUTER SOFTWARE

The Volume Estimation Tool (VET) was designed by Steven Muir of the Medical Physics and Bioengineering Department of Christchurch Hospital. The original software was designed for a study calculating the area of infarcted brain after haemorrhagic stroke and following it over time.

The software was modified for use on CT scans of the orbit. All CT scans were analysed from the coronal sections. The software is designed to display DICOM (Digital Imaging and Communications in Medicine) images and allow the operator to make area and volume measurements of the extraocular muscles and orbital area by subjectively placing control points on each 2D slice of a CT scan. Area of extraocular muscle and bony orbit are calculated for each slice through summated pixel counts. Volume is then the area multiplied by the slice thickness. Volumes for each slice are summated to give a total bony orbital volume and volumes of all 4 recti muscles. Outlines of the areas are saved and the area and volume data exported to a spreadsheet file for further processing.

4:5:1 LOADING DICOM FILES

Images are downloaded from PACS (picture archiving and communications system) to a local computer hard-drive using Efilm computer software. The images are stored on the local hard drive as DICOM files. DICOM is a standard for handling, storing, printing, and transmitting information in medical imaging. It includes a file format definition and a network communications protocol. DICOM files can be exchanged between two entities that are capable of receiving image and patient data in DICOM format. The DICOM files are then opened using the VET software.

4:5:2 USING THE VET

Areas are calculated by the investigator placing control points around the muscles for each slice of the CT scan. Clicking the mouse onto the first control point, changes the colour of the outline indicating the loop has been closed. The number of pixels within the loop is counted and the number multiplied by the pixel size^2 to get the area. The area is multiplied by slice thickness to calculate the volume. After the 4 muscles have been outlined for the slice, the orbit area can be outlined in the same manner.

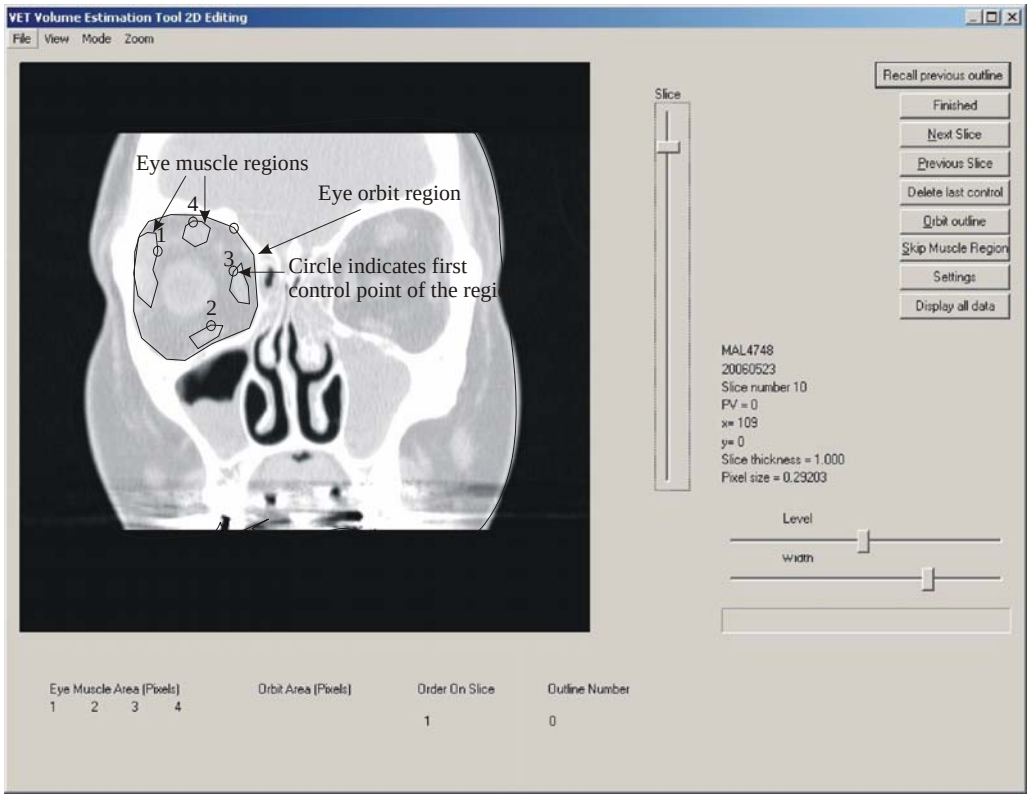


Figure 4:1 Image from the VET showing the coronal CT scan loaded and outlines of the 4 muscle regions and the orbit

4:5:3 STANDARISING THE TECHNIQUE

In order to standardise the calculations as much as possible, outlines were entered on each coronal slice of the CT scan for the 4 rectus muscles and their tendons and the bony orbit, from the equator of the globe to the most posterior aspect of the orbital apex possible. The equator was determined as the widest diameter of globe visible.

CT scans were analysed with a variety of slice thicknesses. The programme was able to adjust calculations of volume from the slice thickness without difficulty.

4:5:4 CALCULATIONS

The volume data was exported to an Excel file where calculations were able to be made. A total was calculated for muscle volume for each eye. A percentage of total muscle volume compared to total orbital volume was also calculated.

The scans analysed included patients with all spectrums of disease activity, from mild to severe and in both active and quiescent phases (see below).

4:6 STATISTICS

The data sets were then analysed to determine what correlations existed between all factors measured including muscle volume, clinical activity and disease severity.

The statistical programme used for all statistical analyses was the StatSoft Statistica package, (StatSoft, Oklahoma 2001). The statistical analyses were done in conjunction with the Medical Physics Department in our institution.

Correlation coefficients (r value) were determined from scatter plots of 2 variables for each of the comparisons made. Scatter plots were drawn for all of the correlations tested. Some formatting of scatter plots was performed using Microsoft Excel.

The correlation coefficient is measured on a scale from +1 through 0 to -1. Complete correlation between 2 variables is expressed as either =1 or -1. Arbitrary limits have been set for the strength of the correlation.[61] For absolute values of r, 0-0.19 is regarded as very weak, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6-0.79 as strong and 0.8-1.0 as very strong. [61]

For each correlation coefficient p values were also calculated. The p value represents the probability that a relationship occurs by chance alone. A p value of 0.001 indicates the chance of a calculated statistic being related to chance alone is 1 in 1000. A p value of less than 5% (0.05) is typically regarded as significant, that is not related to chance alone. [61]

To tests the difference between means of two samples the paired Student's *t* test was used and given with the p value. This version of the test is preferable for comparing means of groups with small sample sizes. It is known as the Student's *t* test as its foundations were laid by WS Gosset, writing under the pseudonym "Student".[62]

SECTION 5

RESULTS

5:1 DEMOGRAPHICS

The patients without thyroid eye disease were age and sex matched controls in which CT scans were reported as normal. The details of the cases, controls and reason for the scan are given in Tables 5.1 and 5.2 below. The cases in bold are those for whom age and sex matched control scans were included. The average age of the cases was 47.5 years and the controls 44.7 years. There were 14 female cases with GO and 7 male cases affected with the condition.

5:2 REASON FOR SCAN

CT scans were ordered for a variety of reasons in patients with TED. The details for each case are given in Tables 5.1 and 5.2 below. In some cases they were requested to help confirm the diagnosis or exclude other pathology, in patients who had clinically deteriorated to determine cause and extent of pathology and the remainder for pre-surgical planning and clearer identification of the anatomy. Pre-surgical scans were in patients with optic neuropathy requiring decompression and in quiescent patients for whom decompression was performed to improve their cosmetic appearance.

	Sex	Age (years)	Time Diagnosis to Scan (months)	Reason for scan
1	M	68	36	Diagnostic
2	**F**	**12**	36	Deterioration
3	M	21	0.3	Diagnostic
4	**F**	**26**	18	Surgical planning
5	F	45	12	Surgical Planning
6	F	52	4	Diagnostic
7	**F**	**66**	120	Surgical planning
8	**F**	**71**	6	Diagnostic
9	F	64	19	Surgical planning
10	F	58	4	Surgical planning
11	F	48	24	Surgical planning
12	**M**	**41**	12	Surgical planning
13	F	43	26	Surgical planning
14	**F**	**40**	6	Diagnostic
15	M	46	6	Surgical planning
16	**M**	**57**	24	Diagnostic
17	M	52	9	Surgical planning
18	F	56	12	Surgical planning
19	F	32	5	Deterioration
20	M	43	1	Diagnostic
21	F	57	8	Surgical planning
	Mean ± SD	47.5 ± 15.9	18.5 ± 25.6	

Table 5:1 Demographic data for cases with GO and reason for CT scan

	Sex	Age (years)	Reason for scan
1	F	12	Retinitis
2	F	26	Lesion on orbital rim NAD
3	F	66	Pseudoproptosis
4	F	71	3rd nerve palsy
5	M	41	Anxiety and orbital pain
6	F	40	Trauma
7	M	57	Plexiform neurofibroma lid
	Mean ± SD	44.7 ± 21.4	

Table 5:2 Demographic data for age and sex matched controls and the reason the CT scan was ordered

5:3 DISEASE SEVERITY AND CLINICAL ACTIVITY

There was a strong correlation between disease severity, as calculated by the DSS, and clinical activity according to the CAS, for our patients with a correlation coefficient of 0.74 ($p<0.001$). This relationship is shown on the scatter plot below.

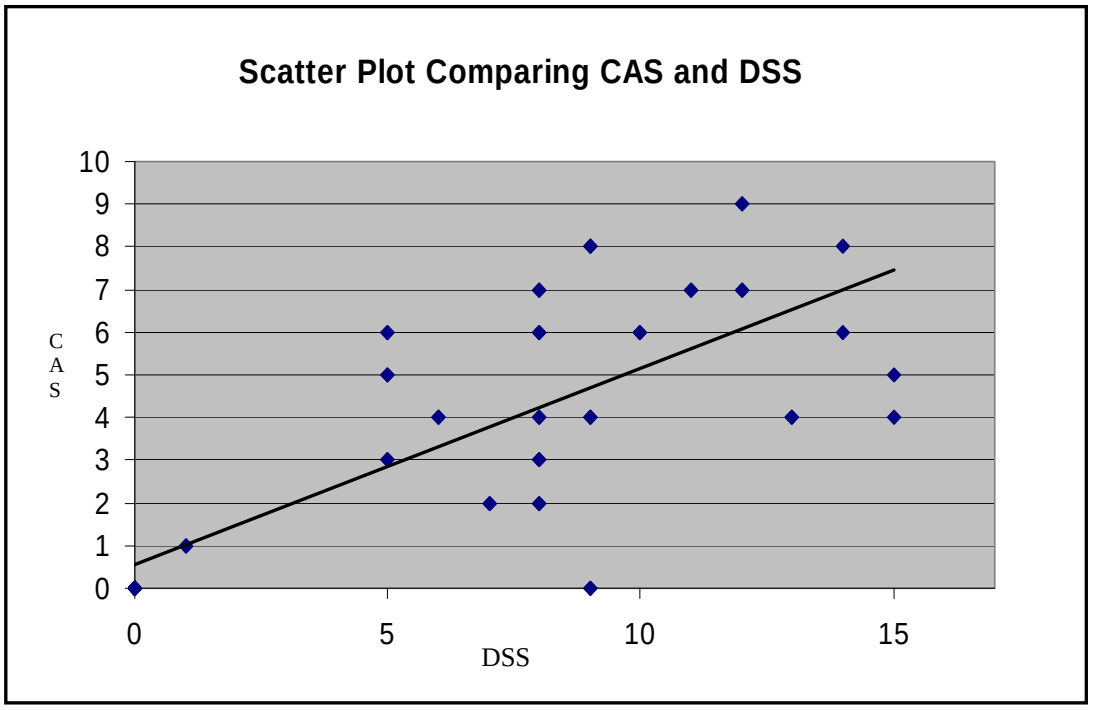


Figure 5:1 Scatter plot including trend line comparing Clinical Activity Score and Disease Severity Score.
$r = 0.741$, $p < 0.0001$

5:4 MUSCLE VOLUME CALCULATIONS

For each of the GO patients, total rectus muscle volume for the left and right eyes was calculated and is given in table 5.3 below. The total muscle volume for each patient was calculated and then compared to both clinical activity as scored by the CAS and disease activity by the modified DSS. These findings are also given in Table 5.3 below. For control patients there were no signs or symptoms consistent with GO and both CAS and DSS were zero. The details of muscle volume for the control patients are given in Table 5.4.

It was shown that extraocular muscle volume was statistically larger for patients known to be affected with GO (mean total volume left plus right eye= 12.88±4.80) than for normal controls (mean total muscle volume left plus right eye= 4.43±1.24) with $p<0.0001$.

Patient	Muscle Volume (mLs)		Total Muscle Volume (mLs)	CAS	DSS
	Right	Left			
1	3.72	3.36	7.08	1	1
2	2.80	2.78	5.58	4	13
3	3.01	2.39	5.40	4	15
4	3.00	2.72	5.72	3	5
5	4.91	4.87	9.78	0	9
6	6.08	6.05	12.13	7	8
7	9.06	10.65	19.71	8	9
8	9.90	10.44	20.34	4	8
9	7.06	6.29	13.35	9	12
10	6.19	6.78	12.97	6	5
11	5.91	5.92	11.83	6	8
12	7.22	4.67	11.89	2	8
13	8.92	13.29	22.21	6	10
14	9.23	8.73	17.96	2	7
15	3.93	4.02	7.95	4	9
16	6.72	6.75	13.47	7	11
17	5.76	5.83	11.59	5	5
18	6.34	6.74	13.08	4	6
19	7.65	8.21	15.86	6	14
20	8.96	8.78	17.74	7	12
21	7.78	6.96	14.74	3	8
Mean±SD	6.39 ± 2.15	6.49 ± 2.76	12.88 ± 4.80		

Table 5:3 Muscle volume for left and right eyes in cases with GO with clinical activity and disease severity scores.

Control	**Muscle Volume (mLs)**		**Total Muscle Volume (mLs)**	**CAS**	**DSS**
	Right	Left			
1	1.28	1.27	5.74	0	0
2	1.75	1.85	5.98	0	0
3	1.76	1.85	3.61	0	0
4	1.95	1.92	3.87	0	0
5	2.88	2.76	5.64	0	0
6	2.68	3.30	3.60	0	0
7	2.98	2.76	2.55	0	0
Mean±SD	2.18 ± 0.61	2.44 ± 0.66	4.43 ± 1.24		

Table 5:4 Muscle volume for left and right eyes in control patients with no evidence of GO.

5:4:1 VARIATION BETWEEN LEFT AND RIGHT EYE

The average total muscle volume was very consistent between the left and right eyes for patients with GO ($p<0.001$) (average left 6.49mLs right 6.39) and normal controls (average left 2.44mLs right 2.18), with a strong correlation co-efficient ($r^2= 0.820$, $p<0.0001$). The relationship between the left and right total muscle volumes is seen on the graph below.

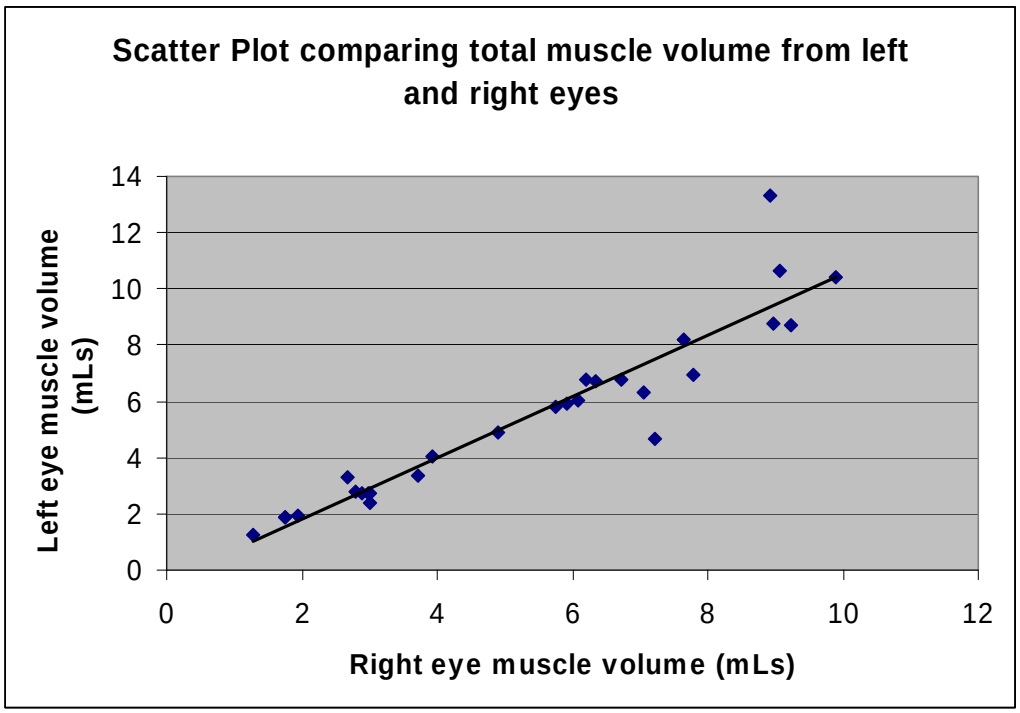


Figure 5:2 Scatter plot including trend line comparing total muscle volume between left and right eyes for cases with GO and controls.
$r = 0.9982$, $p < 0.0001$

5:4:2 MUSCLE VOLUME AND EXTENT OF DISEASE

Both CAS and DSS were compared to total muscle volumes for each eye for each of the 21 patients and the controls and there was again a moderate correlation for each of the scores.

Clinical Activity

Muscle volume compared to clinical activity had a correlation coefficient of 0.659 ($p<0.0001$) proving a strong correlation between these 2 groups. The comparison is shown on the scatter plot below with the trend line indicated in black.

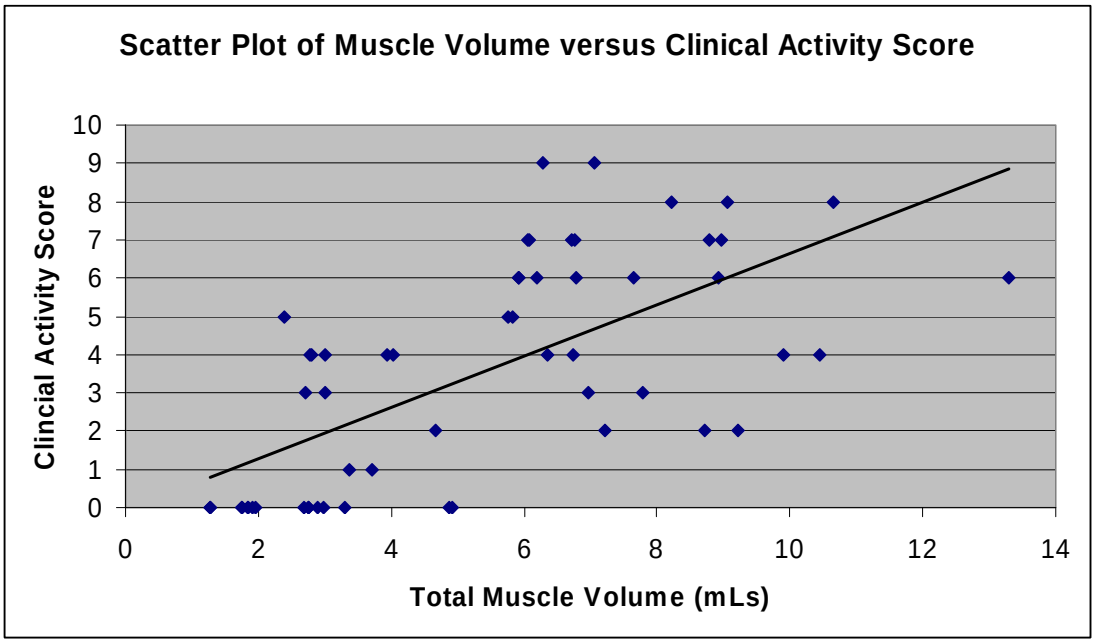


Figure 5:3 Scatter plot including trend line comparing total muscle volume to clinical activity score
$r = 0.659$, $p < 0.0001$

Disease Severity

When comparing total muscle volume to disease severity, the correlation was also strong with a correlation coefficient of 0.664 ($p<0.0001$). The scatter plot for these values is given below with the trend line again shown in black.

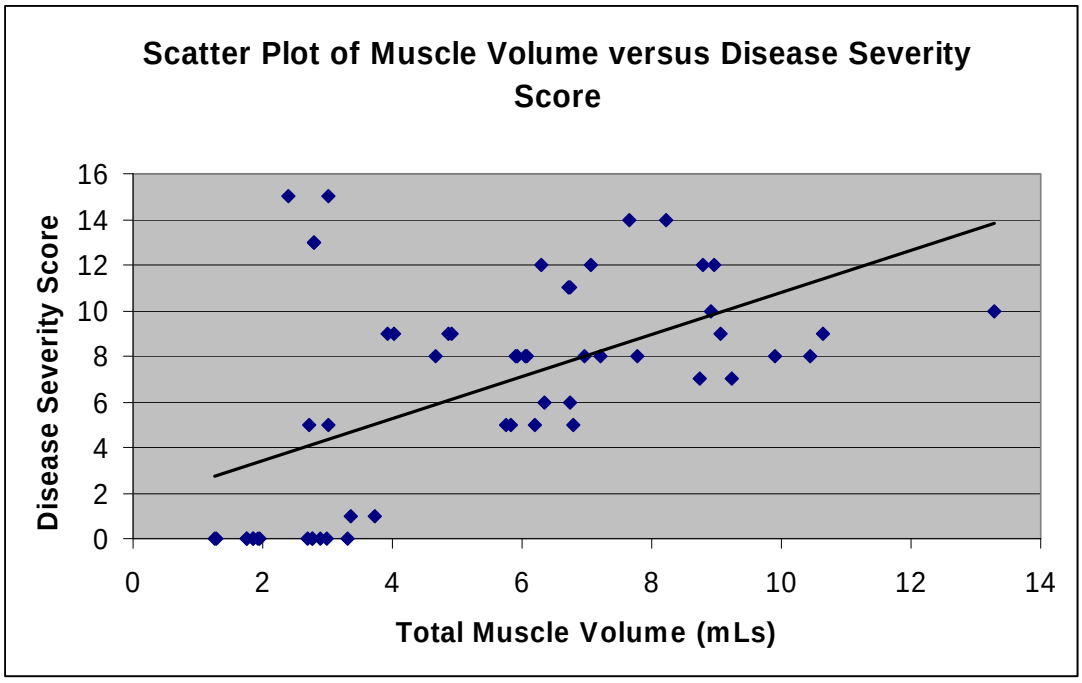


Figure 5:4 Scatter plot including trend line comparing total muscle volume to disease severity score
$r = 0.664$, $p < 0.0001$

5:5 ORBITAL VOLUME

The total orbital volume for each side was measured for the patients with GO and the control group. The percentage of orbital volume made up of total muscle volume was also calculated. These figures are given in the Tables below.

The mean value for orbital volume in patients with GO (right 31.3, left 30.3) was significantly higher than the mean orbital volume for the control group (right 17.7, left 18.5) using the students t-test for mean comparison with $t=3.26$ ($p=0.003$).

Patient	**Orbital Volume (mLs)**		**Percentage muscle/orbit vol (%)**		**CAS**	**DSS**
	Right	Left	Right	Left		
1	22.61	23.15	16.5	14.5	1	1
2	22.02	16.56	12.7	16.8	4	13
3	18.00	18.65	16.8	12.8	4	15
4	19.20	17.78	15.6	17.6	3	5
5	24.77	15.61	19.8	17.9	0	9
6	21.11	18.73	28.8	32.3	7	8
7	44.54	43.23	20.4	24.6	8	9
8	45.04	43.40	22.0	23.0	4	8
9	32.63	30.79	21.8	23.4	9	12
10	38.16	43.08	16.2	18.4	6	5
11	24.60	25.11	24.0	23.8	6	8
12	53.10	44.24	13.6	10.6	2	8
13	51.52	57.46	17.3	23.1	6	10
14	32.81	33.21	28.1	26.3	2	7
15	19.87	18.29	19.8	22.0	4	9
16	24.90	25.01	27.0	27.0	7	11
17	29.43	28.32	19.6	20.6	5	5
18	27.23	29.54	23.3	22.3	4	6
19	29.32	32.14	26.1	25.5	6	14
20	35.44	32.23	25.3	27.2	7	12
21	41.12	40.12	18.9	17.3	3	8
Mean±SD	31.3±10.7	30.3±11.5	20.6±4.7	21.3±5.3		

Table 5:5 Orbital volume for left and right eyes in patients with GO and the Clinical Activity and Disease Severity Scores.

Control	**Orbital Volume (mLs)**		**Percentage muscle/orbital volume (%)**		**CAS**	**DSS**
	Right	Left	Right	Left		
1	17.60	17.16	16.9	16.1	0	0
2	18.87	24.49	14.2	13.5	0	0
3	13.80	16.39	11.1	11.3	0	0
4	19.33	20.31	10.1	9.5	0	0
5	22.75	20.24	12.7	15.9	0	0
6	19.94	17.46	14.2	9.6	0	0
7	11.60	13.10	10.6	9.7	0	0
Mean±SD	17.7 ± 3.8	18.45 ± 3.6	12.8 ± 2.4	12.2 ± 2.9		

Table 5:6 Orbital volume for left and right eyes in control patients with no evidence of GO.

5:5:1 ORBITAL VOLUME AND CLINICAL FACTORS

Total orbital volume was not correlated with clinical activity (r=0.19, p=0.24) nor with disease severity (r=-0.05, p=0.75). Neither was orbital volume correlated to proptosis (r=0.21, p=0.18). These relationships were not shown on scatter plots.

Muscle volume as a percentage of total orbital volume did not correlate well with proptosis (r=0.22, p=0.16) nor did it correlate with disease severity (r=0.16, p=0.32).

However there was a moderate correlation with percentage muscle volume of total orbital volume and clinical activity (r=0.51, p=0.001), suggesting as clinical activity increased the proportion of the orbit taken up by the muscles increased.

The same correlation did not hold when % of total volume made up by muscle was compared to disease severity. Here r= 0.157, p=0.32 which showed no correlation. These relationships are illustrated on the scatter plots (figure 5.5 and figure 5.6) below.

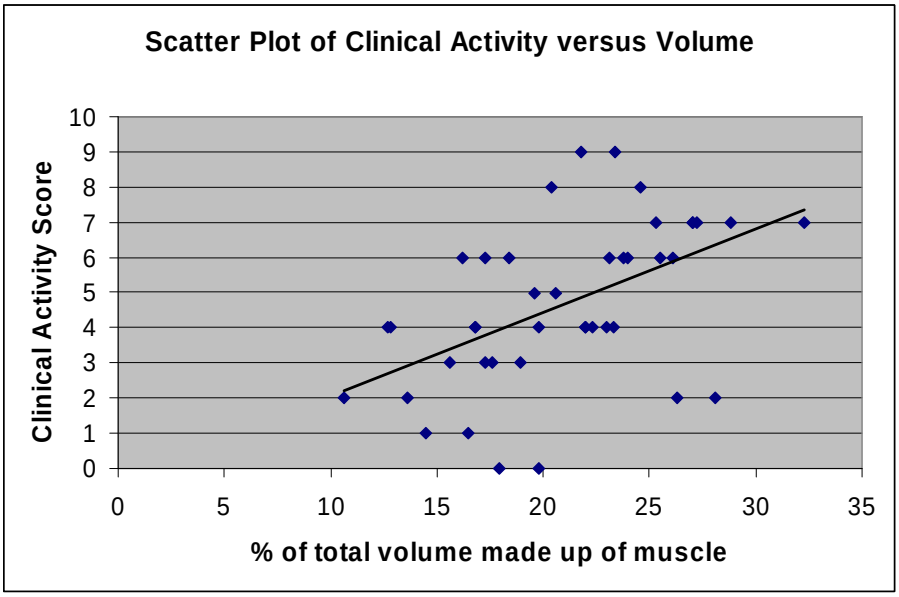


Figure 5:5 Scatter plot including trend line comparing % of total orbital volume made up by muscle with Clinical Activity Score.
r=0.51, p<0.001

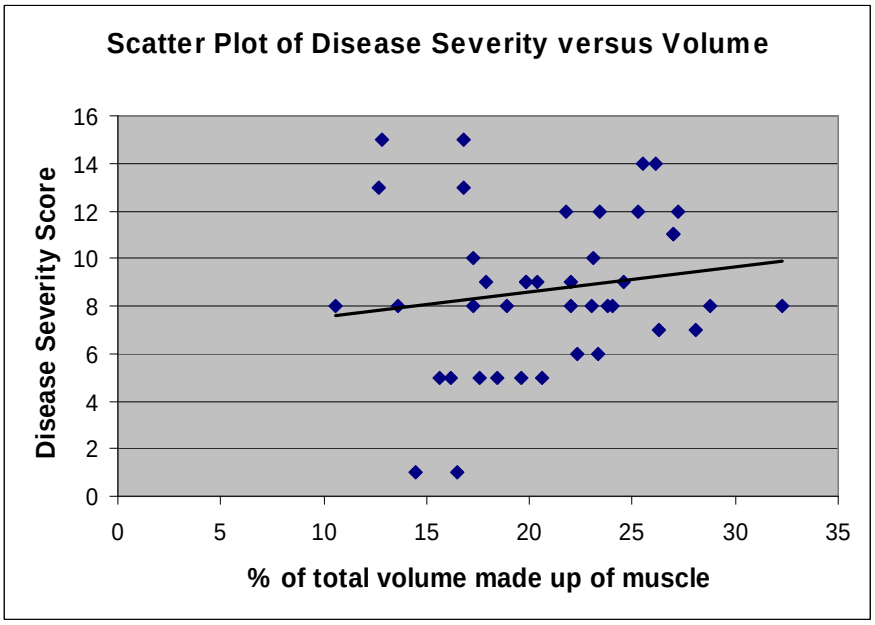


Figure 5:6 Scatter Plot comparing % of total orbital volume made up by muscle with Disease Severity.
r=0.157, p=0.32

5:6 ANALYSIS OF CLINICAL FEATURES

We then analysed individual factors making up the clinical activity and disease severity to determine which of these were most strongly correlated with disease activity. The intention was to determine a new grading scale for GO than those currently in practice. The results for the factors we analysed together with muscle volumes are shown in Table 10 below.

Each clinical factor was measured by the same investigator (RRS) or the orthoptist (LP). Proptosis was measured on the same Oculus exophthalmometer (in mm). Lid retraction (in mm) was the height of the upper lid above the corneo-scleral limbus. Horizontal and vertical restriction was the percentage limitation of ductions for each eye measured in horizontal and vertical gaze respectively. This was measured as a simple subjective percentage reduction and where there was discrepancy between the orthoptist and investigator, the investigators measurements were used for consistency. Measurement of restriction by simple observation is subjective, but detects restriction even when diplopia is not present. Hess charts and fields of uniocular vision only provide useful information in the presence of diplopia.

Patient	**Proptosis**		**Lid retraction**		**Horizontal restriction (%)**		**Vertical restriction (%)**	
	Right	Left	Right	Left	Right	Left	Right	Left
1	18	18	0	0	0	0	0	0
2	23	24	3	4	10	10	10	10
3	17	15	0	0	50	0	75	0
4	23	23	0	0	50	50	50	50
5	25	28	3	2	0	0	25	25
6	21	21	1	0	25	25	0	0
7	22	25	0	3	0	10	0	30
8	21	22	1	0	0	0	50	50
9	30	27	1	2	0	0	10	10
10	26	26	0	1	0	0	10	10
11	28	27	0	0	25	25	5	5
12	26	21	0	1	0	50	0	80
13	21	24	1	4	10	15	10	80
14	27	25	2	1	25	50	15	15
15	18	19	1	1	0	0	15	15
16	22	23	0	0	0	0	20	20
17	24	26	1	1	0	0	5	5
18	23	22	0	0	15	10	5	0
19	20	19	1	2	30	30	10	25
20	25	26	3	2	25	25	10	10
21	23	21	0	0	0	15	0	0

Table 5:7 Value for the specific clinical factors measured for each patient with GO.

5:6:1 PROPTOSIS

Scatter plots looking for a correlation between proptosis, disease severity, clinical activity and muscle volume are shown below. The correlation coefficient of r= 0.21 shows there was no correlation between proptosis and clinical activity. With r= 0.08 there was not a correlation with proptosis and disease severity either. When comparing proptosis and muscle volume the r value is 0.31 which showed a weak correlation.

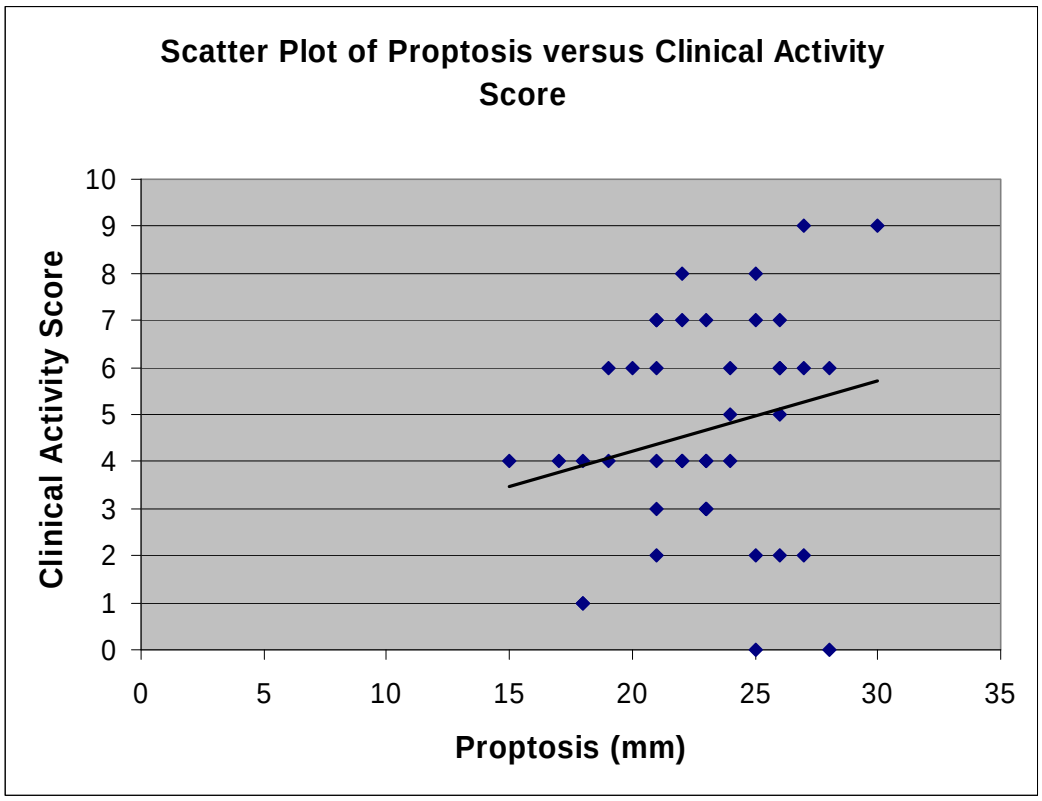


Figure 5:7 Scatter plot including trend line comparing proptosis and Clinical Activity Score.
r=0.21, p=0.18

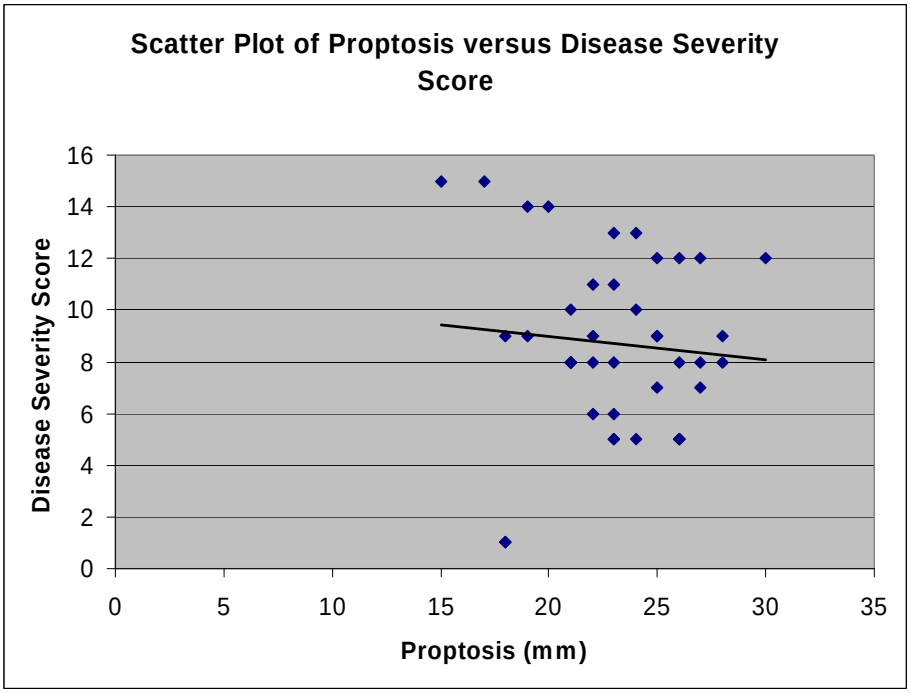


Figure 5:8 Scatter plot including trend line comparing proptosis and disease severity
r=-0.08, p=0.56

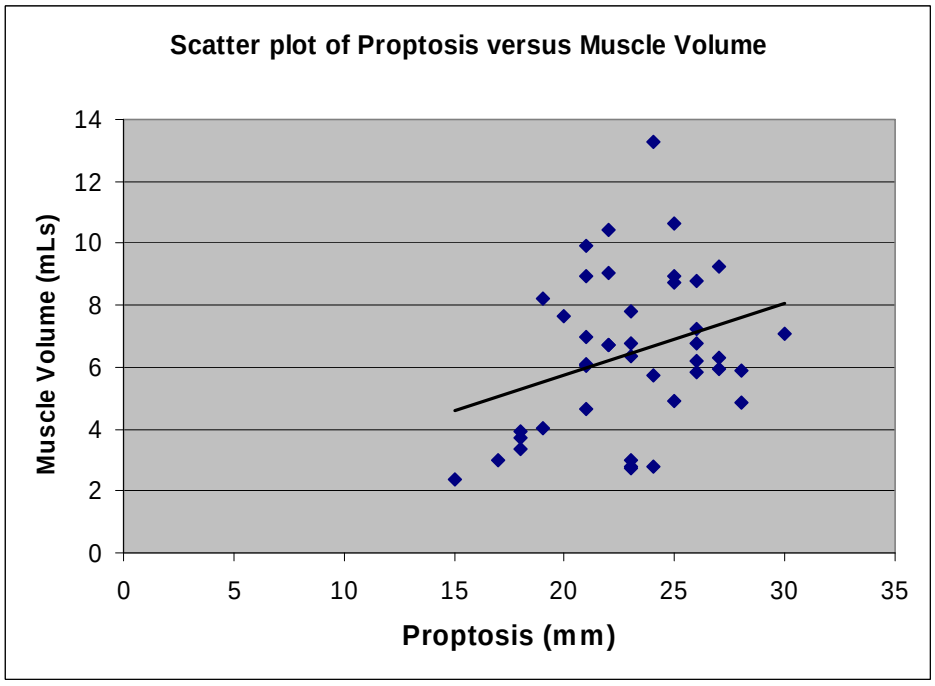


Figure 5:9 Scatter plot comparing proptosis and muscle volume
r=0.31, p=0.05

5:6:2 LID RETRACTION

The second clinical factor we analysed was lid retraction. This was measured in mm as the height of the upper lid above the corneo-scleral limbus. Scatter plots for each combination are shown below.

The correlation coefficients showed no relationship between degree of retraction and clinical activity (r=0.08), disease severity (r=0.38) and muscle volume (r=0.25). There was a trend suggesting the greater the retraction the more severe the disease.

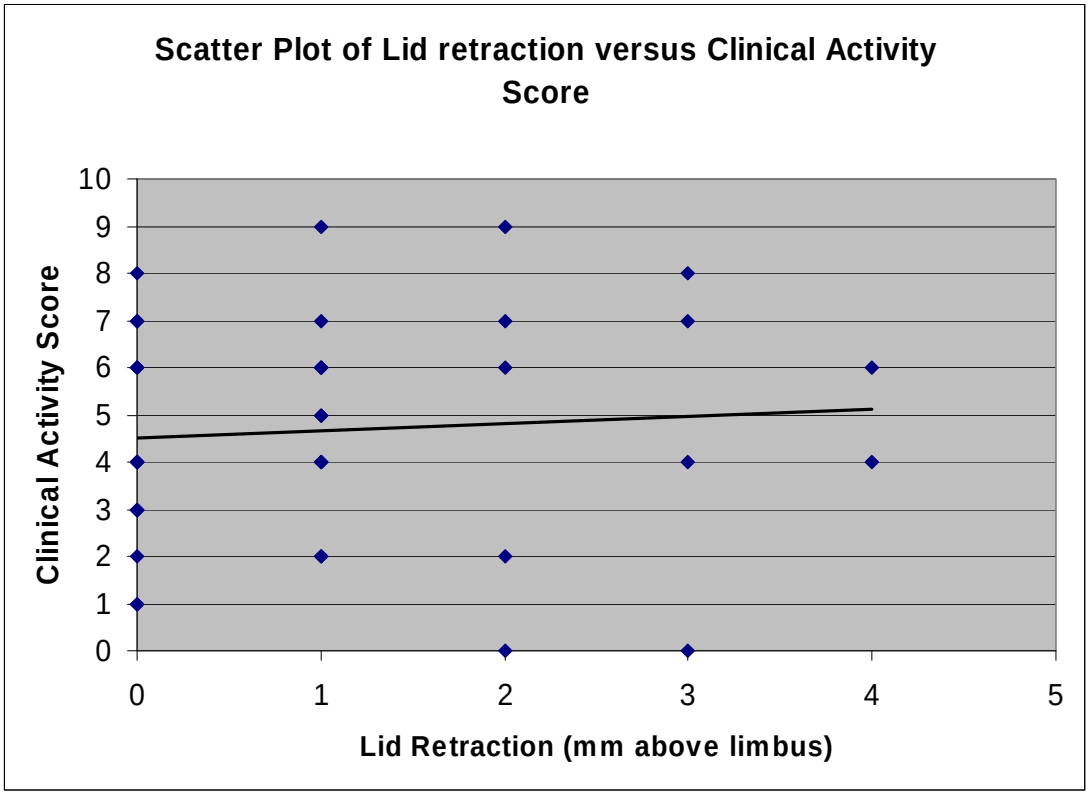


Figure 5:10 Scatter plot comparing lid retraction with Clinical Activity Score.
r= 0.25, p= 0.12

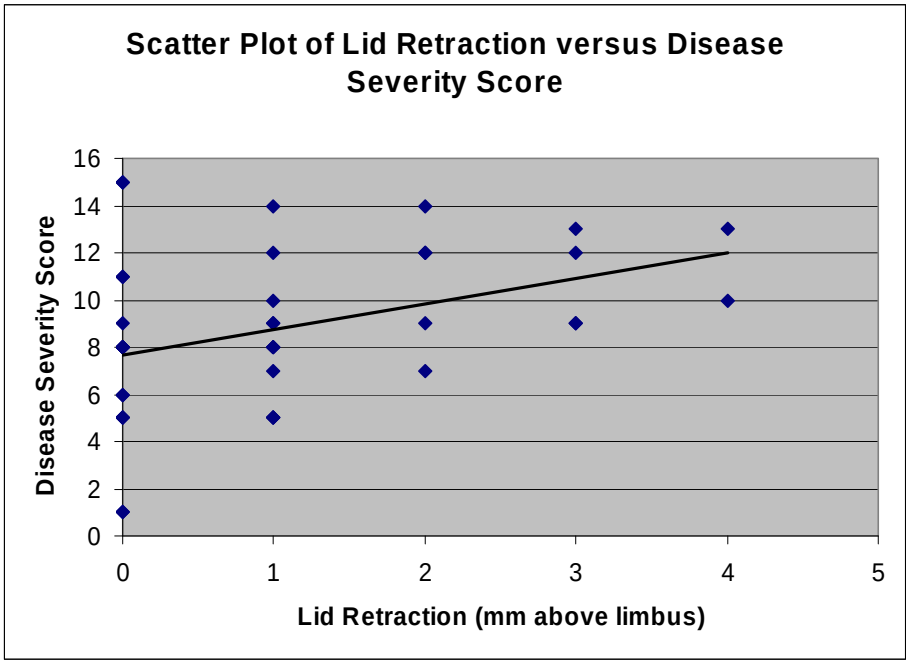


Figure 5:11 Scatter plot comparing lid retraction and disease severity. r= 0.38, p=0.01

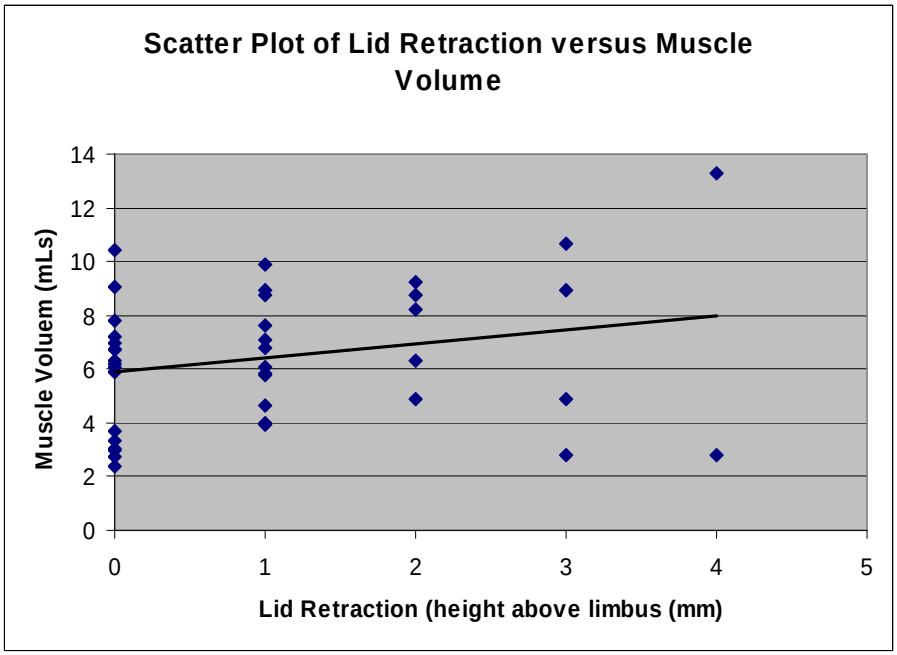


Figure 5:12 Scatter plot comparing lid retraction and muscle volume r=0.25, p=0.12

5:6:3 HORIZONTAL MUSCLE RESTRICTION

Horizontal muscle restriction was recorded as the percentage limitation in ductions for each eye. It was measured by the orthoptist or the investigator (RRS). This factor was not correlated with muscle volume, disease severity or clinical activity either. The scatter plots for each are shown below.

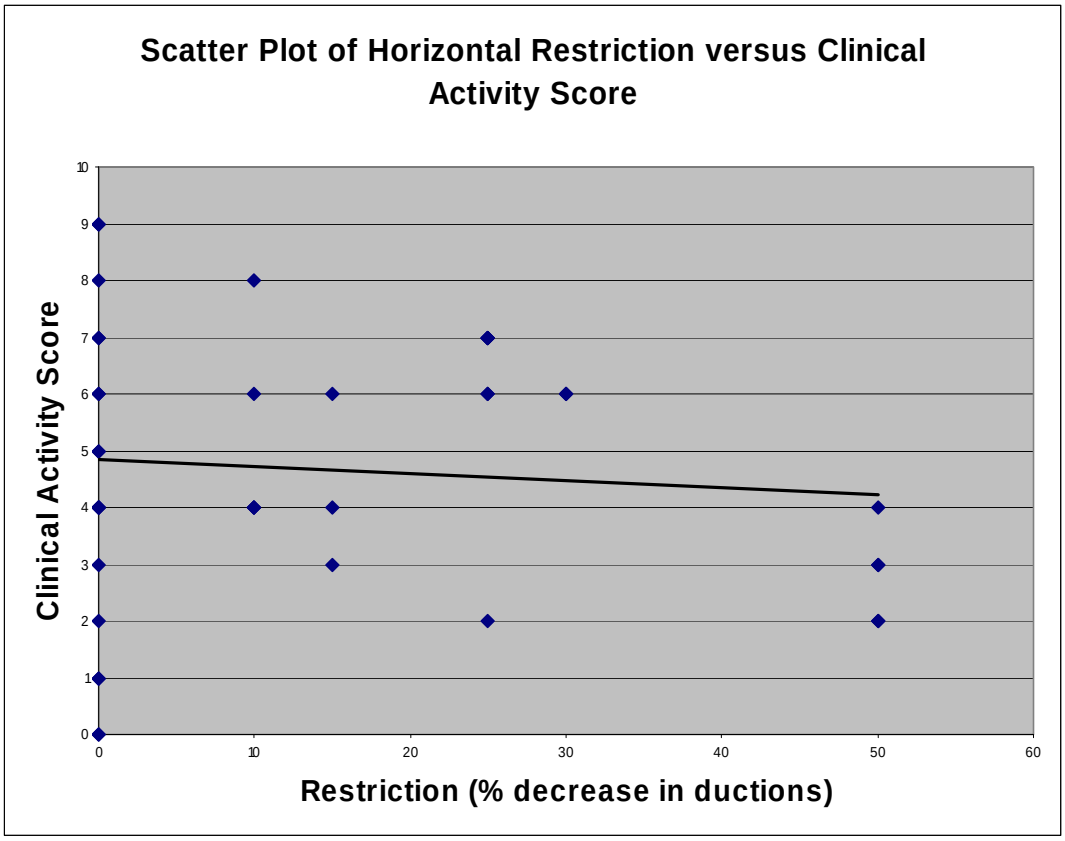


Figure 5:13 Scatter plot of horizontal restriction with Clinical Activity Score. r=-0.09, p=0.58

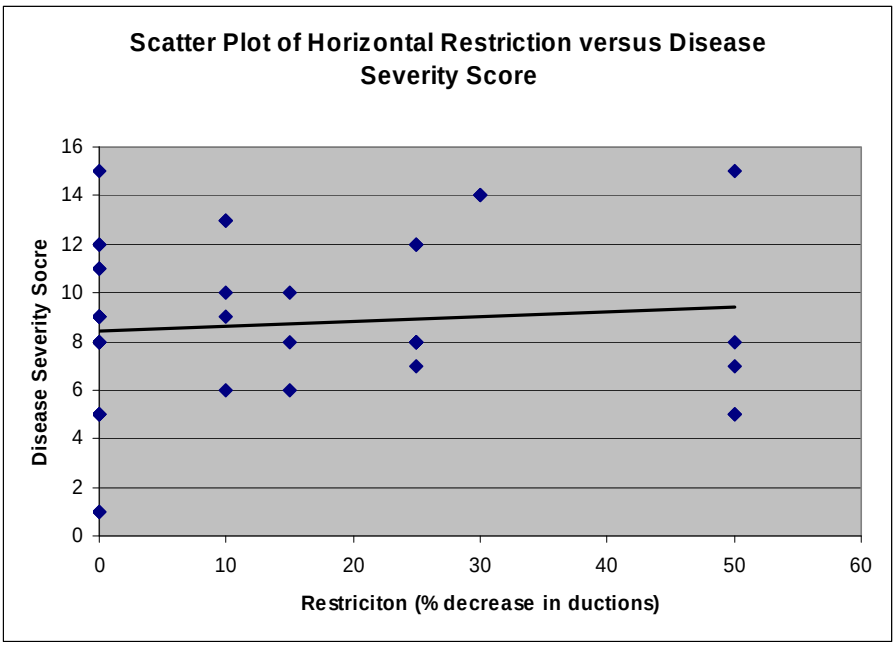


Figure 5:14 Scatter plot of horizontal restriction and disease severity. r=0.10, p=0.53

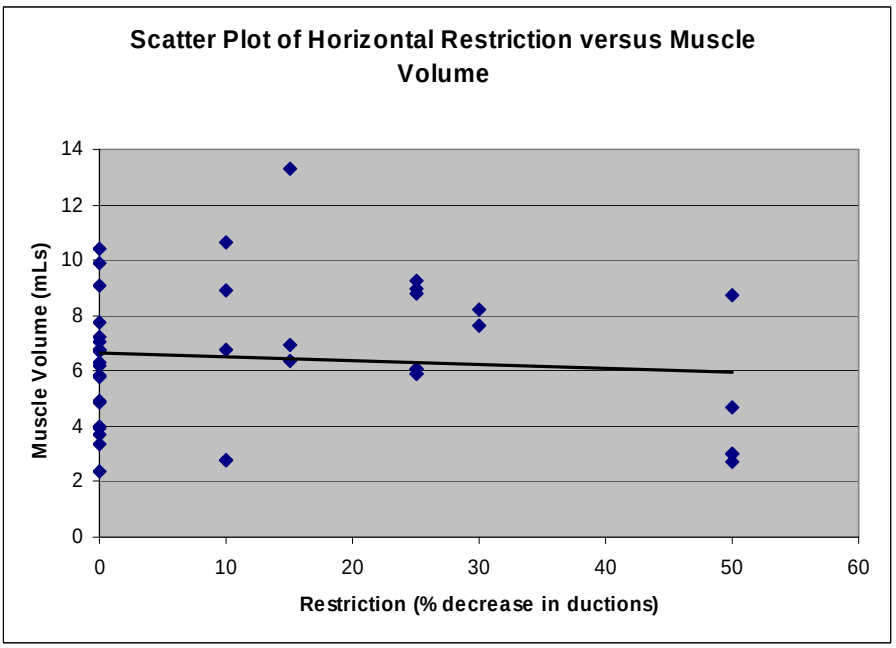


Figure 5:15 Scatter plot of horizontal restriction versus muscle volume r=0.09, p=0.56

5:6:4 VERTICAL MUSCLE RESTRICTION

For vertical muscle restriction we did not find a correlation between clinical activity, disease severity or muscle volume either. This was graded as the percentage limitation of vertical ductions, measured by the orthoptist or the investigator (RRS).

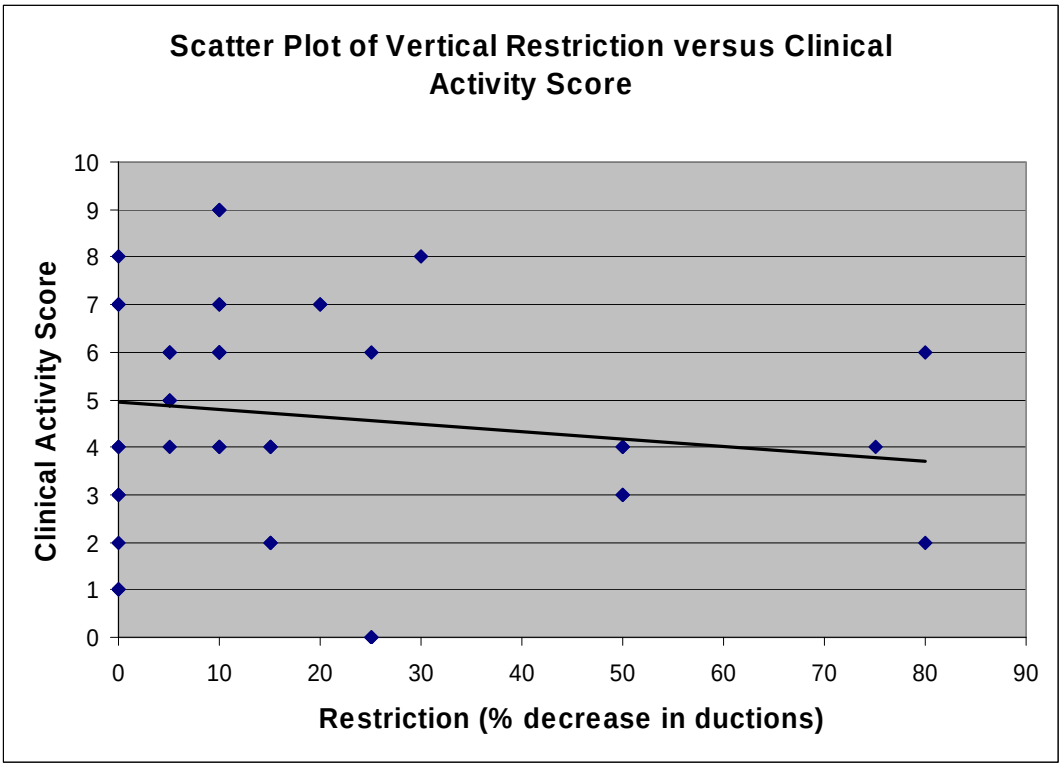


Figure 5:16 Scatter plot of vertical restriction versus Clinical Activity Score. r=0.12, p=0.44

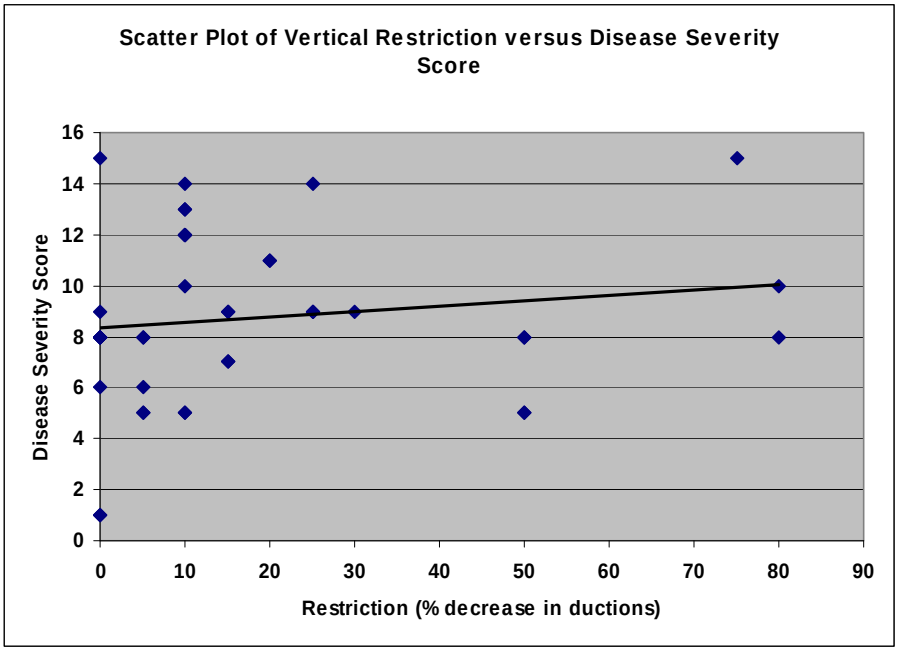


Figure 5:17 Scatter plot of vertical restriction versus disease severity. r=0.14, p=0.37

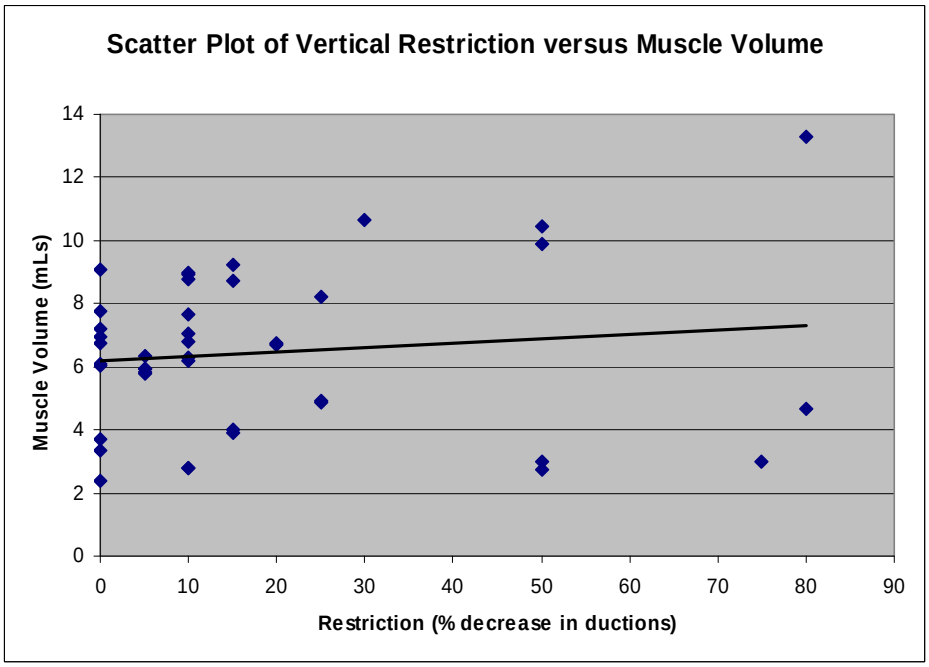


Figure 5:18 Scatter plot of vertical restriction versus muscle volume. r=0.12, p=0.44

5:6:5 ADDITIONAL ANALYSES

In order to increase the numbers of our small sample to determine if findings were truly significant we looked at some additional correlations.

Muscle restriction was analysed for each patient by both a single orthoptist and the investigator. Muscle restriction was measured by estimated reduction in versions and quantified with Hess testing. A field of single binocular vision was completed when diplopia was present.

Horizontal and vertical restriction measurements from the Hess test, were grouped together as any muscle restriction and compared to clinical activity there was no correlation $r=-0.119$, $p=0.28$.

When any restriction was compared to disease severity neither was there a correlation $r=0.12$, $p=0.27$.

5:7 SUMMARY OF CLINICAL FINDINGS

A summary of the clinical findings and their correlation factors related to muscle volume, disease severity and clinical activity are given in the Tables below.

	Proptosis	**DSS**	**CAS**
Muscle Volume	r=0.31 p=0.05	r=0.664 p<0.0001	r=0.66 p<0.0001
Total Orbital Volume	r=0.21 p=0.18	r=-0.05 p=0.75	r=0.19 p=0.24
% of total volume made up of muscle	r=0.22 p=0.16	r=0.157 p=0.32	r=0.51 p<0.001

Table 5:8 Summary of findings related to muscle volume, orbital volume and disease status

	Muscle Volume	DSS	CAS
Proptosis (a)	r=0.31 p=0.05	r=-0.0.8 p=0.56	r=0.21 p=0.18
Horizontal Restriction (b)	r=-0.09 p=0.56	r=0.10 p=0.53	r=-0.09 p=0.58
Vertical Restriction (c)	r=0.12 p=0.44	r=0.14 p=0.37	r=-0.12 p=0.44
Lid Retraction (d)	r=0.25 p=0.12	r=0.38 p=0.01	r=0.08 p=0.61

Table 5:9 Summary of correlation coefficient (r) and p values for each of the clinical criteria compared to muscle volume, Disease Severity Score (DSS) and Clinical Activity Score (CAS)

a) Proptosis was measured in mm on an Oculus Exophthalmometer
b) Horizontal restriction was a percentage of limitation of ductions.
c) Vertical restriction as a percentage of limitation of ductions.
d) Lid retraction is height of upper lid above corneoscleral limbus in mm.

SECTION 6

DISCUSSION

6:1 STUDY OUTLINE

Many patients with GD and clinically obvious eye disease have recognizable abnormalities on the CT scan.[63] In cases where the abnormality is confined to a single muscle group, subjective analysis may be sufficient. In cases with more diffuse involvement, abnormalities are better detected with volume analysis. [63]

CT scan impressions reported by radiologists for patients with suspected GO often state muscle size to be "enlarged or abnormal."[64] The findings are qualitative and subjective and generally evaluated in respect to extraocular muscle size and shape. [58] In an attempt to define more quantitative features investigators have calculated CT extraocular muscle density ranges for normal subjects and those affected with Graves disease, as well as normal ranges for the diameter and volume of normal extraocular muscles. [58]

In this paper we measured total extraocular muscle volume in 21 patients affected with GO and compared this to their disease severity and the clinical activity of their disease. We have also compared the total muscle volume to unaffected controls.

6:2 MUSCLE VOLUME IN "NORMAL" CT SCANS

From our series of 21 patients affected with GO there were 3 for whom the CT scan was reported as normal with no extraocular muscle volume increase seen.

One patient had a vague history of elevated thyroid levels in the past, but has been euthyroid for several years. His complaint was of periorbital edema and with the history of abnormal thyroid levels he was diagnosed with GO. The muscle volumes for this patient were right 3.72mL and left 3.36mL which fall outside 1 standard deviation of the normal controls, but are also less than 1 standard deviation from the mean of our affected patients (6.39±2.15 and 6.49 ±2.76). His disease severity and clinical activity were both assessed as 1. After reviewing his file and scans we reassessed this patient and believe he does not have GO but is in fact suffering from acne rosacea and his periorbital oedema is due to this inflammatory condition. This patient's data was excluded from further analysis of the GO patients.

The other two patients have clinical symptoms and signs consistent with GO as well as laboratory testing confirming GD with altered thyroid hormone levels and positive antibody titres. For one of these patients the total muscle volume of right 2.80mL and left 2.78mL fell within 1 standard deviation of the normal controls. For the second patient muscle volume was significantly increased at right 5.91mL and left 5.92mL. This may suggest that careful calculation of muscle volume is more sensitive than subjective viewing of CT scans to look for evidence of muscle enlargement. In patients without obvious extraocular muscle enlargement on CT scan, careful muscle volume analysis may give additional information supporting or refuting a diagnosis of GO.

6:3 MUSCLE VOLUME CALCULATIONS

A few investigators have looked at muscle volume in normal patients as well as those affected with GO. Forbes *et al.* [63,65,66] found the mean volume of normal extraocular muscles to be 4.69mL (range 3.66-6.2mL) in females and 4.79mL (3.07-6.18mL) in males. In this study the mean value for total muscle volume in the controls was 2.21± 0.66 mLs. This may represent a difference in measurement technique as patient demographics were similar.

In a past study investigators made a correlation between extraocular muscle volume and the degree of clinical ophthalmopathy in patients with GO.[67] In this study the clinical severity of GO was determined by evaluating clinical signs as proposed by Feldon and Unsold and described in previous sections of this paper on clinical activity. [49] These were the same criteria we modified and the used to assess disease severity in our patients.

In their study axial CT images were obtained of 8 patients with GO (16 orbits) and the bony orbit, extraocular muscles, optic nerve and globe were outlined. [67] Volumes were calculated of these structures. They showed that the degree of clinical ophthalmopathy related quantitatively with the amount of increased bulk in the orbit. They calculated a total muscle volume of 2.2mL in normal controls, 3.7mL in those with Class I and II disease and 7.2mL in those with class III disease. They also found an increase in medial and lateral extraocular muscle volume with increasing clinical ophthalmopathy. [68]Inferior rectus muscle volume was increased in all patients with GO, but did not alter with increasing severity of disease. [68]

For the cases in our series the average total muscle volume was 6.44 ± 2.51 mLs.

When we analysed muscle volume with increasing disease severity, as Feldon and Weiner had done, [67]we also found a strong correlation. The correlation coefficient for these 2 groups was r=0.66 (p<0.0001). We further assessed the patients with GO to look at the activity of the disease as well as the severity at the time of the muscle volume calculation. The correlation coefficient for Clinical Activity Score versus muscle volume was r=0.66 (p<0.0001) indicating a strong correlation.

Thus, we confirm extraocular muscle volume increases as the clinical activity of the disease increases. Further, when there are severe residual changes in patients with GO their muscle volume is also enlarged. We propose that this confirms previous physiological findings of swelling in the muscles at the time of increased clinical activity. This swelling has been suggested to be oedema as a result of increased secretion of glycosaminoglycans by orbital fibroblasts. [8]

Other groups have compared extraocular muscle size with disease activity in the past. There has been the suggestion that muscle diameter is more likely to be enlarged in patients with a disease course of less than 2 years. [62] Muscle density has also been found to increase in the initial active phase of the disease and then reduce as duration of disease increases[62]. This and other findings led these investigators to suggest that muscle enlargement, by swelling, occurs during the active stage of the disease and later fibrosis develops and the fibrotic muscles return to a more normal diameter.[62]

However, we refute this finding. Our results indicate that muscle volume in the patients with severe residual disease, as indicated by a high Disease Severity Score (DSS), have a larger mean total muscle volume. The strong correlation indicates that the more severe the residual disease the larger the muscle volume is likely to be. A longitudinal study of serial CT's would confirm this. We are unable to

comment from this clinico-radiographic study what the pathophysiological findings causing enlargement in the muscle bellies are.

6:3:1 MUSCLE VOLUME AND CLINICAL INDICES OF GO

Physiologically it has been proposed that restriction of ductions is due to fibrosis in the extraocular muscle bellies after stimulation by the disease process of the orbital fibroblasts.[33] We therefore compared horizontal and vertical muscle restriction with muscle volume. We found there to be no correlation (horizontal restriction r=0.09 and vertical restriction r=0.12). Even when we combined these groups (to increase the sample size) and compared any muscle restriction with muscle volume there was no correlation (r=0.08).

Furthermore, there is no correlation with restriction of muscles and either the clinical activity or the severity of the disease (r= 0.12 and r=0.12 respectively).

It has been suggested previously that fibrosis in muscle bellies leads to a reduction in volume of the muscle.[62] The results of this study indicate that whatever the pathophysiologic process in the muscles, it causes the muscle volume to remain enlarged late in the disease course in the severely affected patients. This process may still be fibrosis as laying down of additional collagen could be expected to increase the diameter of the muscle. If the process leading to persisting enlarged volume is fibrosis, this is not related to restriction of the extraocular muscles, at least for the patients in our small sample. We have shown that patients with more severe disease have larger muscle bellies, but this does not correlate with more restriction of movement in these same muscles.

It would be interesting to perform volume estimations of extraocular muscles on a group of patients with restrictive eye disease from any cause. If histological comparisons could also be made this may help clarify whether fibrotic muscles are larger, smaller or the same size as normal extraocular muscles.

6:3:2 ASSOCIATION WITH PROPTOSIS

When muscle volume is compared to proptosis there is a weak, but significant correlation ($r=0.31$, $p=0.05$). We propose that with a larger group of patients this trend would probably reach higher degrees of correlation. This correlation suggests that as muscle volume increases within the orbit the globe is pushed forward.

6:4 ORBITAL VOLUME CALCULATIONS

Commonly quoted normal values for soft tissue volumes within the bony orbit are 29-30mLs.[1,69] Feldon and Weiner [67], using a similar technique to that used in this study, found smaller volumes ranging from 20 to 28.55mLs. They suggested that larger values were probably due to inclusion of the bony rim in the volume estimation.

We have found larger orbital volumes with an average of 30.6mLs ± 11.0mLs. We found a statistically significant difference between orbital volumes of patients with GO compared to the controls without. ($p=0.003$). This finding has not been seen previously. Although Feldon and Weiner [67] found an increase in all soft tissue volumes, they did not report an increase in total orbital volume.

Increased orbital volume correlated only weakly with proptosis (r=0.21) and not with clinical activity or disease severity at all (r=0.21, r=0.05 respectively).

We propose that those patients in whom clinical features of ophthalmopathy develop may have an anatomical difference in their orbit which predisposes them to develop the condition. It may be that these patients have larger orbits to begin with. It may also be possible that smaller outlet foramina such as the superior and inferior orbital fissures could alter venous congestion causing increased orbital volumes. This area needs further investigation.

In this study we have not attempted to measure orbital fat volumes as it was beyond the scope of the thesis. Calculating fat volumes would have required outlining the globe, optic nerve and other orbital structures and subtracting these, with total extra-ocular muscle volume, from the total soft tissue orbital volume. Normal volumes for orbital fat of 10.1mL (8.2-12.2mL) in females and 11.19mL (8.6-14mL) in males have been quoted with fat volumes in patients with GO as high as 22mL. [32]

6:5 OPTIC NERVE INVOLVEMENT

In a study of 96 orbits with GO researchers compared muscle volume in patients with optic nerve involvement to those with no optic nerve involvement. [68] They found total extraocular muscle volume was double in patients where there was optic nerve involvement (4.76 mL) compared to those without (2.20mL). [68] When total muscle volume was expressed as a percentage of total orbital volume the same increase was seen in patients with the optic nerve involvement.[68] They suggested that increase in muscle volume was a significant risk for predicting the development of optic neuropathy.

In our series of 21 patients we had only 2 cases in which optic nerve involvement was seen. The total muscle volume in these patients for the left and right eyes were patient 1 right 6.08mL, left 6.05mL and for patient 2 right 5.76mL and left 5.83mL. These values were within one standard deviation of the mean for each eye for our series.

Interestingly our muscle volumes were significantly higher than those calculated by Feldon *et al.* [68]. The total muscle volumes in our control group were 2.18mL and 2.44mL similar to the values found in their patients with GO, but no optic nerve involvement (2.20mL). There is no mention made in their paper of the degree of clinical ophthalmopathy of these patients.[68]

Our findings suggest that there are factors other than just total muscle volume relating to development of optic neuropathy. We found muscle volumes significantly higher than they reported in the majority of our patients and only 2 had any sign of optic nerve involvement. We do not believe increased total muscle volume is independently predictive of risk of optic nerve involvement in patients with GO. Unfortuantely the small numbers in this series mean we are unable to complete statistical analysis on this subgroup.

The 2 patients who developed optic neuropathy had large values for the percentage of orbital volume made up of extraocular muscle. For patient 1 the orbital volumes were 21.11mLs right and 18.73 mLs left with % muscle 28.8% right and 32.3% left. For patient 2 orbital volumes were 32.81 right and 33.21mLs left. Percentages of volume as muscle were 28.1% right and 26.3% left. These were in the higher end of the spectrum for these figures.

We propose that it is not the muscle volume alone that is important to predict the risk of optic neuropathy, but the muscle volume compared to the orbital volume. In patients with smaller orbits increase in muscle belly volume may be more likely to result in development of optic nerve compression. Anatomical variation in orbit size may be the factor that determines which patients will develop optic neuropathy due to compression. It would be interesting to measure orbit size and percentage of orbital volume taken up by muscle in other patients in whom optic neuropathy has developed to see if this relationship holds.

6:6 CRITERIA FOR ASSESSING EXTENT OF GO

We have used Feldon and Unsolds [49]criteria to assess disease severity as well as Mourits' Clinical activity score[42]. Both of these factors need to be assessed when managing a patient with GO. Those with severe and active disease are likely to benefit from medical treatment or radiotherapy, but those with severe, inactive disease need surgical intervention[34].

We have shown that these 2 assessment methods correlate highly. This finding indicates that although measuring different features of GO, if the activity of the disease is high this is likely to lead to more severe outcomes. This confirms Rundles initial findings in cadavers and follows the commonly held belief that intervening early in the active phase to reduce activity may lead to reduced final severity of GO.

6:6:1 DETECTING SUB-CLINICAL DISEASE

In a small sample, Forbes *et a.* were able to show that abnormalities in volume measurements were present in 70% of patients with GD, but no significant clinical

ophthalmic manifestations. [63] We were hoping to be able to measure volume in patients with low disease activity and severity to detect alterations in muscle volume as an early manifestation of the disease. Unfortunately there were too few patients in this group to enable analysis.

This is likely to reflect the difficulty we have obtaining radiological investigations in our institution. CT scans are only performed in patients when the diagnosis is in doubt, if there is clinical deterioration or if surgery is planned. Routine CT scanning is not performed on all patients presenting with endocrine abnormalities consistent with GD and mild or no eye symptoms.

It is possible that measuring muscle volume in newly diagnosed patients with GD may be able to predict those that will progress to develop GO. If muscle volume was normal at diagnosis they would not need to be followed in an ophthalmology clinic. If it was elevated they could be educated on symptomatic symptom relief and monitored more closely in case intervention was required. This is a further area requiring more investigation.

6:7 REPRODUCIBILITY

Previous studies measuring extraocular muscle volume with CT imaging have shown large variation in the measured volume of normal extraocular muscles.[66,70,71] [63] One problem has been determining the start and end points for the muscle and tendon. Thus the range of slices on which muscle outlines may differ from subject to subject. [72] Another problem with standardizing measurements has been that the anterior insertion of the muscle to the globe is altered in patients with proptosis. [72]We have attempted to overcome these difficulties by including the tendon in our measurements and outlining the muscle/tendon complex from the equator of the

globe to the apex of the orbit for all subjects. The equator of the globe is the widest part of the globe and a reproducible end point.

Another consideration thought to result in large variation of normal values for muscle volume is variation in muscle outlining. Firbank *et al.* showed that a single observer was consistent in their outlining, but there was marked variability between observers. [72] The consistency in our sample is confirmed by the very close average total muscle volumes between left and right eyes for both the affected (average left 6.49mLs right 6.39) and normal controls (average left 2.44mLs right 2.18).

6:8 ALTERNATIVES TO TOTAL VOLUME

The time and equipment necessary to calculate extraocular muscle volume limits the clinical application of the technique. The time taken for analysis of a single patient (2 eyes) by this examiner at the start of the study was 90 minutes. Even with training and practise entering the data points for 2 globes took more than 30 minutes.

Because of this, investigators have attempted to find a measurement from a single section or at a single anatomical location that may correlate with total extraocular muscle volume.[73] This would mean the analysis might be more easily accomplished in the clinical setting. Although some sites have shown high correlation, such as an area calculation of a mid-orbital slice, none have proved to be easy enough or accurate enough to replace total volume calculation of extraocular muscles. Medial rectus width from a mid-orbit CT section has been suggested to correlate with risk of optic neuropathy,[74] but we have found that

muscle volume alone is not the sole contributing factor to development of the neuropathy.

6:8:1 OTHER TECHNIQUES TO MEASURE VOLUME

CT has the disadvantage of subjecting patients to ionizing radiation, and multiple thin CT sections are required to achieve volume estimations within acceptable limits of error. [72] The need to repeat the examination at intervals to monitor disease progress makes the radiation dose implications of CT even less acceptable. [72] MRI does not involve ionizing radiation and has excellent tissue contrast making it an alternative medium for estimating the volume changes in extraocular muscles associated with GO.[72] The cost of MRI and the time taken to perform an examination mean its use is not widespread for the diagnosis of orbital conditions, at least in our institution, despite the benefit in reduced ionising radiation exposure.

Ultrasound has also been used to measure extraocular muscle size to assist in the diagnosis of GD. [64]When comparing A-scan ultrasound with CT scanning in patients with clinically evident GD, 30% had enlarged muscles on CT interpretation and 70% on A-scan ultrasonography. [64] Maximum muscle diameters were imaged, photographed and compared to standard tables for evaluation of size. Their findings prompted some of our interest in creating 3D images of extraocular muscles and calculating muscle volumes in affected and normal patients. Unfortunately ultrasound is a difficult technique which requires skilled technicians and the quality of the images we achieved were not suitable for further analysis.

The use of 3D imaging in combination with automated outlining in the estimation of extraocular muscle volume has been proposed as more accurate, [72] but this facility is expensive and not available routinely in clinical institutions.

6:9 LIMITATIONS OF THIS STUDY

The main limitation with this study is the small sample size. Only 40 globes, of 20 patients, with GO were examined. The small sample size means that it is difficult to prove correlations are statistically significant. Some of our findings show a trend towards significance and with a larger sample may prove to be so. The small numbers are due to the low incidence of this condition as well as the fact that not all patients with a diagnosis of GO have a CT as a diagnostic test.

We used all scans for patients with GO in this institution over a 5 year period. Patients were included on the basis of having had a CT scan at the time of assessment, which could potentially introduce bias as the decision to request the CT scan would have been made for a variety of reasons. It would be ideal to perform the same measurements on a complete cohort of patients with thyroid eye disease and scan all of them for the purpose of measurement rather than due to clinical need. Due to limited resources, at least in our institution, this is unlikely to ever happen. There is also the risk of radiation exposure to patients and CT scanning should be undertaken only for clinical need.

A significant number of scans were not able to be analysed due to poor quality. This also potentially introduces bias if for example, there was a relationship between GO activity or severity and scan quality.

The only exclusions were due to inadequate clinical or radiographical information. No patients refused to participate in the study and this reduces recruitment bias.

This study was a retrospective cohort study. Controls were chosen to be as similar to the cases as possible with the exception of the GO. They were chosen from the CT scan data base of orbital CT scans which were reported as normal. They were selected if their age and sex were the same as a control and the scan was performed in the same 5 year period.

As much of the clinical information as possible was recorded from measurements performed by the investigator, with assistance from the orthoptist. However, as some scans were historical, some clinical data had to be taken from the notes. This information was recorded by other clinicians in our institution. Assumptions have to be made that it is accurate and that examinations are performed and recorded in the same way by these clinician's. The assessments were performed as close as possible to the time of the CT scan. The lag between does introduce the potential for change in clinical activity or disease severity.

It was necessary to use the data from the notes to calculate activity and severity scores as close to the time of the CT scan as possible. Although this may introduce some error in the clinical information several factors are important to note; all measurements of proptosis were done on the same brand of exophthalmometer, which will reduce variability in the measurement and measurements of eye movement restriction were all taken from the orthoptist's clinical notes.

The investigator (RRS) who outlined all the muscle and orbit volumes and analysed the results was not blinded to the diagnosis. It is possible bias may have been introduced as the outlining was performed. In order to reduce bias, scan outlines were completed sequentially, but over a number of sessions, from a

mixed list of cases and controls. Clinical details were not analysed until after the outlining of all cases and controls had been performed and analysis of volume data had been performed.

6:10 CHANGES IN PROCESS DUE TO THE STUDY

As a result of this study some changes have been made within the Ophthalmology Department. A new coding system means that all patients with thyroid related eye disease are given a unique code and will be retrievable directly in future.

At present, any new referrals for patients with thyroid abnormalities and eye symptoms or signs, independent of severity, are made directly to the investigator (RRS). It is hoped that due to increased collaboration between the Ophthalmology Department and Thyroid Clinic Physicians during this study, a combined clinic is being established to manage patients with GO in the future. This will further increase the standard of care patients presenting to this institution receive with this condition.

SECTION 7

CONCLUSIONS

7:1 THE TECHNIQUE

Graves' disease (GD) is an autoimmune disease affecting the thyroid gland, orbital soft tissues and subcutaneous tissues of the extremities. GO is the most common orbital disorder and the most common cause of exophthalmos in adults. Ophthalmic signs are clinically evident in 25-50% of patients with GD and 3-10% of cases develop severe disease.

Imaging of the extraocular muscles and orbital soft tissue in GO provides valuable information for both diagnosis and treatment decisions. Many patients with GD and clinically obvious eye disease have recognizable abnormalities on the CT scan, but cases with more diffuse involvement subtle changes can be missed.

In this study we have shown that using axial CT scans and a specially designed software programme, the Volume Estimation Tool, accurate calculation of extraocular muscle volume is possible. Muscle volume may be a more sensitive indicator of muscle enlargement that subjective viewing alone. Muscle volume may also help us predict those at risk of more severe residual disease and those with potential to develop sight threatening complications.

This technique adds an additional tool to our armamentarium for assessing and managing patients with GO.

7:2 EXTRAOCULAR MUSCLE VOLUME

It is known that muscle size increases in some patients with GO and we have confirmed this in this study by showing muscle volumes significantly larger in patients with clinical evidence of GO compared to normal controls with no ophthalmopathy.

We suspect that having larger muscle volumes leads to proptosis although were able to show only a weak correlation between these factors with our small sample.

7:3 CLINICAL ACTIVITY AND DISEASE SEVERITY

We have also shown that the more active the GO the larger the muscles are likely to be. Furthermore, if a patient is left with severe residual manifestations of the disease there muscle size also remains large.

When assessing and managing a patient with GO it is essential to measure both the activity of the disease at the time of the assessment and the severity of the disease. We have shown these factors, while independent, strongly correlate. If the activity of the disease is high it is likely the patient will end up with severe residual disease. This confirms what other investigators have found and supports the view that intervening if activity is high is likely to reduce the severity of the residual disease.

7:4 RESTRICTIVE EYE DISEASE

It has been proposed that in the late stages of GO, extraocular muscles become fibrotic and further suggested that this is the cause of the restrictive eye movements commonly seen in patients with moderate or severe ophthalmopathy. We have shown that patients with increased volume of extraocular muscles are not more likely to have restricted eye movements. Patients with very active disease or severe residual disease do not have an increased risk of restrictive eye movements. We are not able to comment on the structure of the muscles fibers or the cause of the increased volume late in the disease process.

7:5 ORBITAL VOLUME

We have shown that patient with GO have a larger soft tissue orbital volume than patients with no ophthalmopathy. When consideration is made of the percentage of orbital volume taken up by muscle this may have particular relevance in the risk for development of optic neuropathy.

7:6 RISK OF OPTIC NEUROPATHY

We propose that it is not the muscle volume alone that is important to predict the risk of optic neuropathy, but that the muscle volume compared to the orbital volume may be an important factor. For the 2 patients in our study with optic nerve involvement their muscles were not larger than normal. However their orbits were normal or small and therefore the percentage of orbital volume taken up by muscle was large. In patients with smaller orbits increase in muscle belly volume may be more likely to result in development of optic nerve compression.

7:7 ROLE FOR MUSCLE VOLUME CALCULATION

Due to the time consuming process of calculating total muscle volume this is not indicated in the clinical setting routinely. However, for patients in whom the diagnosis of GO is suspected, and CT scans do not show obvious extraocular muscle enlargement, total muscle volume calculation using the VET may be useful. It may provide evidence of significant muscle volume enlargement which may confirm the diagnosis or prove muscle volume to be normal making a diagnosis of GO less likely. Measuring orbital volume, in addition, may help predict those at risk of going on to develop optic neuropathy.

SECTION 8

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APPENDIX 1

INFORMATION SHEET FOR PARTICIPANTS IN THE STUDY ON THYROID EYE DISEASE

INTRODUCTION

You are invited to take part in a scientific study looking at thyroid eye disease. This is part of a Masters Study project. Participation is on a purely voluntary basis and all information will be entirely confidential. The study has the approval of the Upper South A Regional Ethics Committee.

THE THYROID EYE DISEASE STUDY

We are recruiting 2 groups of participants; one group from those who have been referred to our service because of abnormal levels of thyroid hormone, and then an equal number who do not have thyroid eye disease, who will act as controls.

If you have thyroid eye disease you will receive a thorough examination of your eyes (which will be done whether or not you take part in this study). Then 2 additional tests will be performed that are not part of the normal examination.

The first is an Optical Coherence Scan of the inner layers of the eye. This involves sitting at a machine like the microscope used in clinic. A laser light is shone into your eye and an image is created. It takes a few seconds to scan each eye and is painless.

The second test is an ultrasound scan of the eye. This involves a metal probe being placed over your closed eyelid. Sound waves are used which create a 3D image of the inside of the eye. This test also takes a few seconds and is painless.

If you do not have thyroid eye disease but have been asked to act as a control, you will have had a thorough eye examination and an Optical Coherence Scan in the normal course of your appointment, and we will perform an additional test (an ultrasound scan of the eye), which is detailed above.

In some cases it may be necessary to refer you for a CT scan of your eyes to help make the diagnosis or your condition or to help in the planning of treatment. The doctor will discuss this with you if the test is necessary.

BENEFITS, RISKS and HARM

The benefits of this study are twofold. We hope to determine a grading system to be used for all patients with thyroid eye disease and monitor their condition. We are also looking for ways to detect damage earlier so treatment can be given prior to sight threatening complications developing.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or a non-earner. ACC usually only provides partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is the result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you

have any questions about ACC, contact your nearest ACC office or the investigator.

PARTICIPATION IN THE STUDY

Your participation is entirely voluntary (your choice). You do not have to take part in this study. If you are currently a patient at the Department of Ophthalmology, Christchurch Hospital, then if you choose not to take part, this will not influence your normal medical care from the Department. If you do agree to take part, you are free to withdraw from the study at any time without having to give a reason and this will in no way affect your future health care. Your participation in this health study will be stopped should any harmful effects appear or if the Doctor feels it is unwise to continue. Reimbursement for travel costs is available up to a maximum of $30 per visit.

PROFESSIONAL COMMUNICATION

Your usual doctor will be contacted about the results of this consultation, as is standard practise.

If an interpreter is required, then this will be provided for you.

If you have any queries or concerns about your rights as a participant in this study you may wish to contact a Health and Disability Advocate at 3777 501 or 0800 377 766 (if you are outside Christchurch).

CONFIDENTIALITY

All details about the study will be entirely confidential. No material, which could personally identify you, will be used in any report in the study. Medical records will be locked in one of the offices of the Department of Ophthalmology, Christchurch Hospital. Access to the records will only be available to the named Investigators of this study. The records will be kept for 10 years.

RESULTS

The results of the study will be presented at medical meetings in New Zealand and abroad and it is planned to have the data published in international journals. A copy of these outcomes will be made available to all the participants. In addition people can also discuss the outcomes with Dr Rebecca Stack (Lead Investigator).

COMMUNICATION DETAILS

The principal investigator of this study is Dr Rebecca Stack (MBChB) who is a senior registrar at the Christchurch Ophthalmology Department. The supervisor of this study is Associate Professor Mark Elder (MD FRACS FRACO) who is a Consultant Ophthalmologist at the Department of Ophthalmology, Christchurch Hospital, 19 St Asaph Street, Christchurch. Either can be reached at 03 3640 640 extension 80976. Dr Ken Tarr and Dr Bevan Brownlee are also supervisors and can be contacted through the Christchurch Hospital operators (phone (03) 3640 640).

APPENDIX 2

CONSENT FORM FOR THE STUDY EXAMINING PATIENTS WITH THYROID EYE DISEASE

I wish to have an interpreter (please circle one) YES / NO

E hiahia ana ahau ki tetahi kaiwhakamaorilkaiwhaka pakeha korero. AE / KAO

Oute mana'o ia iai se fa'amatala upu. IOE / LEAI

Oku ou flema'u ha fakatonulea. IO / IKAI

Ka inangaro au i tetai tangata uri reo. AE / KARE

Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu E / NAKAI

I have read the Information Sheet Determining a Grading Scale for Thyroid Eye Disease, November 2005. I have had the opportunity to discuss this study with the investigator. I am satisfied I understand the study and my role.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and that this will in no way affect my continuing health care.

I understand that my participation in this study is confidential and that no

material that may identify me will be used in any reports on the study. I understand that the investigation will be stopped if it should appear harmful to me.

I understand the compensation provision for this study. I have had time to consider whether to take part. I know whom to contact if I have any side effects from the study. I know whom to contact if I have any questions about the study.

I agree to an approved auditor appointed by the Upper South A Regional Ethics Committee reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

I wish to receive a copy of the results Yes/No

I would like the researcher to discuss the outcomes of the study with me Yes/No

I consent to my GP being informed of my participation in this study Yes/No

CONSENT FORM FOR THE STUDY EXAMINING PATIENTS WITH THYROID EYE DISEASE

I _____ hereby consent to take part in this study.

Signed _____ Date_____

Project explained by:_____

Project role:_____

Date _____ Signed_____

Lead Researcher: Rebecca Stack