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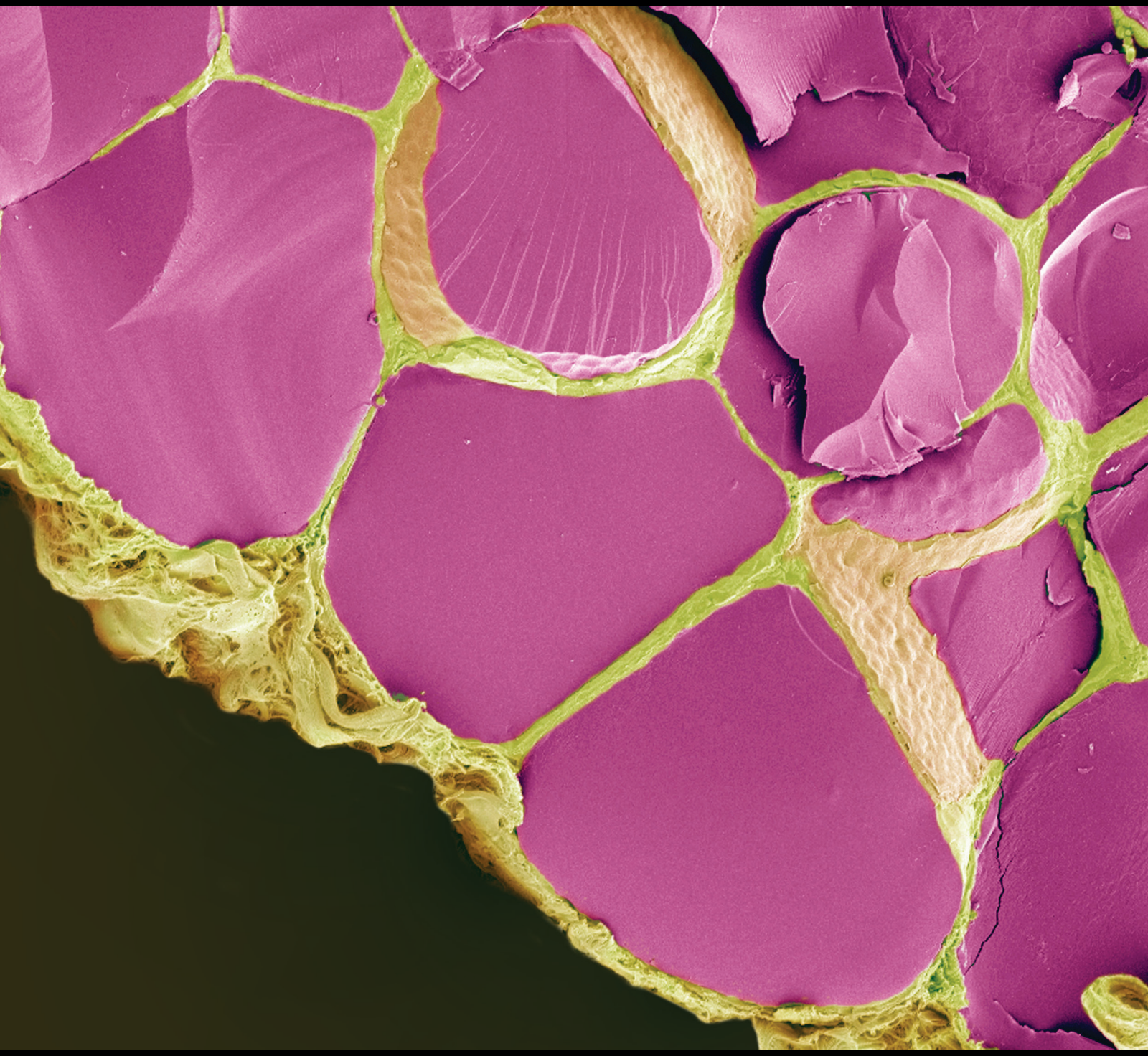
# Graves' Orbitopathy

Guest Editors: Yuji Hiromatsu, Jack R. Wall, George J. Kahaly, and Hirohiko Kakizaki



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# Editorial Board

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*Editorial*

# Graves' Orbitopathy

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Graves' orbitopathy (GO) is an autoimmune disorder of the orbit that is closely associated with autoimmune thyroid diseases (AITD). Although the primary autoantigen(s) and precise mechanisms underlying the association between GO and AITD remain unclear, TSH receptors are thought to be the primary target of autoimmune reactions in GO patients. However, other antigens such as insulin-like growth factor 1 receptor, thyroglobulin, thyroid peroxidase, calcium binding protein calsequestrin, and collagen XIII are also involved in the orbital reactions in GO. This special issue is a great opportunity for the reader to learn the latest and emerging findings on the management of GO.

Recently the analytical performance and clinical utility of the functional thyroid stimulating autoantibodies (TSAb) and thyroid blocking autoantibodies (TBAb) have been extensively evaluated. In this special issue, E. Kampmann et al. performed a prospective study on the clinical relevance of the functional TSH receptor autoantibodies in a large collective of patients with GO. They noted that TSAb, not TBAb, were highly prevalent in severe and active GO. Serum TSAb levels correlated with all specific ophthalmic signs of the thyroid eye disease and mirrored the severity of GO. Thus, TSAb may be regarded as useful and reliable biomarkers for Graves' disease and associated GO.

The current first-line treatment for patients with severe and active GO is the administration of intravenous infusions of methylprednisolone pulses (IVMP). The European Group on Graves' Orbitopathy (EUGOGO) recommends single doses of 0.5 g of IVMP per day and a maximal cumulative dose of 8 g. In this issue, H. Eguchi et al. performed a retrospective study to look for risk factors of liver dysfunction during and after the IVMP therapy in a single center. Liver dysfunction was more frequently observed in males, in patients receiving high-dose methylprednisolone, and in patients aged over 50 years. Preexistent viral hepatitis was significantly associated with liver dysfunction (65% in patients positive for hepatitis B core antibody and patients positive for hepatitis C virus antibodies). Therefore, evaluation of preexisting risk factors and careful weekly monitoring of liver function during IVMP therapy and monthly thereafter for one year are warranted.

Also in this issue, M. Lin et al. introduced in a pilot and open study the subantimicrobial dose of doxycycline (50 mg daily for 12 wks.) for patients with moderate to severe and active GO. Eight of 13 patients showed improvement at 24 wks.; unfortunately this study lacks a control group. Since the subantimicrobial dose of doxycycline displays an anti-inflammatory and immunomodulatory function, it might serve as a new promising therapeutic strategy for GO. Future multicenter, double blind, randomized, controlled trials are therefore needed.

Orbital decompression surgery is indicated for rehabilitative reduction of the GO-induced exophthalmos and for restoration of the visual function in dysthyroid optic neuropathy. In this issue, N. Fichter and R. F. Guthoff performed a retrospective study and proposed that lateral

wall decompression with orbital fat resection is the first choice in patients without disturbance of binocular functions and where moderate exophthalmos reduction is required.

Finally, the involvement of inferior rectus muscles (IRM) is a common but severe sequel in patients with GO. Recession of inextensible IRM is the first step in the correction of a restrictive hypotropia in GO. Y. Takahashi and H. Kakizaki performed a retrospective study to evaluate the predictive factors for the dose-effect relationship regarding unilateral IRM recession in GO. They found that the IRM thickness, the degree of intramuscular adipose changes, and the smoking status were relevant to it. Magnetic resonance imaging can detect both a thickened IRM and adipose change, enabling an accurate preoperative estimation.

In conclusion, the original articles in this special issue on Graves' orbitopathy provide new insights on diagnosis and management of GO. Future efforts to understand both the molecular pathology and mechanisms for the development of GO as well as to search for biomarkers of this complex disorder are indicated, and the performances of randomized clinical trials in patients with moderate to severe GO are keenly warranted.

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*Clinical Study*

# Efficacy of Subantimicrobial Dose Doxycycline for Moderate-to-Severe and Active Graves' Orbitopathy

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*Aim.* To study the efficacy and safety of subantimicrobial dose (SD) doxycycline(50 mg/d) in patients with active and moderate-to-severe Graves' orbitopathy (GO). *Methods.* Thirteen patients with active and moderate-to-severe GO received once daily oral doxycycline (50 mg/d) for 12 wk. Treatment response at 24 wk was used as the primary outcome, measured by a composite of improvement in Clinical Activity Score (CAS), diplopia, motility, soft tissue swelling, proptosis, and eyelid aperture. Secondary outcome was the change of quality of life score (QoL, including visual functioning subscale and appearance subscale). Adverse events were also recorded. *Results.* Overall improvement was noted in eight out of 13 patients (61.5%, 95% CI 31.6%–86.1%). Both CAS and soft tissue swelling significantly ameliorated in eight patients at 24 wk. Five patients (38.5%) had improvement in ocular motility of ≥8 degrees. Eyelid aperture (46.2%) also decreased remarkably. For QoL, a significant improvement in appearance subscale ($P = 0.008$) was noted during the study, whereas no difference was observed in visual functioning subscale ($P = 0.21$). Two patients reported mild stomachache at 12 wk. *Conclusions.* SD doxycycline appears to be effective and safe for the treatment of active and moderate-to-severe GO. It might serve as a new promising therapeutic strategy for GO. This trial is registered with NCT01727973.

## 1. Introduction

Graves' orbitopathy (GO) is a condition usually associated with autoimmune Graves' disease (GD), and it might be caused by immunological cross-reactivity between thyroid and retrobulbar tissue autoantigens [1]. The natural history of GO varies greatly among patients. It can either progress or spontaneously regress, and a typical process can be divided into three phases: active (inflammatory) phase, stabilization, and remission (inactive) phase [2, 3]. The active phase can last for months or even years, and this has a profound impact on patients' vision and quality of life. Therefore, the goal of treatment is to inactivate the autoimmune process. Immunosuppressive treatments are effective to arrest the active phase. So far, many immunosuppressive therapies have been reported, such as glucocorticoids (GCs), orbital radiotherapy, and cyclosporine, of which GCs represent the first-line treatment [4–6]. Oral GCs are successful in about 60% of patients with moderate-to-severe and active GO, but they often cause adverse events (81%) [7, 8]. Although intravenous (i.v.) GCs have a greater efficacy (around 80%) and adverse events are less common (39%), severe events (fatal acute liver failure and cardiovascular events) are more common [8, 9]. Other immunobiological therapies (e.g., rituximab) are currently under investigation and the efficacy and safety are not yet clearly presented [10, 11].

Doxycycline is known as a semisynthetic antibiotic. Independent of its antibiotic properties (200 mg/d), subantimicrobial dose (SD) doxycycline (40–50 mg/d; administered for a duration of 2 wk or 16 wk) displays a strong anti-inflammatory and immunomodulatory function [12, 13]. Data from clinical trials demonstrated that SD doxycycline was effective in moderating inflammation in a variety of autoimmune diseases, such as rheumatoid arthritis, multiple

sclerosis, rosacea, and periodontitis [14–16]. And few minor side effects (gastrointestinal events and photosensitivity) were observed. The anti-inflammatory activities may be related to its ability of inhibiting many cytokine factors, including interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-$\alpha$), and matrix metalloproteases (MMPs), and of decreasing level of inflammatory cell infiltration and B lymphocyte proliferative responses [12, 17, 18]. Given that these cytokines and inflammatory responses are also seen among patients with active GO [1, 19, 20], SD doxycycline may serve as a treatment option. With this hypothesis, we investigated the efficacy and safety of SD doxycycline in patients with moderate-to-severe and active GO in the pilot study.

## 2. Patients and Methods

*2.1. Patients and Study Design.* From October 2012 to October 2013, consecutive patients aged 18 to 60 years, presenting with untreated active and moderate-to-severe GO, were recruited to participate in the study in Zhongshan Ophthalmic Center if they met inclusion criteria (see Supplementary Information in the Supplementary Material available online at http://dx.doi.org/10.1155/2015/285698). GO was diagnosed on the basis of typical features of the disease, such as eyelid retraction and swelling, proptosis, impaired motility, and enlarged extraocular muscles on orbital computed-tomography (CT) scans or magnetic resonance imaging (MRI) [7]. The severity and activity of GO were assessed according to the proposed criteria of the European Group on GO (EUGOGO) [21]. Patients had been euthyroid for a mean of 3 months before the date of inclusion.

All patients were treated on an outpatient basis and received 50 mg of doxycycline tablet once daily for 12 wk. We called patients every week to make sure that they took medicine exactly as ordered. Since euthyroidism was required for the study, antithyroid drugs (carbimazole, benzylthiouracil, and propylthiouracil) or levothyroxine was permitted throughout the study period, as long as the dosage was not significantly modified during the study. Also permitted were topical products (artificial tears and ocular lubricants).

The study was approved by the Institutional Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University, and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. It was registered on http://www.clinicaltrials.gov/ (NCT01727973).

*2.2. Study Procedures.* All patients were examined at baseline and 4, 12, and 24 wk after the start of treatment. A senior ophthalmologist with 20 yr experience of working on GO, who was masked to patients data, was asked to examine the patients throughout the study. Eye examinations were performed according to the Color Atlas evaluation (http://www.eugogo.eu/). At each visit, the subjective diplopia score was graded as no diplopia, intermittent, inconstant, and constant diplopia [22]. The eyelid aperture was measured as the distance in the midline between the eyelids, with the eyes in primary position. The lid lag was measured with a ruler as the distance between the limbus and lid margin in downgaze [23]. The soft tissue swelling was graded as no swelling, mild, moderate, or severe swelling [24]. Proptosis was measured using the same Marcus exophthalmometer and same intercanthal distance for each patient. Elevation, depression, adduction, and abduction of the individual eye were measured with a modified perimeter and recorded in degrees. BCVA was tested with a Snellen chart. The eye fundus was checked by fundoscopy. The activity of the disease was scored with the CAS. Finally, quality of life score (QoL), consisting of visual functioning subscale and appearance subscale, was evaluated with the Graves' orbitopathy-specific quality of life (GO-QoL) questionnaire (http://www.eugogo.eu/).

*2.3. Outcome Measurements.* Considering that the natural course of GO usually has an active phase lasting for 6 to 18 months, we chose the treatment response at 24 wk as the primary outcome because the response would be expected within that time frame. As for the definition of treatment response, we referred to the major and minor criteria proposed by van Geest et al. [25, 26]. The treatment response was graded as follows: improvement, deterioration, and no success (see the Supplementary Information).

The secondary outcome included the changes of GO-QoL and adverse events. At each visit, details of all possible adverse events were collected. Patients were inquired about physical discomfort and the information was noted. Changes of blood pressure, body weight, and plasma concentrations of thyroid hormones were also recorded.

In addition, the quantitative changes of proptosis, eyelid aperture, lid lag, ocular motility, and CAS after treatment were recorded and compared with baseline.

*2.4. Statistical Analysis.* Analysis was performed using the "intention to treat" method. For example, patients withdrawn from the study prematurely for any reason were included in the final analysis if the evaluation at 4 wk visit was available. Results of their last assessment were carried forward and evaluated as the last visit. Patients lost to follow-up before the visit at 4 wk were excluded from the analysis.

Baseline characteristics of the patients were expressed as means (±SD) or numbers (proportions) or median (25th to 75th percentiles), as appropriate. For parameters expressed on a continuous scale, SAS PROC MIXED (SAS Institute Inc) with time modeled as a continuous variable was used to obtain the $P$-trend over 24 wk. Due to the discrete nature of the CAS, time trends during the trial were tested with a nonparametric approach (Jonckheere-Terpstra test). Mann-Whitney $U$ test was used to compare the ophthalmological variables between baseline and 24 wk. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed with the Statistical Analysis System (SAS) software package for windows, version 9.2 (SAS Institute Inc., Cary, NC).

## 3. Results

*3.1. Patients.* 68 patients (38 females and 30 males) with GO were referred for screening. Due to stringent inclusion and exclusion criteria, 20 patients were eligible and invited to participate in the study. Of these 20 patients, four declined to participate because of fear of the treatment or a wish to receive other treatments. The remaining 16 patients were administered 50 mg of doxycycline tablet daily for 12 weeks. Three patients dropped out because of immigration (one male) or lost to follow-up (two females) before the visit at 4 wk, and these three patients were not included in the final analysis. Out of the remaining 13 participants, 11 completed the study at 24 wk, while 2 patients finished the evaluation at 12 wk. Results of their last assessment were carried forward and evaluated as the last visit. The baseline characteristics of the subjects were shown in Table 1. The majority of patients were male (10/13 patients). Four patients had euthyroid Graves' disease (4/13, 30.8%), and all of them were males.

*3.2. Efficacy.* Based on predefinition criteria, 12 wk doxycycline treatment led to successful response in eight out of 13 patients (61.5%, 95% CI 31.6%–86.1%) at the end of the trial. Deterioration occurred in two males at 12 wk, with worsening of soft tissue swelling. Both patients completed the evaluation at 12 wk and were subsequently treated with oral prednisone. No success was observed in the remaining three participants.

Table 2 showed the changes in individual variables. CAS significantly decreased during the trial ($P < 0.0001$). Two patients had a decrease of three points at 24 wk, and six patients had a two-point decrease. Soft tissue swelling also improved in eight out of 13 patients (61.5%) at 24 wk. A significant improvement was found when compared with baseline ($P = 0.044$). Interestingly, the majority of patients (9/13) reported that spontaneous orbital pain was relieved at 4 wk.

Only three patients (23.1%) reported improved diplopia at 24 wk: one from inconstant to no diplopia, one from inconstant to intermittent diplopia, and one from intermittent to no diplopia. Nevertheless, five patients (38.5%) had remarkable improvement in motility of ≥8 degrees at the end of trial. By investigating the motility at different directions in detail, we found that elevation, which represented the function of inferior rectus, significantly improved ($P = 0.0496$).

Proptosis decreased in the minority of patients (2/13). No difference was observed compared with baseline. Both eyelid aperture (6/13, 46.2%) and lid lag (7/13, 53.8%) had substantial decrease at 24 wk. In particular, lid lag significantly decreased at 24 wk, compared with baseline ($P = 0.008$).

The mean scores on the GO-QoL questionnaire at baseline and after the intervention were also shown in Table 2. A significant improvement in appearance subscale ($P = 0.008$) was found during the study, whereas no difference was noted in visual functioning subscale ($P = 0.21$). The typical changes of appearance were demonstrated in Figure 1.

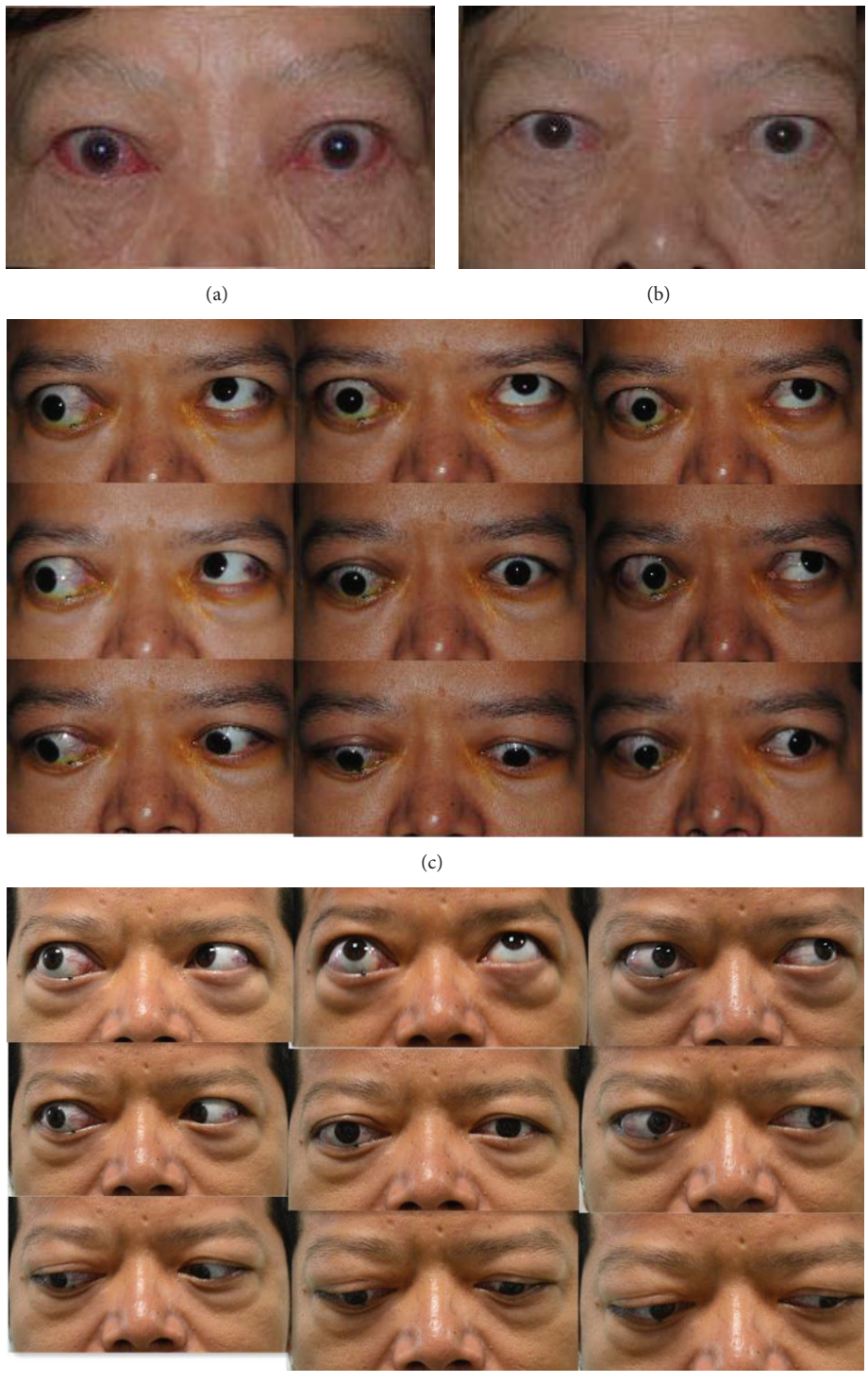
There were no differences measured throughout the study in any of the other parameters, including FT3, FT4, TSH, BCVA, corneal evaluation, and fundus examinations.

Table 1: Baseline characteristics of patients.

| Characteristic | |
|---|---|
| Demographic and clinical characteristics | |
| Age (yr) | 43.38 ± 11.82 |
| Gender (female) | 3 (23.1%) |
| Weight (kg) | 68.08 ± 12.87 |
| Smoking history | |
| Current smoker | 6 (46.2%) |
| Ex-smoker | 1 (7.6%) |
| Never-smoker | 6 (46.2%) |
| History of thyroid disease | |
| Graves' hyperthyroidism | 9 (69.2%) |
| Euthyroid Graves' disease | 4 (30.8%) |
| Others | 0 (0%) |
| Previous antithyroid treatments | |
| Antithyroid drugs | 5 (55.6%) |
| Radioiodine | 1 (11.1%) |
| Thyroidectomy | 3 (33.3%) |
| Duration of Graves' disease (months) | 15 (6–24) |
| Duration of Graves' orbitopathy (months) | 6 (3–12) |
| Duration of euthyroidism (months) | 3 (1.5–3.5) |
| Biochemical characteristics | |
| FT3 (pmol/L) | 5.02 (4.08–6.17) |
| FT4 (pmol/L) | 14.32 (12.56–15.80) |
| TSH (mU/L) | 0.54 (0.04–1.01) |
| Eye symptoms and signs | |
| Proptosis (mm) | 21.19 ± 1.95 |
| Eyelid aperture (mm) | 12.31 ± 2.32 |
| Soft tissue involvements | |
| Absent | 0 (0%) |
| Minimal | 4 (30.8%) |
| Moderate | 8 (61.5%) |
| Severe | 1 (7.7%) |
| Diplopia (Bahn and Gorman's score) | |
| Absent | 3 (23.1%) |
| Intermittent | 2 (15.4%) |
| Inconstant | 3 (23.1%) |
| Constant | 5 (38.4%) |
| Clinical Activity Score | 4 (3–5) |
| Ocular motility | |
| Elevation (degrees) | 22.53 ± 13.07 |
| Depression (degrees) | 45.85 ± 15.97 |
| Adduction (degrees) | 41.62 ± 7.79 |
| Abduction (degrees) | 37.31 ± 11.40 |

FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyrotropin.

*3.3. Adverse Events.* SD doxycycline was well tolerated. No patients discontinued the study due to drug-related adverse events. Two patients reported mild stomachache at 12 wk, which disappeared when the treatment ended. No instances of vaginitis or photosensitivity were reported. Both body weight and blood pressure remained stable during the trial.



(a) (b)

(c)

(d)

Figure 1: Representative example of patients status at baseline and at 24 wk after the start of treatment. (a) (baseline) and (b) (24 wk) showed that soft tissue involvements and redness of conjunctiva were remarkably improved in a female at 24 wk. (c) (baseline) and (d) (24 wk) showed the improvement of eyelid aperture, lid lag, and elevation in a male treated by doxycycline.

Table 2: Eye signs, Clinical Activity Score, and Graves' orbitopathy-specific quality of life (GO-QoL) score at baseline and at 12 and 24 wk evaluation.

| Variable | Baseline | Change at 12 wk | Change at 24 wk | $P$ value, trend over time/baseline versus 24 wk |
|---|---|---|---|---|
| Proptosis (mm) | 21.19 ± 1.95 | 0.04 (−0.6; 0.67) | −0.59 (−1.34; 0.16) | 0.26[a] |
| Improved (*n*, %) | | 2 (18.2%) | 2 (18.2%) | |
| Unchanged | | 11 (81.8%) | 11 (81.8%) | |
| Deteriorated | | 0 (0%) | 0 (0%) | |
| Eyelid aperture (mm) | 12.31 ± 2.32 | −0.15 (−1.07; 0.76) | −1 (−2.24; 0.24) | 0.13[a] |
| Improved (*n*, %) | | 2 (15.4%) | 6 (46.2%) | |
| Unchanged | | 9 (69.2%) | 5 (38.5%) | |
| Deteriorated | | 2 (15.4%) | 2 (15.4%) | |
| Lid lag (mm) | 1.62 ± 1.94 | −0.54 (−1.54; 0.47) | −2.55 (−4.06; −1.03) | 0.008[a] |
| Improved (*n*, %) | | 5 (38.5%) | 7 (53.8%) | |
| Unchanged | | 6 (46.2%) | 5 (38.5%) | |
| Deteriorated | | 2 (15.4%) | 1 (7.7%) | |
| Clinical Activity Score | 4 (3–5) | −1.07 ± 0.95 | −1.82 ± 0.87 | <0.0001[b] |
| Improved | | 4 (30.8%) | 8 (61.5%) | |
| Unchanged | | 9 (69.2%) | 5 (38.5%) | |
| Deteriorated | | 0 (0%) | 0 (0%) | |
| Soft tissue signs (*n*, %) | | | | 0.044[c] |
| Absent | 0 (0%) | | 7 (53.8%) | |
| Minimal | 4 (30.8%) | | 2 (15.4%) | |
| Moderate | 8 (61.5%) | | 2 (15.4%) | |
| Severe | 1 (7.7%) | | 2 (15.4%) | |
| Diplopia (*n*, %) | | | | 0.614[c] |
| Absent | 3 (23.1%) | | 5 (38.5%) | |
| Intermittent | 2 (15.4%) | | 2 (15.4%) | |
| Inconstant | 3 (23.1%) | | 1 (7.7%) | |
| Constant | 5 (38.4%) | | 5 (38.5%) | |
| Ocular motility | | | | |
| Elevation (degrees) | 22.54 ± 13.07 | 0.69 (−1.06; 2.44) | 4 (0.48; 7.52) | 0.0496[a] |
| Depression (degrees) | 45.85 ± 15.97 | −0.38 (−2.95; 2.19) | −1.91 (−5.97; 2.15) | 0.35[a] |
| Adduction (degrees) | 41.62 ± 7.79 | −1.64 (−4.10; 0.83) | −0.09 (−3.25; 3.07) | 0.78[a] |
| Abduction (degrees) | 37.31 ± 11.40 | −1.00 (−4.17; 2.17) | −1.91 (−3.87; 0.05) | 0.14[a] |
| GO-QoL score | | | | |
| Visual functioning score | 61.99 ± 25.9 | 3.03 (−8.01; 14.07) | 9.65 (−0.28; 19.57) | 0.21[a] |
| Appearance score | 46.17 ± 20.97 | 18.28 (7.77; 28.79) | 21.59 (5.83; 37.35) | 0.008[a] |

[a]These parameters were expressed on a continuous scale, and repeated-measures regression model was used to evaluate the 24 wk trend over time.
[b]This parameter was presented as median (25th to 75th percentiles), and a nonparametric approach (Jonckheere-Terpstra test) was adopted to assess the 24 wk trend over time.
[c]These parameters were presented as numbers, and Mann-Whitney $U$ test was employed to compare the difference between baseline and 24 wk.

## 4. Discussion

This study is the first trial to evaluate the efficacy of SD doxycycline for patients with moderate-to-severe and active GO. An anti-inflammatory dose doxycycline (administered once daily (50 mg) for a duration of 12 wk) appeared to be effective and safe for the treatment of moderate-to-severe and active GO.

The success rate of those treated by SD doxycycline was 61.5% at the end of the trial. This was comparable to those treated by oral GCs (51–63%) or radiotherapy (60%) but lower than those treated by i.v. GCs (77–83%) [7, 8, 27]. Although i.v. GCs treatment yielded a greater efficacy, it was associated with severe adverse events, mostly consisting of fatal acute liver failure and cardiovascular events. In this study, the adverse events in those treated by doxycycline were mild and

the rate (15%) was significantly lower than those treated by i.v. GCs (39%) or oral GCs (81%) [8].

It is worth noting that the proportion of patients with euthyroid Graves' disease is much higher (4/13, 30.8%) compared to data in the literature (19/221, 8.6%) [28]. Although no clear explanation can be offered for this finding, one possibility could be related to the sex distribution of patients. A study by Marcocci et al. found that patients with euthyroid Graves' disease had a F/M ratio of 0.7, whereas ophthalmopathy associated with hyperthyroidism was significantly more frequent in females, with a F/M ratio of 2.1 [28]. This indicates a higher prevalence of euthyroid Graves' disease in males. We therefore consider that the high proportion of patients with euthyroid Graves' disease in our collective may be explained by the high proportion of male patients recruited. It is unusual that the majority of our patients are males (76.9%). This is possibly due to the small number of eligible subjects recruited, since more female patients had been referred for screening. On the other hand, it confirms previous work that male subjects show severe forms of GO [29, 30]. Reportedly, female subjects respond better to anti-inflammatory therapy [29, 30]. Therefore, it stands as a chance that this study may be underpowered to detect the efficacy of doxycycline in treating GO.

Soft tissue swelling and, particularly, CAS ameliorated significantly at the end of the trial. 61.5% of patients showed an improvement of soft tissue swelling and a decrease of CAS by at least two points at 24 wk. The beneficial effect of SD doxycycline on soft tissue swelling is similar to that on those treated by GCs [7]. Moreover, nine out of 13 patients reported that the spontaneous orbital pain (one point in the CAS) diminished at the visit of 4 wk. These effects may be explained by the rapid anti-inflammatory potential of SD doxycycline. The rapid effect has also been found for rosacea, in which SD doxycycline exerted a significant reduction of inflammatory lesions within the first 3 weeks of therapy [13].

We also assessed several quantitative ocular parameters, including proptosis, eyelid aperture, and lid lag. Although proptosis showed minor change, both lid aperture and lid lag had substantial improvement. In particular, lid lag decreased remarkably in 53.8% of patients by at least 2 mm at the end of the trial. Muller's muscle hyperactivity was previously considered to account for lid abnormality, on the basis of excessive sympathetic activity of thyroid hormones [31]. Recently, Shih and his coworkers found a positive correlation between macrophage count in the Muller's muscle and severity of upper lid retraction [32]. And they concluded that the degree of inflammatory cells infiltration of Muller's muscle is associated with clinical severity of upper eyelid retraction in GO. In the current study, all patients were euthyroid, and improvement of CAS and eyelid swelling was also observed in patients with a decrease of lid lag. We suggest that the improvement of eyelid aperture and lid lag may be associated with the amelioration of orbital inflammation by doxycycline.

Additionally, we found that doxycycline demonstrated an effect in improving eye motility (5/13, 38.5%) by ≥8 degrees, but insufficiently to influence the subjective diplopia score (3/13. 23.1%). The efficacy observed in our study (38.5%) is similar to those treated by oral GCs (42%) but weaker than those treated by orbital radiotherapy (60%) [7]. The rationale for radiotherapy in significantly improving motility resides in both its nonspecific anti-inflammatory effects and inhibiting orbital fibroblasts producing glycosaminoglycans, both of which are the main actors in extraocular muscle dysfunction [33]. Considering that SD doxycycline only possesses anti-inflammatory activity, it is reasonable that the effect of doxycycline in improving motility is lower than radiotherapy.

In this study, SD doxycycline also exerted a favorable effect in improving quality of life, as assessed by the GO-QoL questionnaire. The improvement was evident in the appearance subscale but less obvious in the visual functioning subscale. This may be attributed to the amelioration of soft tissue swelling and decreased lid fissure, which reflect the changes of appearance. In contrast, visual acuity remained stable during the trial, and improved diplopia was only reported in 23.1% of patients. These two factors dominantly contribute to the visual function. Hence, it is reasonable that the visual functioning subscale was less affected.

Of note, adverse events associated with SD doxycycline are rare. Only two patients reported mild stomachache at 12 wk, not requiring additional medication. No patient complained about photosensitivity or vaginitis. These findings are in line with previous studies for patients with rosacea and periodontitis [34, 35]. By extensive investigations of the oral, gastrointestinal, genitourinary, and skin microflora of patients receiving SD doxycycline for 6 to 18 months, no reduction in the microflora was observed, and no development of resistant organisms was found [36, 37]. Unlike GCs, which frequently lead to weight gain and hypertension, SD doxycycline did not impact weight and blood pressure. Taken together, the minor side effect of SD doxycycline highlights its good tolerability in long-term usage. According to previous studies, the most common dose of subantimicrobial doxycycline used as anti-inflammatory agent is 40 mg (20 mg per tablet) [38]. Since the formulation of 20 mg for doxycycline is unavailable in China, we adopted the common formulation of 50 mg, administered once daily. The long half-life of doxycycline permits once-daily dosing. Still, it turned out that the side effects were minor.

We must acknowledge that this study bears the limitation of being an uncontrolled trial. To minimize the bias, a senior ophthalmologist, who was masked to patients data, performed the examination throughout the study. Considering that the clinical assessments and outcome measurements were objective and were largely consistent with those introduced by prior studies [5, 25, 27], we think the findings are representative. A multicenter, double-blind, randomized, and controlled trial (doxycycline versus GCs) is urgently needed to confirm its effect. Such kind of study is in progress in China, led by our group.

## 5. Conclusion

Subantimicrobial dose doxycycline appears to be effective and safe in treating active Graves' orbitopathy. This finding may suggest a new promising therapeutic agent for active GO.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Authors' Contribution

Miaoli Lin and Yuxiang Mao contributed equally to the paper.

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*Clinical Study*

# Results after En Bloc Lateral Wall Decompression Surgery with Orbital Fat Resection in 111 Patients with Graves' Orbitopathy

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*Purpose*. To evaluate the effect of en bloc lateral wall decompression with additional orbital fat resection in terms of exophthalmos reduction and complications. *Methods*. A retrospective, noncomparative case series study from 1999 to 2011 (chart review) in Graves' orbitopathy (GO) patients. The standardized surgical technique involved removal of the lateral orbital wall including the orbital rim via a lid crease approach combined with additional orbital fat resection. Exophthalmos, diplopia, retrobulbar pressure sensation, and complications were analyzed pre- and postoperatively. *Results*. A total of 111 patients (164 orbits) with follow-up >3 months were analysed. Mean exophthalmos reduction was 3.05mm and preoperative orbital pressure sensation resolved or improved in all patients. Visual acuity improved significantly in patients undergoing surgery for rehabilitative or vision threatening purposes. Preoperative diplopia improved in 10 patients (9.0%) but worsened in 5 patients (4.5%), necessitating surgical correction in 3 patients. There were no significant complications; however, one patient had slight hollowing of the temporalis muscle around the scar that did not necessitate revision, and another patient with a circumscribed retraction of the scar itself underwent surgical correction. *Conclusions*. The study confirms the efficiency of en bloc lateral wall decompression in GO in a large series of patients, highlighting the low risk of disturbance of binocular functions and of cosmetic blemish in the temporal midface region.

## 1. Introduction

Orbital decompression surgery in Graves' orbitopathy (GO) represents an established treatment for rehabilitative exophthalmos reduction and for restoration of visual function in dysthyroid optic neuropathy (DON). A vast number of surgical techniques with regard to orbital decompression are described in the literature. Each orbital surgeon usually favors a particular technique either tailored to the individual patient's needs or the surgeon's preference. The problem in comparing different techniques for orbital decompression is the lack of randomized controlled trials (RCTs). Boboridis and Bunce [1] systematically reviewed the data from all RCTs addressing the issue of orbital decompression surgery. After searching electronic databases, oculoplastic surgery textbooks, conference proceedings, and personal communications from researchers, they found just one RCT comparing different decompression techniques [2] and a second trial comparing medical versus surgical decompression [3]. Furthermore, analysis of data after decompression surgery or comparison of results from different studies is often hampered by the pool of patients, which is highly heterogeneous in terms of both preoperative clinical characteristics and methodological backgrounds and outcome measures.

Hence, our knowledge concerning surgical treatment of disfiguring exophthalmos or compressive neuropathy in GO patients frequently derives from case series involving small patient numbers. Overall there seems to be a trend in favor of lateral wall decompression surgery, as advocated by different authors with excellent track record [4–8]. This technique, in which the rim of the orbital wall is usually preserved or repositioned at the end of surgery, offers the advantage of effective decompression of the orbit combined with a low complication rate. For more than 15 years we successfully used a modified technique with en bloc resection of the lateral wall, including removal of the orbital rim, in order to better

visualize the deep lateral orbit and therefore facilitate deep resection towards the greater wing of the sphenoid. The aim of the present study was to evaluate outcomes with this en bloc technique in our patients over a 12-year period.

## 2. Methods

A retrospective case record analysis of GO patients after complete (en bloc) resection of the lateral orbital wall, including the lateral rim, with additional orbital fat resection was performed. The study was approved by the Ethics Committee of the Medical Faculty of the University of Rostock and all investigations were performed according to the current version of the Helsinki Declaration.

*2.1. Patients.* During the period from June 1999 to June 2011 a single surgeon (RFG) performed a total of 201 lateral wall decompression procedures in 130 patients with GO. Patients with a minimum follow-up of 3 months were considered eligible for analysis, and the charts of 111 patients (87 females, 24 males; 164 orbits) were reviewed in detail. The indication for surgery was disfiguring exophthalmos with or without retrobulbar pressure sensation in inactive eye disease in 146 orbits. An additional subset of 18 orbits was found to have mild DON. In 53 patients in whom bilateral decompression was planned, surgery was usually performed in a two-step procedure with a minimum interval of 4 weeks between the two surgical sessions. The mean age of the patients at the time of surgery was 48.8 ± 11.7 years (range: 24–76 years).

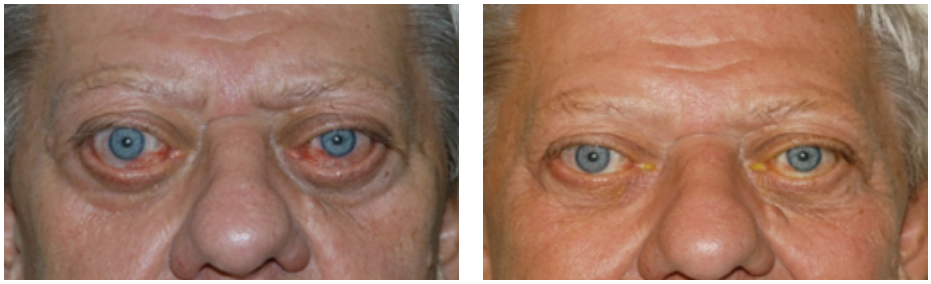
Patients who had a surgical orbital intervention before the first consultation were not included in the study. One patient who needed a further medial wall decompression 4 weeks after lateral wall decompression and therefore within the defined follow-up of at least 3 months was not excluded from the study because this shows the importance of a careful and critical preselection of the patients. In this case the endpoint was before the second intervention.

*2.2. Pre- and Postoperative Measurements.* The results of clinical examination before and after surgery concerning visual acuity, exophthalmometer readings, diplopia (Gorman score), and retrobulbar pressure sensation were extracted from the case records. The last follow-up was either the last consultation in our clinic in those patients without further surgical interventions or the last consultation before the next surgical step in rehabilitative surgery (e.g., extraocular muscle surgery or lid surgery).

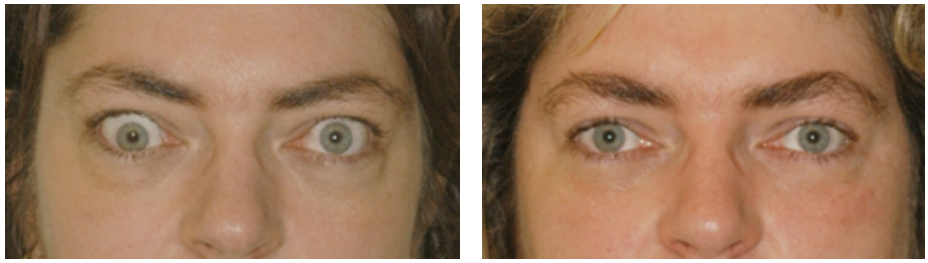
Conventional lateral rim-supported Hertel exophthalmometers were not suitable for postoperative exophthalmos assessment because our surgical technique involves complete en bloc resection of the lateral orbital wall, including the orbital rim. Therefore we used the superior and inferior orbital rim-based exophthalmometers developed by Naugle Jr. and Couvillion [9] and the measurements were done by multiple examiners. A comparative study by Cole III et al. [10] has concluded that accuracy was comparable for the Naugle and Hertel instruments, justifying our use of the Naugle exophthalmometer for pre- and postoperative measurements. Extraocular muscle involvement was assessed using the Gorman score for classification of diplopia: 1 = no diplopia, 2 = intermittent diplopia (when tired), 3 = inconstant diplopia (depending on direction of gaze), and 4 = constant diplopia in primary or reading position (with or without prism). Information concerning the presence of retrobulbar pressure sensation before and after surgery was also reviewed and documented in a qualitative manner (yes/no). We diagnosed DON if two or more of the following features were present: visual acuity less than 6/6 (decimals), visual field defects in the automated visual field analyser (Humphrey 24-2), impaired color vision (Lanthony panel-D15: >2 minor errors or >1 major error), pathologic visual evoked responses with a prolongation of latency and/or reduction of amplitude, presence of a relative afferent pupillary defect (RAPD), presence of optic disc swelling, or apical crowding in orbital imaging. Patients were led to orbital decompression surgery if there was no adequate response to the medical pretreatment with systemic steroids or steroids were contraindicated. Reported complications and subsequent need for further (rehabilitative) surgical interventions were analyzed in detail.

*2.3. Surgical Technique.* Surgery was performed under general anesthesia and started with an upper eyelid crease incision in the lateral third of the upper lid crease that was extended down to the zygomatic bone about 2 cm lateral to the orbital rim and blunt exposure of the lateral orbital rim. The temporalis muscle was carefully detached from the temporal surface of the lateral orbital wall, followed by incision of the periosteum along the lateral orbital rim. After preparation of the lateral orbital wall with the periosteal elevator the superior osteotomy was marked above the frontozygomatic suture, and the inferior osteotomy was marked just above the zygomatic arch. The osteotomies were performed with an oscillating saw and the fragment of the lateral orbital wall was outfractured using a hammer and osteotome. The amount of bone resection was increased towards the height of the greater wing of the sphenoid using the bone nibbler and burr down to the level of bone marrow. The landmark for the lower border of resection was the inferior orbital fissure. During this procedure the globe and its soft-tissue contents were protected and carefully pulled nasally with malleable retractors. After removing the deep parts of the lateral wall the periorbit was opened superiorly and inferiorly to the lateral rectus muscle and carefully excised. This procedure is usually accompanied by a variable degree of orbital fat prolapse, which is resected mainly from the inferolateral orbit. Additional fat prolapse can be achieved with only minimal risk of orbital bleeding by exerting slight axial pressure on the globe. The amount of fat resection in our series was 2.0 ± 1.0 mL.

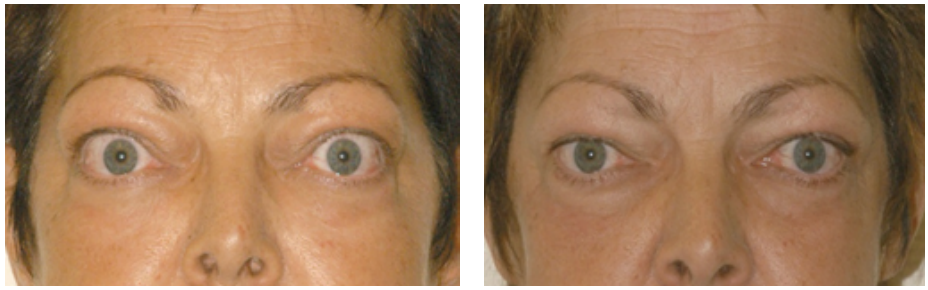
Finally a suction drainage system was placed into the fossa temporalis and the wound incision was accurately closed in layers. A temporary compression bandage was used for the first 24 hours in order to maintain axial retropositioning of the globe in the newly created space. This required frequent checks of visual functions and pupillary reflexes. The volume of blood in the suction balloon was monitored every 6 hours in order to be aware of possible postoperative orbital bleeding.



(a) Exophthalmos reduction (5 mm right eye, 4 mm left eye)



(b) Exophthalmos reduction (3 mm right eye, 4 mm left eye)



(c) Exophthalmos reduction (4 mm right eye, 3 mm left eye)

Figure 1: Exemplary cases after bilateral orbital decompression: (a) 69-year-old male patient before and 6 months after surgery. (b) 35-year-old female patient before and 2 years after additional squint surgery. (c) 55-year-old female patient before and 6 months after surgery.

*2.4. Statistical Analysis.* Spearman's rho coefficient was calculated for nonparametric correlations, and $P$ values were analyzed using the Wilcoxon nonparametric test. $P$ values $< 0.05$ were accepted as statistically significant, with $P < 0.01$ being regarded as highly significant. Calculations were done using SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA).

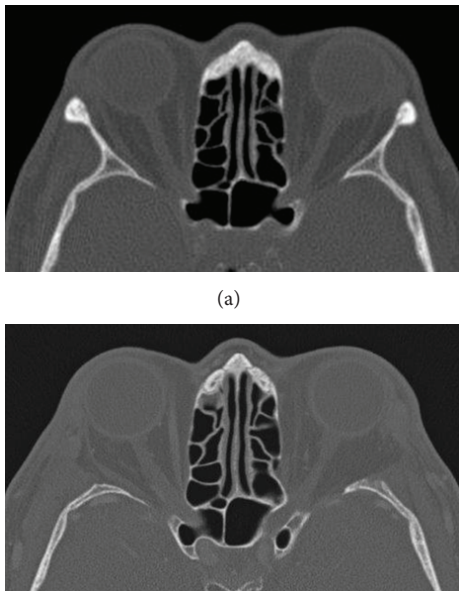
## 3. Results

Mean follow-up was 16.4 ± 20.4 months (range: 3 months to 10.5 years; median: 8 months).

*3.1. Exophthalmos.* Mean exophthalmos improved significantly from 21.40 ± 2.3 mm preoperatively to 18.32 ± 2.6 mm postoperatively ($P < 0.001$), resulting in a mean exophthalmos reduction of 3.05 ± 1.45 mm. A moderate correlation was noted between exophthalmos reduction and preoperative exophthalmos. The greater the degree of exophthalmos before surgery, the greater the reduction achieved ($r = 0.431$; $P < 0.001$). For some exemplary pre/postoperative photographs and axial CT scans see Figures 1 and 2.

*3.2. Visual Acuity.* Mean visual acuity (VA) in patients being operated for rehabilitative purposes was 0.91 ± 0.22 preoperatively, increasing to 0.93 ± 0.23 postoperatively ($P = 0.03$). Those patients undergoing surgery because of suspected mild DON initially presented with a mean VA of 0.73 ± 0.21 that increased significantly to 0.83 ± 0.22 ($P = 0.02$) after decompression surgery. Interestingly, the increase was significantly greater in patients with preoperative signs of DON compared to patients without preoperative suspicion of DON ($P = 0.015$).

The DON group included one 52-year-old euthyroid female smoker with inadequate recovery and slowly progressing visual impairment postoperatively, necessitating an additional medial wall decompression. Furthermore one female nonsmoking, euthyroid patient who was treated before for DON on the contralateral eye had no clinical evidence of DON at the time of surgery. She required an additional medial wall decompression 4 weeks after lateral wall decompression because of new-onset visual loss, visual field defects, and prolonged latency in visual evoked responses due to a compressive optic neuropathy with increased extraocular muscle volume. The patient received intravenous high-dose



(a)

(b)

Figure 2: Preoperative (a) and postoperative (b) axial CT scan of the orbit. Note the missing lateral orbital wall after bony decompression without repositioning of the orbital rim.

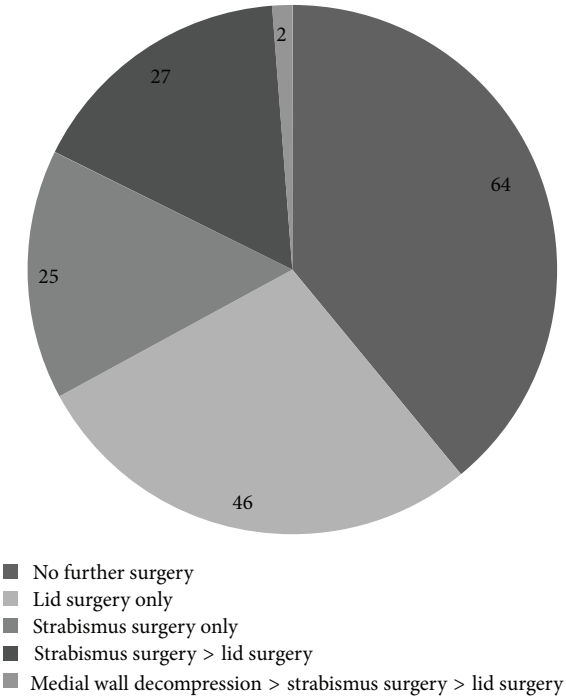



Figure 3: Additional surgical interventions. One or more additional surgical interventions were required in fewer than two-thirds of the orbits after lateral wall decompression. Strabismus surgery was performed in 54 orbits (32.9%) of 43 patients, lid surgery in 75 orbits (45.7%) of 59 patients, and additional medial wall decompression in 2 orbits (1.2%) of two patients.

steroids and immediately underwent additional medial wall decompression. Both patients showed a rapid restoration of visual acuity within one week after additional endonasal medial wall decompression surgery.

*3.3. Retrobulbar Pressure Sensation.* A disturbing retrobulbar pressure sensation was reported in 98 out of 164 orbits preoperatively; for 9 orbits the chart records contained no information concerning this symptom. Postoperatively, retrobulbar pressure sensation was reported to be completely resolved in 71 orbits and markedly improved in 3 orbits. No information on this aspect was found in the chart records for 24 orbits.

*3.4. Strabismus.* Preoperatively about one-third of our patients presented without diplopia (Gorman score: 1). Postoperatively, overall distribution within the four Gorman categories showed a slight improvement, that is, a shift to a lower Gorman score, although not statistically significant (Table 1).

Postoperatively, unchanged Gorman scores were observed in 88 patients (87.1%, 135 orbits), diplopia improved in 10 patients (9.0%, 14 orbits), but new-onset diplopia was also noted in 5 patients (4.5%, 6 orbits) (Tables 2(a) and 2(b)). Detailed analysis of patients with an improved diplopia score revealed that preexisting vertical squint improved in 5 of the 10 patients and horizontal squint improved in 3 patients, while 2 patients improved in the sense of resolved intermittent diplopia.

One patient (listed as number 4 in Table 2(b)) moved from "no diplopia" to "inconstant diplopia" 2 months after surgery because of impaired elevation presented with signs of recurrent GO activity in conjunction with recurrent hyperthyroid function and a persisting smoking habit. While worsening of extraocular muscle function was probably not the result of decompression surgery, correction was subsequently done by inferior rectus recession. Two other patients showed deterioration of vertical motility. One patient had a satisfactory field of binocular single vision without impairment of routine daily activities and did not require any further treatment. The deterioration in the second patient who moved from Gorman 1 to Gorman 4 could not be accounted for from the chart record (no intraoperative anomalies; inactive eye disease 5 years after orbital irradiation prior to surgery). After inferior muscle recession a satisfactory field of binocular single vision was obtained.

Worsening of horizontal motility occurred in two patients (adduction in one patient and abduction in the other) with diplopia at the extremes of lateral gaze. The patient with worsened adduction required surgical correction in order to increase the field of binocular single vision. Altogether 5 out of 111 patients (4.5%) showed worsening of extraocular muscle motility presumably due to lateral wall decompression; surgical correction was required in 3 of these patients (2.7%), resulting in a favorable outcome in all of them.

None of the DON patients showed either worsening or improvement of diplopia score.

*3.5. Additional Surgical Interventions.* No further surgical intervention was needed in 64 of the 164 orbits. The remaining 100 orbits (60.9%) required one or more additional surgical procedures (Figure 3). In detail, lid surgery included

Table 1: Pre- and postoperative results of diplopia analysis (Gorman score (GS): 1–4). In patients undergoing bilateral decompression surgery postoperative analysis after the first surgical intervention was performed before surgery on the fellow eye.

| | GS 1 (no diplopia) | GS 2 (intermittent, diplopia when tired) | GS 3 (inconstant, gaze-dependent diplopia) | GS 4 (constant, diplopia in primary or reading position) |
|---|---|---|---|---|
| Preoperative (total of 158 orbits) | 58 (37.4%) | 10 | 55 | 35 |
| Postoperative (total of 155 orbits) | 61 (39.4%) | 9 | 51 | 34 |

Table 2: (a) Detailed characteristics of patients whose Gorman score improved after decompression surgery. In patients who underwent bilateral orbital decompression "a" refers to the right orbit and "b" to the left orbit. (b) Detailed characteristics of patients whose Gorman score worsened after decompression surgery. Three patients experienced worsening of elevation and two patients had deteriorations in horizontal motility. In patients who underwent bilateral orbital decompression "a" refers to the right orbit and "b" to the left orbit.

(a)

| Patient number | Gorman score before surgery | Gorman score after surgery | Subsequent strabismus surgery |
|---|---|---|---|
| 1a | 3 | 1 | None |
| 1b | 3 | 1 | None |
| 2a | 3 | 1 | None |
| 2b | 3 | 1 | None |
| 3 | 2 | 1 | None |
| 4a | 3 | 2 | None, only rare intermittent diplopia |
| 4b | 3 | 2 | None, only rare intermittent diplopia |
| 5a | 4 | 3 | None, satisfactory field of binocular single vision after surgery of left eye |
| 5b | 4 | 3 | Inferior/internal rectus recession |
| 6 | 2 | 1 | None |
| 7 | 3 | 1 | None |
| 8 | 3 | 1 | None |
| 9 | 3 | 2 | None, only rare intermittent diplopia |
| 10 | 3 | 1 | None |

(b)

| Patient number | Gorman score before surgery | Gorman score after surgery | Subsequent strabismus surgery |
|---|---|---|---|
| 1 | 1 | 3 | None |
| 2 | 1 | 4 | Inferior muscle recession |
| 3a | 1 | 3 | Faden procedure (lateral rectus muscle) |
| 3b | 1 | 3 | Faden procedure (lateral rectus muscle) |
| 4 | 1 | 3, probably not due to surgery | Inferior muscle recession |
| 5 | 1 | 3 | None |

58 upper lid lengthening procedures, 16 lower lid lengthening procedures, 10 upper/lower lid blepharoplasties, 4 lateral tarsal sling procedures, 3 lateral tarsorrhaphies, 1 ptosis repair, and 4 wound revisions. Some of the interventions were performed during the same surgical session. Strabismus surgery included 62 rectus muscle recessions (inferior 33, medial 23, lateral 5, and superior 1), 3 Faden procedures (lateral rectus muscle), 1 lateral rectus resection, and 1 inferior oblique muscle recession. Again, some of the procedures were done during the same surgical session.

Further decompression surgery with additional removal of the medial orbital wall was required in two orbits, as mentioned previously.

*3.6. Complications.* Complications concerning extraocular muscle motility and visual acuity are mentioned in the preceding section. Further complications related to wound healing, scar formation, infection, hyperesthesia, and oscillopsia.

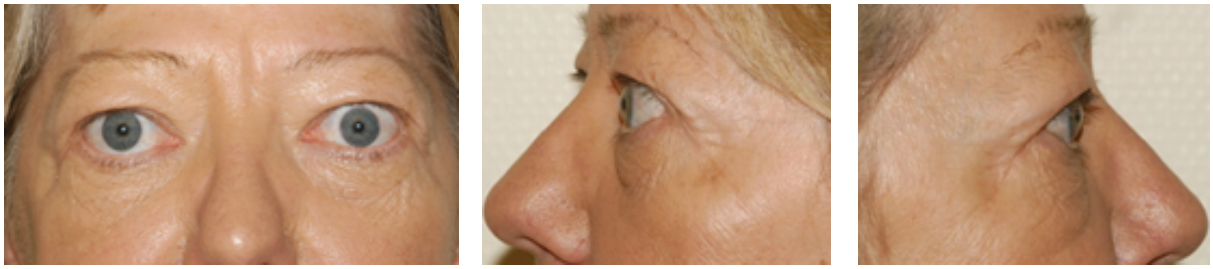


Figure 4: Postoperative hollowing of the temporal fossa region around the scar without any need for treatment (6 months postop).

Table 3: Complications after lateral wall decompression surgery in 164 orbits.

| Complication | Number of patients/orbits | Treatment |
|---|---|---|
| Local hyperesthesia | 5 patients, 6 orbits | Revision in 1 patient (1 orbit) → resolved |
| Wound infection | 1 patient, 1 orbit | Revision |
| Oscillopsia | 1 patient, 1 orbit | No intervention required |
| Sicca | 1 patient, 1 orbit | Lubricants |
| Visible/subjectively bothersome scar formation | 4 patients, 6 orbits | Revision in 1 patient (1 orbit) |
| Temporal hollowing | 1 patient, 2 orbits | No intervention |
| Early postoperative orbital bleeding | 1 patient, 1 orbit | Immediate revision/hemostasis |

Visible scar formation manifesting as a retracted scar necessitated revision in one patient. Furthermore one female patient undergoing bilateral decompression experienced a slight hollowing of the temporal fossa region that did not require any further intervention (Figure 4). Oscillopsia when chewing was noticed by one patient but did not affect her related quality of life. Expulsive orbital bleeding shortly after wound closure occurred in one patient; immediate revision with hemostasis led to complete restitution without any functional deficits. An overview of these cases is presented in Table 3.

## 4. Discussion

To our knowledge this study represents the largest retrospective case series after en bloc resection of the lateral orbital wall in conjunction with orbital fat resection. The first results regarding this technique were published in 1966 by Long and Ellis [11] who described a series of 45 decompression procedures. In 1989 Leone Jr. et al. [12] combined this technique with an additional medial wall decompression using Sewall's external approach. In 1991 Matton [13] presented data on 56 decompression procedures in 29 patients following en bloc resection of the lateral wall and lateral floor. Exophthalmos improved in all patients, complications encompassed postoperative bleeding and hypesthesia of the infraorbital nerve, and there was no flattening of the malar contour. Most recently, describing their results after two-wall inferolateral decompression in 44 patients, Schaaf et al. [14] reported an average exophthalmos reduction of 3.8 mm, with one patient developing new-onset diplopia after surgery that required surgical correction.

In the present study we found an average exophthalmos reduction of 3.05 mm, ranging up to 7 mm, after en bloc lateral wall decompression with orbital fat resection. These results are in accordance with our data in an earlier and smaller patient series [15]. Either data do not clarify the extent to which orbital fat resection contributed to exophthalmos reduction, but a review of the literature suggests an additional effect on proptosis reduction to be assumed [16–18]. To achieve this goal our practise is to resect a moderate amount of intraconal fat mainly from the inferolateral orbit as this location is associated with the lowest risk of injury to vulnerable orbital structures [19, 20]. Mourits et al. from the EUGOGO Working Group found a mean exophthalmos reduction after two-wall decompression of 4.3 mm independent of the surgical approach [16]. Thus, exophthalmos reduction after single wall decompression combined with moderate orbital fat resection appears to be slightly less effective than a two-wall decompression technique. However, Ünal et al. [18] postulated that orbital fat resection allows an additional wall to be spared from decompression, thereby reducing the risk of postoperative diplopia. These findings underline the ongoing controversy concerning the role of orbital fat resection in orbital decompression surgery. Additional factors potentially influencing the amount of orbital volume expansion relate to the anatomical variability of the bony orbit [21], variations in the fat-to-muscle volume ratio, the elastic capacity/amount of fibrosis of the orbital contents that determines the ability to fill the newly created space, the orbital opening angle between medial and lateral walls, and the axial lengths of orbit and globe and their relation to each other [22, 23]. Interestingly, orbital irradiation has been shown not to influence the outcome after orbital decompression surgery [24]. But from our personal experience and considering the pathophysiological processes and morphological changes of the orbital soft tissues after irradiation, these results need to be clarified by further studies.

In our study lateral wall decompression surgery produced significant improvement in visual functions in patients with and without DON. The results showed a significantly greater improvement of visual acuity in DON patients compared to patients without preoperative signs of compressive neuropathy, showing that lateral wall decompression can be a sufficient treatment in selected patients with DON. We presume that the improvement of visual functioning in these patients was probably due to a relief of orbital pressure in the sense of an orbital compartment syndrome [25], and in patients without DON this presumably reflected an improvement in ocular surface conditions. Only one of the DON patients (1/18 orbits) was not sufficiently cured and needed further medial wall decompression. This patient was a severe smoker who showed recurrent inflammatory signs in repeated orbital imaging but again without compression of the nerve in the deep orbital apex. Goldberg et al. published their results after decompression of the deep lateral orbit and recommend this technique also for use in DON, but not for cases in the acute inflammatory stage where they advocate additional apical decompression of the medial orbital wall [5]. One comparative study found no difference between lateral and medial walls' decompression in terms of efficacy in treating DON, although lateral wall decompression resulted in greater exophthalmos reduction [26]. Our approach to orbital decompression in DON is to restrict lateral wall decompression to cases with mild DON without signs of optic nerve compression in the deep orbital apex. In patients with a crowded orbital apex we prefer a combined lateral and (endonasal) medial wall decompression to sufficiently decompress the optic nerve and to restore visual functions.

In the present study about one-third of our patients were preoperatively unaffected by diplopia in their routine daily activities and this number did not change significantly after surgery. Detailed scrutiny of the data revealed that some patients (9%) had an improved Gorman score, while a smaller number (4.5%) became worse. The latter underwent surgery between 2003 and 2008, indicating that this complication was probably not related to the surgeon's experience. Interestingly, none of the DON patients showed worsening of preexisting diplopia or new-onset diplopia after surgery. The fact that vertical deviation was equally affected as horizontal deviation indicates that the underlying mechanism relates more to the vulnerability of extraocular muscle balance than possible direct damage to the lateral rectus muscle itself. In line with our findings and using the same surgical technique, Schaaf et al. found an improvement in preexisting strabismus in 14% of their patients and new-onset diplopia in 4.7% (one out of 21 patients) [14]. They found a slight worsening of eye motility on average by 2.4° on upgaze and 0.5° on lateral gaze. Though the authors give no detailed information about the orthoptic assessment these postoperative changes in eye motility do not seem to influence binocular functions and therefore do not seem to influence the patients' quality of life. Further investigations are required to clarify the causative mechanism underlying that observation. Nevertheless, the reported incidence rates of induced diplopia or worsening of motility after different other than lateral wall approaches for orbital decompression are generally higher than those with our technique. A literature review reveals worsening of binocular functions in 16–74% after inferomedial decompression [27, 28], in up to 45% after balanced decompression [5, 29], in 2.6–8% after rim-sparing (deep) lateral wall decompression [5, 30, 31], and in 0–5% after en blocresection of the lateral wall [13, 14].

These latter reports reflect our finding of a low risk for worsening or new-onset diplopia after lateral wall decompression.

Some authors have raised concerns about the potential creation of disfiguring hollowing of the temporal fossa after lateral wall decompression and about complications due to periorbital incisions (e.g., retracted scars or lid retraction) [32] or increased postoperative morbidity as a result of orbital rim removal [8]. Sasim et al. reported temporal bossing in 3 out of 46 patients after coronal 3-wall decompression involving a rim-sparing lateral wall resection that required surgical correction in one of the patients [33]. Bailey described temporalis muscle atrophy after lateral wall decompression via a swinging eyelid approach in 1 out of 55 patients though the lateral rim was repositioned at the end of surgery [34].

In our study one patient had slight hollowing of the temporalis region around the scar that did not require any intervention and was probably due to circumscribed atrophy of the temporalis muscle, such as is known also to occur with the above-mentioned procedures, where the lateral rim was preserved or reconstructed. Hence, the postoperative phenomenon of temporalis wasting does not seem to be caused by the removal of the lateral rim itself rather than by intraoperative temporalis muscle trauma or scarring of the periorbital incision, respectively. The same applies to our patient with a retracted scar and the lady who reported oscillopsia when chewing; both phenomena were probably caused by deep cicatricial adhesions. While the circumscribed retraction of the scar was sufficiently treated by scar revision, mild oscillopsia when chewing remained until the last follow-up at 1 year after surgery but did not affect the patients quality of life. This coincides with a recently published retrospective study which showed the incidence of postoperative oscillopsia after rim-sparing lateral wall decompression to be surprisingly high (35%), but showed it to resolve or improve spontaneously in all but one out of 34 affected patients within 2 years [35].

In summary, these fortunately rare observations underline the importance of an appropriate surgical technique when detaching the temporalis muscle and of a precisely layered wound closure. In addition to our observations in this retrospective study on postoperative temporalis fossa appearance we found no significant influence of the lateral rim removal technique on canthus formation and stability in a prospective study published recently [36]. Furthermore none of the patients ever reported any kind of eye injury after orbital trauma though this could be possible in theory considering the surgical technique removing the lateral orbital rim.

One way to completely avoid these potential problems would be to perform a lateral wall decompression ab interno [31], though this is offset according to some authors by the disadvantage of a more difficult access to the deep lateral orbit with a higher risk for severe complications like CSF leaks and

lesser exophthalmos reduction [8, 37, 38]. On the other hand, Rocchi et al. from the Sellari-Franceschini working group [39] who published their results after rim-sparing lateral wall decompression via the internal approach found comparable results for exophthalmos reduction with a negligible risk for new-onset diplopia in primary gaze if patients were free of diplopia preoperatively, while 26.1% of the patients with preoperative inconstant diplopia developed constant diplopia in primary gaze position.

In conclusion, en bloc resection of the lateral orbital wall offers the advantage of good visualization of the surgical field that facilitates resection of the deep lateral wall with a lower risk for severe complications like CSF leaks. Though the limitation of the study is its retrospective, noncontrolled, and noncomparative design the analysis of a huge number of patients supports the recent trend towards lateral wall decompression: the technique has proved to be effective and safe in terms of exophthalmos reduction, postoperative motility disturbances, overall morbidity, and lowest incidence of induced diplopia compared with other orbital decompression techniques. In our opinion, repositioning of the orbital rim does not seem to be necessary with regard to scar retraction and circumscribed hollowing of the temporalis fossa. Concerning exophthalmos reduction Rocchi et al. found comparable results to our technique with a modified internal approach to the lateral orbital wall sparing the anterior orbital rim.

Lateral wall decompression with orbital fat resection is our preferred first choice in patients without disturbance of binocular functions and where moderate exophthalmos reduction is required. Additional medial wall decompression is reserved for patients in whom a lateral wall decompression with or without fat resection might not be sufficient, that is, patients with thickening of the extraocular muscles predominantly in the orbital apex that places the patient at risk to optic nerve compression or in patients where more than 3 mm exophthalmos reduction is needed. The surgical approach therefore has to be customized for each patient according to individual characteristics and the clinical situation.

It therefore seems reasonable to compare our technique with Stellaris' ab interno technique in randomized controlled trials.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Research Article*

# Thyroid Stimulating but Not Blocking Autoantibodies Are Highly Prevalent in Severe and Active Thyroid-Associated Orbitopathy: A Prospective Study

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The clinical utility of the functional TSH receptor autoantibodies was prospectively evaluated in patients with thyroid-associated orbitopathy (TAO). Ophthalmic, endocrine, and serological investigations were performed in 101 consecutive patients with severe and active TAO. Serum thyroid stimulating (TSAb) and blocking (TBAb) antibody levels were measured with two bioassays using cells that express a chimeric TSH receptor and CRE-dependent luciferase. TSAb results are expressed as percentage of specimen-to-reference ratio (SRR %). Blocking activity is defined as percent inhibition of luciferase expression relative to induction with bovine TSH alone. All 101 consecutively followed-up patients with severe and active TAO were TBAb negative. In contrast, 91 (90%) were TSAb positive of whom 90 had Graves' disease. Serum TSAb levels correlated with the diplopia score ($P = 0.016$), total severity eye score ($P = 0.009$), proptosis ($P = 0.007$), lid aperture ($P = 0.003$), upper lid retraction ($P = 0.006$), keratopathy ($P = 0.04$), and thyroid binding inhibiting immunoglobulins (TBII, $P < 0.001$) and negatively with the duration of TAO ($P = 0.002$). Median serum values of TSAb were SRR% 418 (range 28% to 795%). TSAb, not TBAb, are highly prevalent in severe/active TAO and serum TSAb levels correlate with clinical disease severity.

## 1. Introduction

Thyroid-associated orbitopathy (TAO) is mostly associated with Graves' hyperthyroidism [1]. Typical and frequently observed signs include eyelid retraction and exophthalmos [2]. The activity of TAO is generally determined by the clinical activity score (CAS) [3], consisting of seven different orbital signs and symptoms. For each positive variable one point is scored with a total sum of 7. Werner proposed the NOSPECS score for assessing disease severity, a score that was revised in 1977 [4]. A disease-specific quality of life questionnaire has been developed [5], which has shown that this disease reduces quality of life by negatively affecting perception of appearance and functionality [6]. The therapeutic options for TAO vary and should be determined individually for each patient, preferably in a multidisciplinary thyroid-eye clinic [7]. The pathogenesis of TAO is not yet fully elucidated but is most likely multifactorial involving an underlying series of autoimmune processes [8].

The presence of autoantibodies to the TSH receptor (TSH-R) is a parameter used for diagnosis of Graves' disease (GD). Functional TSH-R autoantibodies can be divided in either blocking (TBAb) [9] or stimulating (TSAb) antibodies. Both TSAb and the thyrotropin binding inhibitory immunoglobulins (TBII) reduce the rate of false anti-TSH-R negative patients with GD [10]. Furthermore, levels of TSAb discriminate between responders and nonresponders during antithyroid drug treatment [11]. The TSH-R is also expressed in the orbit and on the surface of the lacrimal cells [12, 13]. Ethnic background (Caucasians or Asians) may have an effect on the correlation of TSH-R antibodies with TAO [8, 14–17]. Previous studies have shown that TSAb influence the course of TAO [18, 19], but the role of TBAb is still a matter of debate due to scarce data.

Therefore, this prospective study aimed to evaluate the clinical relevance and diagnostic role of the functional (TSAb and TBAb) TSH-R autoantibodies in a large group of consecutive patients with severe and active TAO regularly followed up and treated at an academic tertiary referral multidisciplinary orbital center with a joint thyroid-eye clinic.

## 2. Methods

*2.1. Subjects.* This prospective study was approved by the local Ethical Committee and all patients gave their informed written consent. We followed the tenets of the declaration of Helsinki. Consecutive patients with severe and active TAO aged 23–75 years followed up at our institution between 2009 and 2014 were included. All patients were euthyroid at the time of inclusion in the study, as indicated by serum concentrations of free T4, free T3, and baseline TSH within the normal range. 36 patients were currently on antithyroid drugs, 47 were on levothyroxine, L-T4, either as a monotherapy or in combination with T3 subsequent to thyroid surgery or radioactive iodine treatment, and 17 patients were not receiving any medication. Diagnosis of TAO was based on clinical criteria according to the consensus statement of the European Group on Graves' orbitopathy (EUGOGO). Clinical disease activity and clinical severity were evaluated according to the clinically activity score (CAS) [3] and the modified NOSPECS score [4].

*2.2. Bioassay for Measurement of Thyroid Stimulating Antibodies (TSAb).* Serum TSAb levels were measured with a novel FDA-cleared cell-based bioassay (Thyretain, Quidel Corp., San Diego, CA, USA) according to the manufacturer's instructions. This assay utilizes Chinese hamster ovary cells (chimeric-CHO-luc) constitutively expressing a chimeric TSH-R and a firefly luciferase gene downstream of a promoter containing cAMP responsive elements as previously described [20]. Briefly, chimeric-CHO-Luc cells were seeded and grown to a confluent cell monolayer in 96-well plates for 15 to 18 hours. Patient serum samples, positive, reference, and normal controls were diluted 1 : 11 in reaction buffer and added to the cell monolayers, and each plate was incubated for three hours at 37°C in 5% $CO_2$. Subsequently, the chimeric-CHO-Luc cells were lysed, and the relative light units were quantified in a luminometer (Infinite M200; Tecan GmbH, Crailsheim, Germany). The samples were measured in triplicate and reported as the percentage of specimen-to-reference ratio (SRR%).

*2.3. Thyroid-Blocking Antibody (TBAb) Bioassay.* Serum TBAb levels were measured with a novel cell-based bioassay as previously described [9]. Blocking activity was defined as percentage inhibition of luciferase expression relative to induction with bovine TSH alone.

*2.4. Thyrotropin-Binding Inhibitory Immunoglobulin (TBII) Assay.* Serum TBII levels were measured using commercially available kits according to the manufacturer's instructions (Thermofisher, Brahms Diagnostic, Berlin, Germany).

*2.5. Statistical Analysis.* The statistical analysis was computed using SPSS (SPSS, Version 18, SPSS Inc., Chicago, IL, USA). The descriptive statistic was performed by calculation of the mean, median, standard deviation, and minimum and maximum values. The Mann-Whitney *U* test was performed to detect statistically significant differences of the mean ranks between two groups with respect to an ordinal or interval type variable. If the independent variable included more than two groups, the differences of the mean ranks were calculated by the Kruskal-Wallis test, another nonparametric test. When there were two interval or ratio type variables or the ordinal type variable contained a sufficient number Spearman's rank correlation coefficient was calculated. A statistical significance was assumed when the $P$ value was $<0.05$.

## 3. Results

*3.1. Demographic Data.* Demographic and clinical parameters are shown in Table 1. The female-to-male ratio was 3 : 1. A total of 70 patients had values above the cut-off of 10 mm for palpebral aperture in at least one eye. Also, 63 patients showed proptosis values above the cut-off of 20 mm (for Caucasians) in at least one eye. Asymmetric exophthalmos or proptosis was defined as the difference between the two eyes of at least 3 mm.

*3.2. Serological and Immunological Data.* All 101 consecutive patients with severe and active TAO were TBAb negative. In contrast, 91 (90%) were TSAb positive. All TSAb positive samples were also positive (negative inhibition) in the blocking assay with negative inhibition values > minus 100%. 90 of 101 TSAb positive patients had GD, while only one had Hashimoto's thyroiditis (HT). The other three HT patients were TSAb negative as were four GD patients who had undergone complete thyroidectomy. Additional two patients had been treated with radioactive iodine (seven and ten years prior to presentation) and one patient had taken antithyroid drugs. The duration of TAO negatively correlated with serum TSAb levels (Spearman's rho = −0.303; $P = 0.002$) and TBII (Spearman's rho = −0.296; $P = 0.003$). Serum TSAb levels also strongly correlated with TBII serum levels (Spearman's rho = 0.538; $P < 0.001$; Figure 1) and the maximum palpebral aperture (Spearman's rho = 0.29; $P = 0.003$; Figure 2) and proptosis (Spearman's rho = 0.27; $P = 0.007$; Figure 3). There was a significant difference in the upper lid retraction when the patients were divided into groups according to their respective TSAb value (negative, low, i.e., SRR% 140–279, moderate, i.e., 280–419, and high, i.e., > 419, positive; $P = 0.006$). Subsequent pairwise Mann-Whitney *U* tests showed that patients negative for TSAb scored lower on upper lid retraction. TSAb levels also correlated with a higher clinical severity score (Spearman's rho = 0.260; $P = 0.009$; Figure 4). Furthermore, we observed a higher serum level of TSAb in patients with diplopia ($P = 0.023$; Figure 5, right panel) and corneal damage or keratopathy ($P = 0.042$; Figure 5, left panel).

Although correlations between TSAb and several clinical findings of TAO were found, in this study there was no

Table 1: Demographic, clinical, and serological data of the 101 consecutively included patients with severe and active TAO.

| | |
|---|---|
| GD | $N = 97$ |
| HT | $N = 4$ |
| Female/male | $N = 76/25$ |
| Current smokers | $N = 53$ |
| Median age | 52 years (range 23–75) |
| Median duration of TAO | 11 months |
| Median palpebral aperture | 12 mm (6–17 mm) |
| Median proptosis | 22 mm (13–30 mm) |
| Asymmetric proptosis | $N = 20$ |
| Median CAS | 4 (3–6) |
| Median CSS | 5.75 (1–11) |
| Diplopia | $N = 63$ (12 constant) |
| Upper lid retraction | $N = 52$ |
| Lower lid retraction | $N = 42$ |
| Chemosis | $N = 27$ |
| Corneal lesions | $N = 14$ |
| TSAb | Median SRR% 418 (28–795) |
| TBII | Median 7.35 IU/l (0.3–174) |

GD: Graves' disease.
HT: Hashimoto's thyroiditis.
TAO: thyroid-associated orbitopathy.
CAS: clinical activity score.
CSS: clinical severity score.
TSAb: thyroid stimulating autoantibodies.
TBII: thyroid binding inhibitory immunoglobulins.

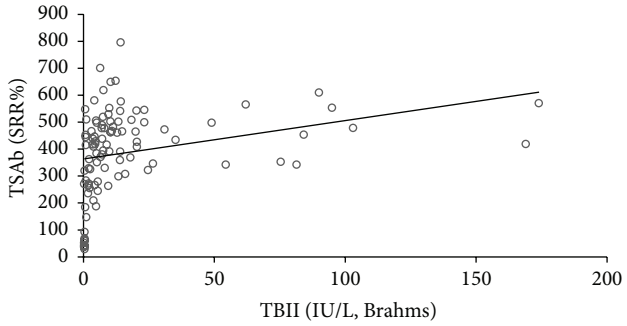


Figure 1: Correlation between serum TSAb and TBII levels. Spearman's rho = 0.538; $P < 0.001$.

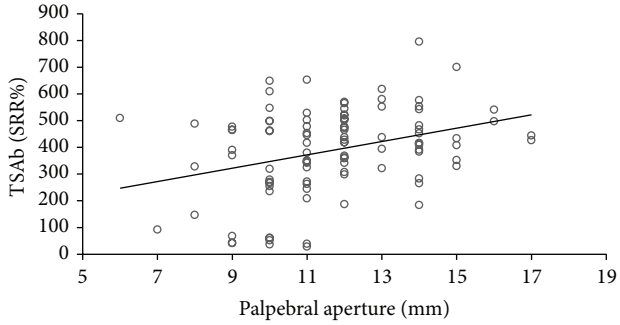


Figure 2: Correlation of serum TSAb levels with palpebral aperture. Spearman's rho = 0.29; $P = 0.003$.

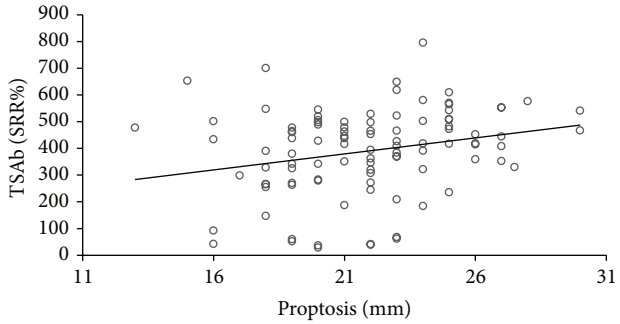


Figure 3: Correlation of serum TSAb levels with proptosis. Spearman's rho = 0.27; $P = 0.007$.

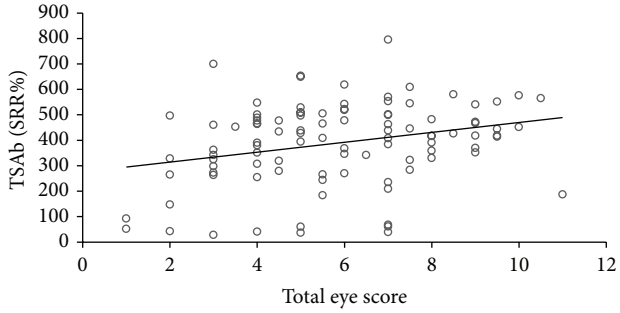


Figure 4: Correlation of serum TSAb levels with the total severity eye score. Spearman's rho = 0.26, $P = 0.009$.

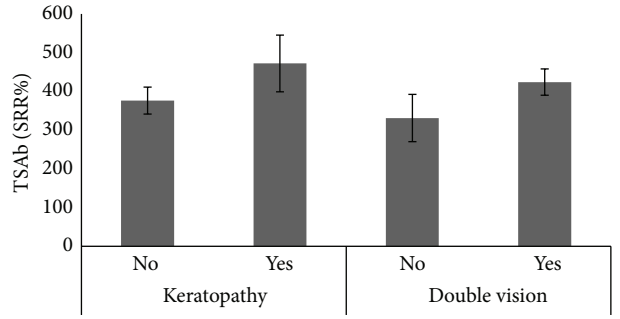


Figure 5: Right panel: mean TSAb levels in patients with or without diplopia (Mann-Whitney $U$ test; $P = 0.023$); left panel: mean TSAb levels in patients with or without corneal lesions (keratopathy, Mann-Whitney $U$ test; $P = 0.042$).

significant correlation in patients with higher CAS ($P = 0.797$) or with chemosis ($P = 0.214$). In cigarette smokers, the number of pack years showed a negative trend with the CSS (Spearman's rho = −0.252; $P = 0.05$), but there was no significant influence of smoking habits on CAS. Daily cigarette consumption or pack years had no significant impact on levels of TSAb ($P = 0.686$ and $P = 0.789$, resp.) or TBII ($P = 0.317$ and $P = 0.857$, resp.).

## 4. Discussion

This study clearly demonstrates in a large collection of patients with TAO that TSAb are highly prevalent in patients with severe and active orbital disease. This is also the first

paper to assess the prevalence of blocking TSH-R autoantibodies in patients with TAO using a newly developed and validated bioassay which is able to measure both blocking and stimulatory activity (i.e., by virtue of observing negative inhibition) [9]. Not a single patient with TAO was positive for TBAb, strongly suggesting that the blocking autoantibodies do not play a major role in the immunopathogenesis of the orbital changes in TAO. However, our results emphasize a putative role of TSAb in the pathophysiology of TAO. Based on these data, as well as those previously published by our group, stimulatory autoantibodies, in strong contrast to TBAb, are valuable and useful biomarkers of TAO. Although causality cannot be proven in this paper, the high correlation of these stimulatory autoantibodies with the presence of severe TAO strongly argues for a functional association.

The correlation curves between TSAb and proptosis and total eye score were weak; nevertheless given that TSAb levels correlate with several signs and symptoms of clinical severity of TAO, it is possible that TSAb may play a role in development of the extrathyroidal manifestations of this complex and systemic disease. It is not unreasonable to speculate that TSAb bind to and stimulate the activity of the TSH-R-expressing target cells in the eye, skin, and bone leading to TAO, thyroid-associated dermopathy, and acropachy. The TSAb effects may be mediated through the TSH-R in orbital tissue and evidence has accumulated that these receptors may be functional. TSAb activation of orbital TSH-R receptors upregulates expression of important proteins in TAO in a similar fashion to that seen by TSH activation [21]. Both supraphysiological doses of TSH and high TSH-R expression on orbital fibroblasts induce adipogenesis and lead to TAO. We thus hypothesize that the production of TSAb is one trigger for the initiation of TAO. Aside from adipogenesis, TSAb may have the potential to upregulate or alter antigens, costimulatory proteins, or other effectors important in TAO. Further support for the role of TSAb in the pathogenesis of TAO comes from animal models showing that a Th2 autoimmune response to the TSH-R may be prerequisite for the development of TAO [22].

In a previous report, serum TSAb levels were significantly higher in patients with TAO and untreated GD compared to those without TAO [17]. In this previous study, logistic regression analysis showed that TSAb levels were independent predictors of TAO. In contrast, no correlation between the binding assay (TBII) and eye disease was found. The prevalence of TAO increased with each incremental quartile of TSAb levels. Furthermore, the odds ratio of TAO was high when TSAb levels were above the median level. In a further study [8], TSAb was the strongest independent predictor of four features of TAO: lid fullness, proptosis, lid retraction, and extraocular myopathy. Also, in a cohort of TAO patients, serum TSAb levels significantly correlated with TAO clinical severity score, but no association was found between TBII levels and TAO scores [23]. With the exception of a trial reporting that both TSAb and TBII levels correlate with CAS [16] these previous studies neither differentiated between activity and severity of TAO, nor examined all the individual symptoms and signs that comprise the CAS.

In our present prospective study, smoking habits did impact neither the clinical phenotype of TAO nor the serum levels of the functional and binding TSH receptor autoantibody levels. This is in contrast to previous reports and to the data published in the consensus statement of the European Group on Graves' orbitopathy [24]. At our institution, we have observed over the last years a significant decrease of the smoking rate in patients with TAO and GD. Furthermore, our data refer to a specialized tertiary referral center with an academic joint thyroid-eye clinic probably differing from the clinical practice. Both the marked reduction of nicotine consumption and the special situation of our specialized center might play a role pertaining to the noted discrepancies. Also and although all patients with TAO had clinically active disease and were widely positive for TSAb with a few exceptions only, there was no positive correlation between serum TSAb/TBII levels and the clinical activity score in the present study. However, this somehow surprising result does not definitely contradict previous reports on the positive association between TSH receptor autoantibody levels and CAS as no patients with inactive TAO were included.

In conclusion, two novel cell-based bioassays for the measurement of functional TSH-R autoantibodies have demonstrated that TSAb, but not TBAb, are widely present in TAO and closely correlate with disease severity.

## Conflict of Interests

G. J. Kahaly consults for and has received research funding from Quidel, CA, USA. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the paper. Therefore, G. J. Kahaly declares that there is no conflict of interests regarding the publication of this paper.

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*Research Article*

# Predictors of the Dose-Effect Relationship regarding Unilateral Inferior Rectus Muscle Recession in Patients with Thyroid Eye Disease

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*Purpose*. To evaluate whether inferior rectus muscle (IRM) thickness, the degree of adipose change in the IRM, smoking status, and the previous history of orbital radiotherapy can predict the dose-effect relationship regarding unilateral IRM recession in thyroid eye disease (TED). *Methods*. Twenty-five patients were retrospectively reviewed. We calculated the largest IRM cross-sectional area and evaluated the degree of adipose change in the IRM using magnetic resonance imaging. The degree of adipose change and smoking status were classified using grading scales (0–3); previous orbital radiotherapy was graded as 0 when a history was not available and 1 when it was available. The correlation between the dose-effect relationship and the hypothesized predictive factors was evaluated using stepwise multiple regression analysis. *Results*. The multiple regression model, with the exception of the history of the previous orbital radiotherapy, estimated a significant dose-effect relationship for the parameters evaluated ($Y_{\text{DOSE-EFFECT}} = 0.013X_{\text{IRM AREA}} - 0.222X_{\text{ADIPOSE}} - 0.102X_{\text{SMOKING}} + 1.694$; $r = 0.668$; adjusted $r^2 = 0.367$; $P = 0.005$). *Conclusions*. The dose-effect relationship regarding unilateral IRM recession in TED could be predicted using IRM thickness, degree of intramuscular adipose change, and smoking status but could not be predicted using the previous orbital radiotherapy history.

## 1. Introduction

Inferior rectus myopathy is a common but severe sequela in patients with thyroid eye disease (TED) [1–3]. TED-related inferior rectus myositis induces fibroadipose changes, which cause inextensibility of the inferior rectus muscle (IRM), resulting in restrictive hypotropia [3–6]. Although mild hypotropia can be compensated for by a chin-up, severe hypotropia cannot be adjusted using any ocular or head positions. This causes impairment of single vision, which has a strong negative impact on the activities of daily living [3, 4].

Recession of inextensible IRM is the first step in the correction of a restrictive hypotropia in TED. For preoperative evaluation of the amount of recession, ophthalmologists use a common dose-effect relationship for IRM recession; namely, approximately 2 degrees of ocular deviation is modified by 1 mm of IRM recession [7, 8]. However, as interindividual variation in fibrous changes in the IRM results in very limited reproducibility, reoperation is frequently required [3, 6, 9]. Although the severity of fibrous changes cannot be directly examined, its evaluation from variation in IRM thickness [10] and adipose changes in the IRM on magnetic resonance imaging (MRI) may be helpful for precise preoperative evaluation of the dose-effect relationship.

Understanding other predictive factors for the dose-effect relationship may also ensure a more tailored IRM recession for TED patients. Smoking and orbital radiotherapy are representative factors involved in the aggravation of strabismus in TED patients. Smoking increases thyroid autoantibodies, causes severe orbital inflammation by inducing hypoxia, and decreases the response to medical treatment [5]. Orbital radiotherapy is used for reducing orbital inflammation in TED patients but occasionally leads to excessive orbital fibrosis [11]. However, the correlation between the dose-effect relationship and these factors has not been elucidated.

In the present study, we examined whether IRM thickness, the degree of adipose changes in the IRM, smoking status, and a previous history of orbital radiotherapy are

predictors of the dose-effect relationship regarding unilateral IRM recession in TED patients.

## 2. Materials and Methods

This study is a retrospective chart review of all TED patients who underwent unilateral IRM recession, which was performed by one of the authors (Hirohiko Kakizaki) between March 2011 and August 2014. The study was approved by the Institutional Review Board (IRB) of Aichi Medical University and followed the tenets of the Declaration of Helsinki. We obtained informed consent from the patients for the IRM recession surgery. However, the IRB granted a waiver of informed consent from the patients for this study, based on the ethical guidelines for epidemiological research established by the Japanese Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare because this study was a retrospective chart review, not an interventional study, and because it was difficult to get consent from all of the patients studied several years prior. However, the IRB requested us to present an outline of this study to the public via the Website of Aichi Medical University, to provide an opportunity for patients to refuse participation in this study. Patient records were anonymized and were deidentified prior to analysis.

Patients with a history of orbital decompression surgery or prior strabismus surgery, with missing clinical data, and with a follow-up time of <3 months were excluded from the study. All patients included in the study were euthyroid and in the static or chronic "burnout" phase; they did not have inflammation in the extraocular muscles (EOMs) on MRI [1].

*2.1. Data Collection.* The following data were collected: age, sex, surgical side, MRI findings, smoking status, past history of orbital radiotherapy, amount of IRM recession, and preoperative and postoperative angles of ocular deviation.

*2.2. MRI Examination.* MRI was performed by means of a 1.5-Tesla scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) using a head-neck surface coil with the patient located in the supine position. Coronal T1- (repetition time, 500 ms; echo time, 10 ms; field of view, 140 × 140 mm; matrix, 256 × 220; and section thickness, 3 mm with 0.6 mm of an interslice gap) and T2-weighted gradient-echo sequences (repetition time, 4000 ms; echo time, 100 ms; field of view, 140 × 140 mm; matrix, 256 × 220; and section thickness, 3 mm with 0.6 mm of an interslice gap) were acquired.

IRM thickness was measured by one of the authors (Yasuhiro Takahashi) using the digital caliper tool of a viewer (ShadeQuest/ViewR, Yokogawa Medical Solutions Corporation, Tokyo, Japan). The major axis of the IRM on the surgical side was measured first on the T1-weighted MR image showing the largest IRM cross-sectional area (Figure 1). Next, the minor axis perpendicularly crossing the major axis was measured on the same MR image. We calculated the area of the largest IRM section, assumed to be an ellipse [12], as follows: (major axis/2) × (minor axis/2) × 3.14.

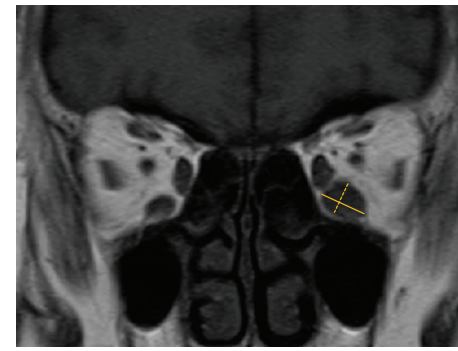


Figure 1: Measurement of the thickness of the inferior rectus muscle (IRM). The major axis of the IRM (solid line) and the minor axis perpendicularly crossing the major axis on the surgical side (dotted line) are measured on the T1-weighted coronal magnetic resonance image showing the largest IRM cross-sectional area.

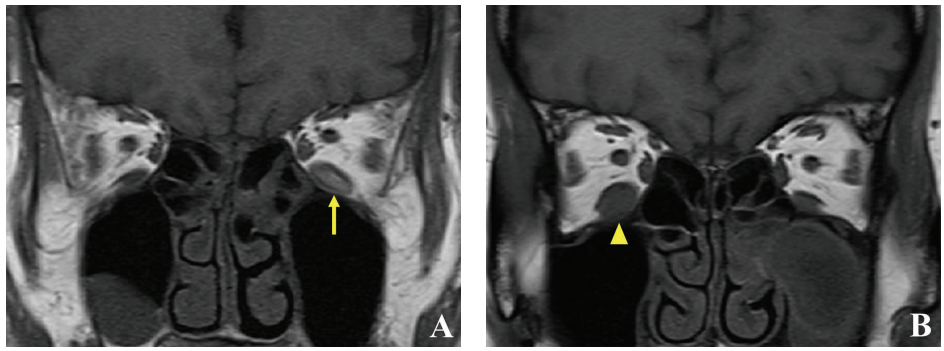
Adipose changes in the IRM were judged by one of the authors (Yasuhiro Takahashi) as high-intensity areas in the IRM muscle on both T1- and T2-weighted MR images. Every three consecutive T1- and T2-weighted images of the main portion of the IRM were used for evaluation. We classified the degree of adipose change in the IRM using an original grading system as follows: 0, no adipose change; 1, <1/4 of the IRM cross-sectional area; 2, 1/4–1/2 of the IRM cross-sectional area; and 3, >1/2 of the IRM cross-sectional area.

*2.3. Smoking Status.* Smoking status was classified by the number of cigarettes smoked per day, according to a report by Pfeilschifter and Ziegler [13] as follows: 0, no smoking; 1, <10 cigarettes/day; 2, 10–20 cigarettes/day; and 3, >20 cigarettes/day. All smokers were current smokers at the first examination, while all nonsmokers had not experienced smoking in their life.

*2.4. Past History of Orbital Radiotherapy.* The dose used for orbital radiotherapy was 20 Gy in all treated patients. The scale of previous orbital radiotherapy was expressed as 0 (without a history) and 1 (with a history).

*2.5. Orthoptic Examination.* The angle of ocular deviation was measured using a synoptophore at 1 day before surgery and 3 months after surgery. During the measurement, the fixing eye was set on the surgical side. The dose-effect relationship for IRM recession was calculated as follows: (preoperative angle − postoperative angle)/amount of IRM recession.

*2.6. Surgical Technique.* Surgery was performed under local anesthesia. A perilimbal conjunctival incision with radial relaxing incisions was undertaken in the inferior quadrant. A muscle hook was used to secure the IRM at its insertion, and Tenon's capsule around the IRM was thoroughly dissected using cotton swabs. The IRM tendon was secured using locking 8-0 polyglactin sutures (Vicryl, Johnson and Johnson Company, New Brunswick, NJ, USA) at 1 mm posterior to the globe insertion. Then, the IRM was detached from




(a) (b)

Figure 2: Adipose changes in the inferior rectus muscle (IRM) of a smoker (a) and nonsmoker (b). A large high-intensity area (arrow) in the left IRM is illustrated on a T1-weighted coronal magnetic resonance image (a). A small high-intensity area (arrowhead) in the right IRM is demonstrated on a T1-weighted coronal magnetic resonance image (b).

its insertion. The sutures were fixed to the sclera at 1 mm posterior to the point estimated from the preoperative ocular deviation angle. The recession of the IRM was calculated as follows: 2 degrees of ocular deviation per 1 mm IRM recession. The conjunctiva was closed using 8-0 polyglactin sutures.

*2.7. Statistical Analysis.* Patient age, the IRM cross-sectional area, and the dose-effect relationship were expressed as means ± standard deviations. The relationship between the dose-effect relationship and the hypothesized predictive factors was analyzed using stepwise multiple regression analysis. To examine whether smoking status and orbital irradiation were associated with the severity of intramuscular fibrous change, we compared the IRM cross-sectional area between smokers and nonsmokers and between patients with and without previous orbital irradiation using the Mann-Whitney $U$ test. In addition, the proportion of patients with each degree of adipose change in the IRM was compared between smokers and nonsmokers and between patients with and without previous orbital radiotherapy using the chi-square test for independent variables. All statistical analyses were performed using SPSS Statistics version 22 software (IBM Japan, Tokyo, Japan). A $P$ value of <0.05 was considered as being statistically significant in all tests.

Table 1: Patient data.

| | |
|---|---|
| Number of patients (male/female) | 25 (9/16) |
| Age (years; range) | 61.3 ± 10.1 (38–78) |
| Surgical side: right/left | 13/12 |
| Number of smokers | 8 |
| Number of patients with a history of orbital radiotherapy | 12 |

Table 2: Inferior rectus muscle thickness in each patient group.

| | IRM thickness ($mm^2$) |
|---|---|
| Mean (range) | 72.52 ± 17.34 (41.82–117.83) |
| Smoker (range) | 76.51 ± 19.57 (57.23–117.83) |
| Nonsmoker (range) | 70.63 ± 16.49 (41.82–91.30) |
| $P$ value | 0.887 |
| Patients with a history of orbital radiation therapy (range) | 76.25 ± 20.09 (47.56–117.83) |
| Patients without a history of orbital irradiation (range) | 69.07 ± 14.32 (41.82–91.30) |
| $P$ value | 0.347 |

IRM: inferior rectus muscle.
Statistical comparison using the Mann-Whitney $U$ test.

## 3. Results

All of the data and the results from the statistical analyses are summarized in Tables 1–3. Twenty-five patients (9 men and 16 women; age, 61.3 ± 10.1 years; range, 38–78 years) were included. Surgery was performed on the right side in 13 patients and the left side in 12. Eight patients (6 men and 2 women) were smokers, and 12 patients (five men and seven women) underwent orbital radiotherapy.

A multiple regression model for the dose-effect relationship, the largest IRM cross-sectional area, the degree of adipose change in the IRM, and smoking status was created; however, previous orbital radiotherapy history was deleted from the model by the stepwise procedure. The model estimated a significant dose-effect relationship ($Y_{\text{DOSE-EFFECT}} = 0.013X_{\text{IRM AREA}} - 0.222X_{\text{ADIPOSE}} - 0.102X_{\text{SMOKING}} + 1.694$; $r = 0.668$; adjusted $r^2 = 0.367$; $P = 0.005$). A coefficient of "$X$" variable indicated a positive or negative correlation to the dose-effect relationship. The mean dose-effect relationship was 2.27 ± 0.6 degrees/mm.

Although there was no significant difference in the largest cross-sectional area of the IRM between smokers and nonsmokers ($P = 0.887$; Table 2), the adipose change was significantly more severe in smokers than in nonsmokers ($P = 0.010$; Figure 2; Table 3). The largest cross-sectional area of the IRM ($P = 0.347$; Table 2) and the degree of adipose change ($P = 0.549$; Table 3) did not differ significantly between patients who had received or had not received previous orbital radiotherapy.

Table 3: Relationship between the degree of adipose change in the inferior rectus muscle, smoking status, and history of orbital radiation therapy.

| | Adipose change in the IRM | | | | $P$ value |
|---|---|---|---|---|---|
| Degree | 0 | 1 | 2 | 3 | |
| Number of smokers | 0 | 2 | 2 | 4 | 0.010 |
| Number of nonsmokers | 6 | 9 | 0 | 2 | |
| Number of patients with a history of orbital radiation therapy | 2 | 7 | 1 | 2 | 0.549 |
| Number of patients without a history of orbital radiation therapy | 4 | 4 | 1 | 4 | |

IRM: inferior rectus muscle.
Statistical comparisons using the chi-square test for independent variables.

## 4. Discussion

The dose-effect relationship regarding unilateral IRM recession in TED was predicted using IRM thickness, degree of intramuscular adipose change, and smoking status, but not by the previous orbital radiotherapy history.

IRM thickness was found to be positively correlated with the dose-effect relationship for IRM recession. A thick IRM commonly contains a large amount of fibrous tissue [10]. Recession of a fibrotic IRM releases a fibrous contraction [3, 5], resulting in the positive correlation between IRM thickness and the dose-effect relationship.

In contrast, the severity of adipose change showed a negative correlation with the dose-effect relationship regarding IRM recession. Adipose change also results in thickening of the IRM [10] but produces little muscle stiffness and inextensibility. Consequently, ophthalmologists need to estimate the amount of EOM recession on consideration of both IRM thickness and the degree of adipose change in the IRM. MRI can detect both a thickened IRM and adipose change, enabling an accurate preoperative estimation.

Smokers showed a negative correlation (−0.102 of the partial regression coefficient) with the dose-effect relationship for IRM recession. Smokers exhibited a higher degree of adipose change with the same IRM thickness as compared with nonsmokers; that is to say, the amount of fibrous tissue in the IRM was lower in smokers than in nonsmokers, although the volume of the IRM was similar. This resulted in less stiffness and inextensibility of the IRM in smokers, causing the negative correlation. Oxidative stress after smoking disturbs lipoprotein metabolism [14], which may be associated with adipose tissue accumulation in the IRM.

Previous studies have demonstrated no significant difference in the surgical success rate between smokers and nonsmokers [2, 11, 15], which appears to be contrary to the findings of the present study. However, these previous studies simply compared the surgical success rate between smokers and nonsmokers [2, 11, 15], while our study evaluated if there was a correlation between smoking and the dose-effect relationship regarding IRM recession. In addition, the previous studies included all strabismus surgeries, including recession of the horizontal rectus muscles and oblique muscles, resection of the EOMs, bilateral recession, and two muscle recessions on the same side [2, 11, 15]. These previous studies also included patients who had undergone orbital decompression surgery before strabismus surgery [2, 11, 15], which occasionally influences the surgical success of strabismus surgery [16]. These factors may have led to the different results between the present and previous studies.

In the present study, it was found that a history of orbital radiotherapy did not significantly influence the dose-effect relationship regarding IRM recession. This finding may be related to those reported in previous studies; these indicated no significant difference in the surgical success rate between TED patients treated with or without previous orbital radiotherapy, although the inclusion criteria were different [2, 11, 15]. Orbital radiotherapy occasionally leads to orbital fibrosis; however, it decreases TED-related orbital inflammation, which may offset the radiation-induced orbital fibrosis.

The multiple regression model used in the current study was created for unilateral IRM recession. A previous study showed that the dose-effect relationship for EOM recession differed among the EOMs [17]. The present model may, therefore, not be used for recession of the other EOMs. Future studies are necessary to determine other models for recession regarding the other EOMs.

The main methodological limitations of the present study were its retrospective design and small sample size. A larger number of patients would provide a stronger statistical power. Moreover, the use of software to calculate the IRM cross-sectional area would provide more accurate results.

## 5. Conclusions

The IRM thickness, the degree of intramuscular adipose change, and the smoking status, but not the previous history of orbital radiotherapy, were predictors of the dose-effect relationship regarding unilateral IRM recession in TED. Evaluation of the largest IRM cross-sectional area, the degree of adipose change in the IRM, and smoking status will be helpful for estimating the amount of IRM recession.

## Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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*Clinical Study*

# Liver Dysfunction Associated with Intravenous Methylprednisolone Pulse Therapy in Patients with Graves' Orbitopathy

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Intravenous methylprednisolone (IVMP) pulse therapy is the first-line treatment for the active phase of moderate to severe Graves' orbitopathy (GO). However, acute and severe liver damage has been reported during and after IVMP therapy. In this retrospective study, we investigated risk factors for liver dysfunction during and after IVMP therapy based on 175 Japanese patients with moderate to severe GO and treated at our center between 2003 and 2011. The results showed that seven patients developed severe liver dysfunction with elevated serum alanine aminotransferase (ALT > 300 U/L). Mild (40–100 U/L) and moderate (100–300 U/L) increases of ALT occurred in 62 patients (35%) and 10 patients (6%), respectively. Liver dysfunction was more frequently observed in males, in patients receiving high-dose methylprednisolone, and patients aged over 50 years. Preexistent viral hepatitis was significantly associated with liver dysfunction (65% in patients positive for hepatitis B core antibody and patients positive for hepatitis C virus antibodies). Our study confirmed the association of liver dysfunction with IVMP during and after treatment. It suggests that, in patients with GO, evaluation of preexisting risk factors—including viral hepatitis—and careful weekly monitoring of liver function during IVMP therapy and monthly thereafter for 12 months are warranted.

## 1. Introduction

Intravenous methylprednisolone (IVMP) pulse therapy is the first-line treatment for patients with active-phase moderate to severe Graves' orbitopathy (GO) [1]. IVMP is widely used because it is more effective and better tolerated than oral steroids [2, 3]. However, acute and severe liver damage has been reported after pulse therapy, with a roughly estimated morbidity and mortality of 0.8% and 0.3%, respectively [4]. The cumulative dose of IVMP in four patients with fatal liver failure was 8.3–15 g [4, 5] but slightly higher in three patients who died (10.8 ± 3.6 g) than in four patients who recovered (7.9 ± 2.9 g) [4]. Therefore, the European Group of Graves' Orbitopathy (EUGOGO) now recommends that the cumulative dose of MP should be less than 8 g [1, 6].

The causes of IVMP-associated liver damage are incompletely understood. Thus, the aim of the present study was to investigate the risk factors for liver dysfunction during and after IVMP pulse therapy for GO.

## 2. Materials and Methods

*2.1. Study Population.* This was a retrospective study of 175 Japanese patients with moderate to severe GO who were treated in one center from 2003 to 2013. The mean age of the 118 females and 57 males was 51.7 ± 15.5 years. They

had been admitted to our university hospital for GO and were treated with an intravenous injection of 1 g of MP daily for 3 consecutive days per week, repeated for three to six cycles, and followed by a tapering dose of oral prednisolone (20 mg/day for 4 weeks, 15 mg/day for 2 weeks, 10 mg/day for 2 weeks, 5 mg/day for 2 weeks, and 5 mg/2 days for 2 weeks). The daily dose of MP was reduced to 0.5 g except in cases with optic neuropathy after the recommendation by EUGOGO in 2008 [1]. Heart rate and ECG were monitored during the intravenous infusion of MP, administered every 2-3 h. In addition, 100 of the 175 patients were treated with orbital irradiation therapy (2 Gy/day, 10 times; total dose = 20 Gy) either during or after IVMP pulse therapy. All patients were given artificial tear drops to protect the cornea. Histamine receptor 2 antagonists or proton pump inhibitors were administered for all the cases. Bisphosphonates were administered in 82 patients to protect steroid-induced osteoporosis.

*2.2. Biochemical Examination and Diagnosis of Thyroid Diseases.* Thyroid diseases were diagnosed by measuring serum-free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin, anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, and anti-thyrotropin receptor antibodies (TRAbs). TRAbs were measured using three commercial kits: TRAb 1st generation (TRAb Cosmic III, Cosmic, Tokyo, Japan), TRAb 2nd generation, human TRAb (Yamasa, Tokyo, Japan) and TSAb (Yamasa TSAb kit), and thyroid $^{123}$I uptake on $^{123}$I scintigraphy. Orbitopathy was estimated by ophthalmologists using a modified NOSPECS classification [7] and the clinical activity score (CAS) [1]. Magnetic resonance imaging was also performed before and after pulse therapy, as previously reported [8]. Graves' disease was detected in 139 patients, 29 patients were euthyroid without a history of Graves' disease, and 7 patients had hypothyroidism without a history of Graves' disease. Orbitopathy with NOSPECS class VI was determined in 8 patients, class V in 3 patients, class IV in 139 patients, class III in 23 patients, and class II in 2 patients.

Liver function tests were performed once a week during pulse therapy and repeated at every visit thereafter for 1 year. Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C virus antibody (HCVAb) were measured before pulse therapy. The one patient who was HBsAg-positive consulted with a hepatologist, who prescribed 0.5 mg of entecavir, during and after pulse therapy. In addition, 43 patients were HBcAb-positive and 17 were HCVAb-positive. They likewise consulted with hepatologists before pulse therapy. Serum HBV-DNA was not detected in any patient. HBV-DNA and HCV-RNA were also monitored. Liver dysfunction was classified based on serum alanine aminotransferase (ALT) and total bilirubin levels as mild (ALT: 40–100 U/L), moderate (ALT: 100–300 U/L), or severe (ALT > 300 U/L or total bilirubin: >3 mg/dL).

*2.3. Clinical Characteristics of Patients with GO.* Female and male GO patients significantly differed with respect to age, body mass index (BMI), smoking habits, alcohol habits, and HBcAb positivity before pulse therapy (Table 1). Human TRAb and TSAb levels were significantly higher in female than in male patients before IVMP pulse therapy.

Table 1: Clinical characteristic of patients with Graves' orbitopathy.

| | Total | Male | Female | Male versus female |
|---|---|---|---|---|
| | $N = 175$ | $N = 57$ | $N = 118$ | $P$ value |
| Age (yr) | 51.7 ± 15.5 | 55.9 ± 16.3 | 49.6 ± 11.9 | 0.012 |
| BMI (kg/m$^2$) | 22.5 ± 3.7 | 23.4 ± 3.8 | 22.1 ± 2.7 | 0.021 |
| HBcAb (+) | 43 (25%) | 21 (37%) | 22 (19%) | 0.0102 |
| HCVAb (+) | 17 (10%) | 9 (16%) | 8 (7%) | 0.0677 |
| HBcAb (−) HCVAb (−) | 122 (70%) | 31 (54%) | 91 (77%) | — |
| IVMP > 8 g | 118 (67%) | 40 (70%) | 78 (66%) | 0.5884 |
| Smoking (+) | 57 (33%) | 27 (47%) | 30 (25%) | 0.0041 |
| Alcohol (+) | 48 (27%) | 28 (49%) | 20 (17%) | 0.0001 |
| CAS | 3.1 ± 1.7 | 3.2 ± 1.8 | 3.0 ± 1.7 | 0.8263 |
| TRAb (%) | 29.3 ± 27.3 | 25.8 ± 26.1 | 30.8 ± 27.8 | 0.2987 |
| hTRAb (IU/L) | 17.7 ± 44.4 | 8.10 ± 11.4 | 21.9 ± 52.2 | 0.0407 |
| TSAb (%) | 1262 ± 1480 | 931 ± 1229 | 1404 ± 1559 | 0.0346 |
| | | | | Mean ± SD |

BMI, body mass index; HBcAb, anti-hepatitis B core antibody; HCVAb, anti-hepatitis C virus antibody; IVMP, intravenous injection of methylprednisolone; CAS, clinical activity score; TRAb, anti-thyrotrophin antibody; hTRAb, human TRAb; TSAb, thyroid stimulating antibody.

*2.4. Statistical Analysis.* Statistical analysis was performed using JMP Pro software (version 11.0.0, SAS Institute, USA). Data are expressed as the mean ± standard deviation. Statistical comparisons were performed using Student's $t$-test, one-way ANOVA, or Mann-Whitney $U$ test for the analysis of continuous variables. The $\chi^2$ test or Fisher's exact probability test was used to analyze 2 × 2 or 2 × 4 tables. Multivariate logistic regression analyses were carried out to evaluate the risk factors for liver dysfunction, using exact method (LogXact, Cytel Inc., USA). In all tests, a $P$ value < 0.05 was considered to indicate significance.

## 3. Results

*3.1. Liver Dysfunction.* Increases of ALT during and/or after pulse therapy were detected in 79 patients (45%) (Table 2). Mild (ALT 40–100 U/L), moderate (ALT 100–300 U/L), and severe (ALT > 300 U/L) increases of serum ALT were measured in 62 patients (35%), 10 patients (6%), and 7 patients (4%), respectively. All patients with severe liver dysfunction were female and most of them were female. Two were HBcAb positive and one of them developed jaundice with ALT 945 U/L, one day after the cessation of IVMP. Her total bilirubin 8 weeks after the cessation of IVMP was 18.45 mg/dL. Single and cumulative doses of IVMP were 0.5 g and 3.5 g, respectively. HBV-DNA was not detected in patients with severe liver dysfunction. Anti-nuclear and

Table 2: Risk factors associated with liver dysfunction during and/or after intravenous methylprednisolone pulse therapy for Graves' orbitopathy.

| | Number of patients | Liver dysfunction ALT (IU/L) | | | | Univariate Fisher's exact probability test | Multivariate analysis Multinomial logit model for an unordered response | | |
|---|---|---|---|---|---|---|---|---|---|
| | | <40 | 40–100 | 100–300 | >300 | 2 × 4 | 95% CI Lower | Upper | 2 sided *P* value |
| Total | 175 | 96 (55%) | 62 (35%) | 10 (6%) | 7 (4%) | | | | |
| Male | 57 | 21 (37%) | 31 (54%) | 5 (9%) | 0 (0%) | $\chi^2 = 18.34$ | | | |
| Female | 118 | 75 (64%) | 31 (26%) | 5 (4%) | 7 (6%) | $P = 0.000278$ | 0.1348 | 1.646 | 0.01895 |
| HBcA b (+) | 43 | 15 (35%) | 24 (56%) | 2 (5%) | 2 (5%) | $\chi^2 = 11.01$ $P = 0.01125$ | | | |
| HCVAb (+) | 17 | 6 (35%) | 6 (35%) | 4 (24%) | 1 (6%) | $\chi^2 = 11.94$ $P = 0.01132$ | | | |
| HBcAb (+) and/or HCVAb (+) | 53 | 19 (36%) | 26 (49%) | 5 (9%) | 3 (6%) | $\chi^2 = 11.36$ $P = 0.008867^*$ | −0.245 | 1.417 | 0.1846 |
| HBcAb (−) HCVAb (−) | 122 | 77 (63%) | 36 (30%) | 5 (4%) | 4 (3%) | — | | | |
| Age | | | | | | | | | |
| >50 yr | 95 | 41 (43%) | 45 (47%) | 8 (8%) | 1 (1%) | $\chi^2 = 20.72$ | 0.03396 | 1.553 | 0.03972 |
| ≦50 yr | 80 | 55 (69%) | 17 (21%) | 2 (3%) | 6 (8%) | $P = 0.00004$ | | | |
| IVMP | | | | | | | | | |
| >8 g | 118 | 57 (48%) | 47 (40%) | 9 (8%) | 5 (4%) | $\chi^2 = 7.187$ | 0.1012 | 1.640 | 0.02426 |
| <8 g | 57 | 39 (89%) | 15 (26%) | 1 (2%) | 2 (4%) | $P = 0.06052$ | | | |
| Smoking | | | | | | | | | |
| (+) | 57 | 26 (46%) | 24 (42%) | 4 (7%) | 3 (5%) | $\chi^2 = 2.969$ | | | |
| (−) | 118 | 70 (59%) | 38 (32%) | 6 (5%) | 4 (3%) | $P = 0.3887$ | | | |
| Alcohol | | | | | | | | | |
| (+) | 48 | 24 (50%) | 19 (40%) | 3 (6%) | 2 (4%) | $\chi^2 = 0.6445$ | | | |
| (−) | 127 | 72 (57%) | 43 (34%) | 7 (6%) | 5 (4%) | $P = 0.9176$ | | | |

*Compared to patients without HBcAb or HCVAb.
ALT, alanine aminotransferase; HBcAb, anti-hepatitis B core antibody; HCVAb, anti-hepatitis C virus antibody; IVMP, intravenous injection of methylprednisolone.

anti-single-stranded DNA antibodies were also negative, as were anti-smooth muscle antibody, and anti-double-stranded DNA antibody in those patients. The HBV carrier taking entecavir prescribed by the hepatologist did not show the elevation of ALT.

*3.2. Factors Associated with Liver Dysfunction during or after Pulse Therapy for GO.* Liver dysfunction occurred more frequently in male patients ($P < 0.0012$) and in patients over the age of 50 years ($P < 0.0009$). BMI was significantly higher in patients with mild liver dysfunction than in those without liver dysfunction ($23.3 \pm 4.33\,kg/m^2$ versus $22.0 \pm 3.39\,kg/m^2$, Student's $t$-test, $P = 0.043$, data not shown). Liver dysfunction was not associated with smoking or alcohol habit but it was associated with a high dose of MP (cumulative dose >8 g versus <8 g, 2 × 2 table, $\chi^2 = 6.280$, $P = 0.0122$). Preexistent viral hepatitis was significantly associated with liver dysfunction during and after pulse therapy ($P = 0.0035$). HBcAb was positive in 43 GO patients (25%) before pulse therapy. In 28 of them (65%), ALT was significantly increased ($P = 0.01125$), although in most the increase was mild. HCVAb was positive in 17 GO patients (10%) before pulse therapy. In this group, 11 patients (65%) had increased ALT levels ($P = 0.01132$).

*3.3. Multivariate Logistic Regression Analysis.* Multivariate logistic regression analysis showed that age, gender, and cumulative MP dose (>8 g) were associated with liver dysfunction (Table 2).

## 4. Discussion

Although IVMP pulse therapy is widely used as the first-line treatment for active moderate-to-severe orbitopathy, severe related side effects have been reported, the most common of which is hepatotoxicity. In the recent review by Zang et al. [9], the morbidity and mortality of GO patients treated with IVMP pulse therapy were 6.5% and 0.6%, respectively. Fatal hepatotoxicity was reported to be associated with a cumulative dose of IVMP > 8 g. In two studies, the cumulative

doses were 8.3–15 g [4, 5]. EUGOGO now recommends that the cumulative dose of IVMP does not exceed 8 g [1].

In our series of 175 patients, seven patients (4.0%) developed severe liver dysfunction. The rate of morbidity was similar to the previous report [9]. The cumulative doses of MP were more than 8 g in 5 out of seven patients. However, single and cumulative doses of IVMP in a patient with jaundice were 0.5 g and 3.5 g, respectively.

Koga et al. [10] reported two fatal cases of HBV carriers after corticosteroid therapy, and the frequent reactivation of HBV after immune suppressive therapy, such as with rituximab, was noted [11]. Therefore, in GO patients during IVMP therapy, the reactivation of HBV leading to acute liver failure remains a concern, although its occurrence is rare [4, 9, 12, 13]. Indeed, in the series of Le Moli et al. [12], none of the 27 patients with GO suffered serious liver damage. Wichary and Gasińska [13] concluded that the risk of HBV reactivation is low, based on their experience with 30 patients treated with IVMP. Those studies suggest that it is difficult to predict who will develop severe liver failure, such that it is important to carefully monitor patients during and after IVMP therapy.

Our study identified risk factors for mild to moderate liver dysfunction during and after IVMP therapy for GO. Among male patients, a mild elevation of ALT was associated with a cumulative dose of IVMP > 8 g; in female patients, a moderate elevation of ALT was associated with age over 50 years. A history of HBV and HCV infection also contributed to a high prevalence of hepatotoxicity, as approximately 25% of our GO patients were HBcAb-positive and 10% were HCVAb-positive before pulse therapy. Within this group, 65% had increased ALT levels during and/or after pulse therapy. Multivariate logistic regression analysis showed that gender, age, and cumulative dose of MP were associated with liver dysfunction. Our study in Japanese patients suggests that viral hepatitis, gender, age, and cumulative dose are predisposing risk factors for hepatotoxicity during and after IVMP therapy. The current study also supports recommendations of a cumulative dose of MP < 8 g. However, as even this dose may not be completely safe, careful monitoring of GO patients receiving IVMP is recommended both during and 12 months after therapy.

Although the mechanisms of mild to severe hepatotoxicity remain unclear, reactivation of viral hepatitis [4, 10, 11], a direct toxicity of MP [12–14], and exacerbation of autoimmune hepatitis have been suggested [15, 16]. Le Moli et al. [12] reported that mild elevations in liver enzymes following IVMP were dose dependent. The toxic effect of glucocorticoids on hepatocytes, leading to drug-induced steatohepatitis, is thought to involve mitochondrial injury because of the impaired $\beta$-oxidation of fatty acids, with subsequent generation of reactive oxygen species and ATP depletion [17].

Salvi et al. [15] and Marinò et al. [16] reported the exacerbation of autoimmune hepatitis with severe liver dysfunction during IVMP therapy. In our series, two patients were positive for antinuclear and anti-smooth muscle antibodies but in both cases liver dysfunction was mild.

The drug-drug interaction may be another possible mechanism of liver dysfunction [18]. None of patients received aspirin in combination of Ramipril or clopidogrel.

There were several limitations to this study. First, it was retrospective in design. However, it allowed us to assess the effect of single and cumulative doses of IVMP, because in line with the EUGOGO's recommendation we reduced the single dose of IVMP from 1 g to 0.5 g. Another limitation of the study was the small number of patients, which prevented definite conclusions because of the low incidence of severe liver dysfunction. Additionally, no histopathological examinations were done and the effectiveness of IVMP for GO was not evaluated. Therefore, further prospective studies are indicated to assess the hepatotoxicity of IVMP during and after pulse therapy for GO.

In conclusion, liver dysfunction is frequently associated with pulse therapy for GO, both during and after treatment. Our study supports the careful evaluation of preexisting risk factors (especially viral hepatitis, age, gender, body mass index, and smoking history) before initiating IVMP therapy in GO patients. In these patients, strict monitoring of liver function once a week during pulse therapy and every month thereafter for the next 12 months is warranted.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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