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1 **Thyroid-associated orbitopathy and biomarkers: where we are and what we**
2 **can hope for the future?**

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19 Running title: Thyroid-associated orbitopathy and biomarkers: state of the art

20

21

22 **Abstract (175 words)**

23 *Background:* Thyroid-associated orbitopathy (TAO) is the most common auto-
24 immune disease of the orbit. It occurs more often in patients presenting with
25 hyperthyroidism, characteristic of Graves' disease, but may be associated with
26 hypothyroidism or euthyroidism. The diagnosis of TAO is based on clinical orbital
27 features, radiological criteria and the potential association with thyroid disease. To
28 date, there is no specific marker of the orbital disease, making the early diagnosis
29 difficult, especially if the orbital involvement precedes the thyroid dysfunction.

30 *Summary:* The goal of this review is to present the disease and combine the
31 available data in the literature concerning investigation of TAO biomarkers.

32 *Conclusions:* Despite the progress done in the understanding of TAO disease, some
33 important pieces are still missing. Typically, for the future, major efforts have to be
34 done in the discovery of new biomarkers, validation of the suspected candidates on
35 multicenter cohorts with standardized methodologies and establishment of their
36 clinical performances on the specific clinical application fields in order to improve the
37 management of the TAO patients but also the therapeutic options and follow-up.

38

39 **Keywords:** Biomarkers, Thyroid-Associated Orbitopathy, tears, orbital fat, blood,
40 inflammation

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45 **Clinical significance**

46 Around 25-50% of patients with Graves' disease develop TAO without any predictive
47 factor. Moreover, the ocular disorder usually appears after the thyroid disease or
48 simultaneously, but may precede it. Identifying new biomarkers of this orbital disease
49 could help to an early diagnosis, especially if the orbital involvement precedes the
50 thyroid dysfunction.

51

52 **Introduction**

53 Thyroid-associated orbitopathy (TAO), also known as thyroid eye disease or Graves'
54 ophthalmopathy, is an autoimmune disease affecting thyroid, orbits and skin. Despite
55 important progress in understanding the pathophysiological mechanisms leading to
56 the development of this disease in the orbits during the last decade, some important
57 questions are still without any answer. The exact nature of the relationship of TAO
58 with thyroid remains enigmatic: hyperthyroidism can be related to the development of
59 this orbital disease but exceptions exist. In contrast, TAO can occur in hypo- or
60 euthyroid patients. Therefore, the prediction of Graves' evolution to TAO is difficult
61 and limits early treatment. At cellular and molecular levels, the reason why only
62 orbital fibroblasts (and not the other fibroblasts of the body), orbital adipose tissue
63 and medial and inferior rectus muscles are more often affected during the disease
64 has not been solved yet. Furthermore, the possibility to have unilateral orbital case
65 and the great variety of clinical presentation are not understood. This last point
66 highlights also in some cases the difficulty to properly diagnose TAO disease by

67 cofounding with mimicking diseases such as orbital myositis, amyloidosis, some
68 tumors or metastatic cancer and IgG4-related diseases [1-12].

69 In this context, the discovery of new biomarkers that could definitively assist the
70 physician to diagnose TAO disease as early as possible, predict prognosis and
71 propose early and appropriate treatment will be clinically useful for improving patient
72 management. After a brief recall of the clinical manifestations and the
73 pathophysiology, we review where we are in the potential biomarkers reported in
74 TAO and which vision we can have for the future.

75 **Review**

76 The natural history of TAO, without any treatment, is described as the Rundle's curve
77 [13-15]. Symptoms and signs of the orbital disease worsen rapidly during an initial
78 phase, reach a maximal severity, and decrease to a plateau known as the sequellar
79 form. The disease appears 2-6 times more frequent in young women but severe
80 cases occur more frequently in men of more than 50 years old [16].

81 The manifestations of the orbital involvement are irritation and redness of the eyes
82 and eyelids, lid tumefaction, double vision and rarely visual loss. The bilateral
83 complete orbital examination should look for lid retraction, proptosis (exophthalmos),
84 limitation of ocular motility, fat hypertrophy, deficit of visual acuity or color vision, the
85 signs of corneal exposure, and signs of orbital inflammation [17-19] (Figs 1 and 2).

86 Clinically, the challenge is to recognize the active, inflammatory phase of the orbital
87 disease. In fact, early diagnosis and rapid introduction of the anti-inflammatory
88 treatment, mainly steroids, improve the final outcome and reduce the functional and
89 disfiguring sequellae of the disease [14, 20]. As in some cases the orbital

90 manifestations precede the thyroid dysfunction and its systemic signs [21], it seems
91 essential to have a biomarker dedicated to the early diagnosis of the orbital disease.
92 The detection of Thyroid stimulating hormone-receptor (TSH-Receptor) antibodies
93 (TSH-R-Abs) may confirm the auto-immunity and the diagnosis of TAO. But these
94 antibodies are not present in all cases [19, 22, 23].

95 So far, we use the clinical activity score (CAS) to determine the indication and the
96 duration of anti-inflammatory treatment [22, 24]. We take in consideration the
97 presence or not of pain, lid and conjunctival edema (chemosis), lid and conjunctival
98 redness. Nevertheless, as for all the clinical scales, this one presents some
99 limitations: CAS is based on few items, mixing different types of clinical information
100 (inflammation *versus* vision worsening) and proposing only binary answers, reducing
101 therefore the accuracy of its interpretation. Furthermore, this is a subjective scale
102 depending therefore on the timing of the evaluation, the willingness and objectivity of
103 the patients regarding their clinical situations and on the level of expertise of the
104 practitioner performing the evaluation. Other scales exist including NOSPECS [25],
105 VISA [26] and EUGOGO [27] but present also advantages and limitations and are not
106 daily used in our hospital.

107 In some difficult cases, the magnetic resonance imaging (MRI) could help to find out
108 the presence of an inflammatory process. Definitely, having molecules that could
109 efficiently complement clinical scores and observation could allow a more precise
110 and rapid diagnosis and also limit the economic burden to useless access to imaging.

111 All the patients with irritation, lid retraction and proptosis, should benefit of a local
112 lubricant treatment (eye drops and ointment). In presence of orbital inflammation,
113 some treatments such as selenium and steroids are indicated, according to the

114 severity [22]. The goal is to stop the inflammatory process and to improve the final
115 outcome. In case of resistance or contraindication, low dose external radiotherapy is
116 suggested. The immunomodulatory treatments such as Tocilizumab (Interleukin (IL)-
117 6 receptor antagonist), Teprotumumab (Insulin-like growth factor-1 (IGF-1) receptor
118 antagonist) or Rituximab (anti-CD20) [28] seem to give promising results in resistant
119 cases [18, 29-31].

120 Rehabilitative surgery should be performed in patients with inactive TAO since at
121 least six months. The main steps are orbital decompression for the reduction of
122 proptosis, squint surgery for the treatment of muscular fibrosis and diplopia, lid
123 lengthening and blepharoplasty for lid retraction and fat hypertrophy.

124 The finding of specific biomarkers of TAO may serve as a predictive factor of
125 development of TAO among patients with Graves' disease, and may also give some
126 information on the severity of TAO.

127 The pathophysiology of TAO is poorly understood. Some classical risk factors
128 including genetic predisposition, environmental factors, infection and stress, have
129 been reported but their real impact on TAO initiation remains debated [32].

130 Nevertheless, some pieces of the puzzle begin to come together in the literature.
131 B-cells, T-cells and orbital fibroblasts have been shown to be the key players of the
132 pathological event. At the origin, T-cells are responsible for the initiation of
133 the disease [19]. Indeed, T helper cells become activated when they
134 recognize TSH-R peptides on antigen-presenting cells. Upon interactions
135 with such T-cells, B-cells secrete anti-TSH-R antibodies. These antibodies
136 lead to stimulation of both thyroid follicular cells, which produce a great

137 quantity of thyroid hormones, and orbital fibroblasts, which proliferate and
138 induce orbital changes.

139 Beside TSH-R, IGF-1 receptor (IGF-1R) was also identified as a potential targeted
140 antigen [32-37] and it seems that the interactions between TSH-R and IGF-1R are
141 more important than individual molecules effect [38]. Furthermore, patients can have
142 either one or both types of auto-antibodies and alternative production of other types
143 of auto-antibodies is not excluded. Indeed, recent studies suggested that auto-
144 antibodies against carbonic anhydrase 1 and alcohol dehydrogenase 1B had higher
145 prevalence in orbital fat in TAO compared to controls [39].

146 Tripartite relationships between orbital fibroblasts, B- and T-cells initiate cascades of
147 immune and chemical reactions [40, 41] resulting in pathological situations:
148 inflammation of the connective tissues, fibrosis and adipogenesis [32, 33].

149 These phenomena cause fundamental and dramatic ocular tissue remodeling. The
150 increased volume of extraorbital muscles, induced by intensive hyaluronic acid (HA)
151 production [42] and expansive growth of adipose tissue via activation of peroxisome
152 proliferator activated receptor gamma (PPAR- γ) [43], leads consequently to the
153 typical eye's protrusion, characteristic of TAO patients. In addition, the compression
154 of orbital tissue causes a compression of vascular structures leading to the reduction
155 of blood flow and subsequent localized hypoxia [44]. In this context, proangiogenic
156 factors seem to be stimulated in order to restore appropriate circulation through the
157 formation of new vessels.

158

159 *Biomarkers*

160 In this context, as previously mentioned, no accurate molecular tool allows to date
161 establishing a rapid, early and robust diagnosis of TAO or predicting the outcome or
162 the efficiency of drug therapy. Nevertheless, the availability of these kinds of tools,
163 objectively measurable and easily interpretable, could greatly enhance the
164 management of TAO patients, especially those with normal thyroid function.
165 However, over the years and regarding the increased number of publications in the
166 biomarker field, only relatively few studies have been focused on the discovery of
167 new biomarkers in TAO disease.

168 The term '**biomarker**' was officially and accurately defined 15 years ago as a single
169 indicator "*that objectively measures and evaluates normal or pathogenic biological*
170 *processes*" [45]. Consequently, a biomarker is not restricted to being a protein, but
171 may be any type of specific molecular signature such as a gene, mRNA or a
172 metabolite. Specific clinical features such as demographic and physiological
173 parameters (age, gender, smoking status, or goiter size), imaging (thyroid volume
174 with ultrasonography or IRM) or clinical scores (CAS, Vision, Inflammation, and
175 Appearance (VISA)) can also be considered as objective biomarkers. However, only
176 the molecular biomarkers will be considered here.

177 In order to be efficient, biomarker discovery in general but also in TAO context should
178 carefully consider the best source of samples in relation to both the clinical question
179 and the methods of investigations. To be applicable on a large-scale, a good source
180 of biomarkers should take into account the feasibility of sample collection and its
181 relevance. Extremely invasive sample collection (e.g. biopsy of orbital fat or
182 extraorbital muscles), even if it is highly specific due to the close relationship with the
183 location of a disease, must not be taken for granted because of (i) the related
184 discomfort and risks of secondary complications for the patient; (ii) the restricted

185 access for clinical diagnosis, and (iii) the great difficulty in collecting such samples
186 from healthy control subjects.

187

188 *Biomarkers – hormones and antibodies - in blood of TAO patients*

189 In TAO disease, traditional biological fluids including blood and urine have been
190 investigated. The majority of the studies rather reported principal actors of the TAO
191 disease as potential biomarkers than discovered new candidates. Considering the
192 dysfunction of the thyroid gland associated to TAO, the traditional circulating thyroid
193 hormones (TSH, triiodothyronine also known as T3 and thyroxine, called T4) used
194 for diagnosing thyroid dysfunction or the antibodies against TSH-R (TSH-R-Abs) [22,
195 46] or thyroid peroxidase (TPO)-Abs [47, 48], would be naively expected to be highly
196 studied and give an interesting insight on the clinical status of the TAO patients.

197 Thus, whatever the generation of assays used, TSH-R levels were shown to be
198 associated to activity and severity of TAO [46, 49-51]. The new generation tests
199 allowed to reach up to 97% sensitivity and almost 90% specificity [51]. However to
200 date, some limitations persist for a clinical use of TSH-R in the management of TAO.
201 The heterogeneous pattern of thyroid dysfunction in TAO patients - hyperthyroidism,
202 euthyroidism (6 to 21% depending on the studies [52-54]), or hypothyroidism - and
203 the fact that various other diseases [55] may disturb thyroid hormones greatly limit
204 their clinical relevance in TAO diagnosis. Indeed, a potential interference of treatment
205 with the TSH-R level has been suspected [56-58] and could disturb their
206 performances in TAO prediction.

207 In conclusion, conflicting data related to different types of generation assays and
208 various experimental designs do not allow to definitively evaluate the clinical
209 performance of TSH-R-Ab on TAO patients and the conditions of its routine use

210 remain to be clarified. In the same context, the association TPO-Ab and TAO is still
211 questionable as different studies reported various results [47, 59-61].

212

213 *Biomarkers – cytokines and others - in blood of TAO patients*

214 As the pathology is driven by an acute inflammatory event, the pro-inflammatory
215 cytokines/chemokines including IL-1 β [62], IL-6 [63], IL-10 [63], IL-8 [64], C-C
216 chemokine ligand 20 (CCL20) [65] and IL-17 [66] have been studied. The reported
217 data reveal an elevation of their level in the blood of TAO patients compared to
218 control patients that could highlight a potential interest of these molecules as
219 diagnosis markers. Furthermore, their levels seem even able to determine the stage
220 of the disease: an active phase is characterized by a higher level of IL1 β , IL6 [62]
221 and IL-17 [66] compared to inactive phase. The data suggested also that the blood
222 levels of some cytokines could reflect the response to treatment: patients presenting
223 refractory TAO have higher level of IL-4, IL-6 and IL-10 than patients in remission
224 [63]. Furthermore, patients present modified blood level of IL-16 (increase) and IL-8
225 (decrease) after steroids treatment compared to the previous state [64, 67].
226 Moreover, a possible association of serum IL-10 polymorphism with incidence of
227 TAO has been reported [68].

228 Based on only two unique studies, controversial data exist on Interferon- γ (IFN- γ)
229 and its potential disturbance in blood of TAO patients [62, 69]. The cytokines involved
230 as mediators of B-cells and/or T-cells have also been largely investigated due to the
231 key roles of these cells in the initiation and the course of the TAO disease.
232 Interleukin-2 [68], IL-16 [67] and IL-33 [69] have been shown to be highly elevated in
233 the blood of TAO patients compared to controls. Serum IL-33 levels were positively

234 correlated with T3 and T4, however negatively correlated with TSH [69]. A
235 polymorphism of IL-2 is suggested to be associated with the disease [68].

236 Due to their mitogenic and angiogenic properties, the potential value of growth
237 factors has also been investigated. Serum hepatocyte growth factor (HGF) increases
238 in TAO patients compared to control subjects and is sensitive to efficient
239 glucocorticoids treatment. Its level decreases in response to drug administration [64].

240 Adhesion molecules belong to another class of molecules investigated as potential
241 TAO markers. They play a role in cell/cell or cell/extracellular matrix interaction,
242 activation and migration. Intercellular adhesion molecule-1 (ICAM-1) and soluble
243 vascular cell adhesion molecule-1 (sVCAM-1) have been found elevated in the blood
244 of TAO patients as compared to control patients but their levels seem also to be
245 influenced by the treatment [70].

246 Selenium is a metabolite implicated in thyroid hormone synthesis and metabolism
247 [71], both actions having high importance in TAO development [72]. Besides, high
248 amounts of selenium are found in thyroid gland. In an Australian population in 2014,
249 TAO patients showed lower levels of selenium in serum than patients suffering from
250 Graves' disease without eye involvement. In addition, selenium levels decrease with
251 TAO increasing severity. The authors conclude that the lack of selenium might be an
252 independent risk factor for TAO [72].

253 The potential interest of several exotic biomarkers in TAO recently emerged notably
254 because of the use of omics strategies. Among these emerging candidates, none of
255 them has been deeply evaluated to date but several can be mentioned for their
256 biological functions that could be directly related to TAO disease. This is the case of
257 osteopontin [65, 73], a multifunctional protein involved in inflammation, cell

258 recruitment, cell adhesion and remodeling. It is inversely correlated with TSH level
259 and positively with T3 and T4 [73]. Another protein called cytotoxic T lymphocyte
260 associated antigen-4 (CTLA-4), a member of the immunoglobulin superfamily, which
261 is found on T-cell surface, negatively regulates these cells. So far, many studies have
262 been focused on a polymorphism localized on CTLA-4 gene, as a consequence of its
263 implication in autoimmune diseases [74-76]. Finally HLA-B8, a MHC class I cell
264 surface receptor, has been observed in association with TAO but its role remains to
265 be elucidated [77, 78].

266 *Biomarkers in urine of TAO patients*

267 Urine and its components have been little investigated as potential source of
268 biomarkers in the context of TAO. However, three compounds showed a potential
269 promising interest and should be more studied in the future. The cotinine level, the
270 main metabolite of nicotine used as marker of tobacco use, seems to correlate in
271 smokers TAO patients with the level of blood TSH-R-Abs, the activity of the disease
272 and secondary ocular complication after radioiodine treatment [79, 80].
273 Glycosaminoglycans (GAGs), the most abundant heteropolysaccharides, display a
274 urinary levels 2-3 times higher in patients with the active form compared to those with
275 the inactive form [81]. Finally, 8-hydroxy-2'-deoxyguanosine (8-OHdG) has attracted
276 attention of scientist's community. This metabolite is used to measure DNA damage
277 in oxidative stress, event that was related with various ocular diseases such as TAO.
278 High levels of 8-OHdG were found in TAO patients urine compared to control
279 patients, and 8-OHdG level was related to CAS [82]. In short, 8-OHdG might be a
280 good biomarker in the future to evaluate the presence of oxidative DNA damage and
281 therefore the oxidative stress generated in TAO patients.

282 *Biomarkers in blood and urine of TAO patients: conclusions*

283 In conclusion, these 2 common fluids usually explored for biomarker discovery seem
284 disappointing in TAO. Several explanations could be highlighted: at this stage, only
285 few studies focus on the same molecules and, in the main cases, the candidates are
286 investigated not for their potential role as biomarkers but rather for their central role in
287 the pathological events. This is particularly illustrated by the absence of clinical
288 performances (sensitivity, specificity, positive and negative predictive values)
289 reported in the publications. Nevertheless, with the democratization of the omics
290 methods, we may speculate that, in a near future, new and probably unexpected
291 biomarkers will be discovered and could offer new clinical and management
292 strategies for TAO.

293 Moreover, no standardized protocol is reported for the evaluation of a specific target
294 and different clinical questions are frequently assessed with a unique cohort design
295 decreasing the power of the analyses. Another aspect could be that the modifications
296 of molecular levels occurring in response to this disease may be too subtle to be
297 efficiently measured in these systemic fluids. We assume therefore that fluids or
298 tissues geographically close to the place of the disease (the eyes) will be more
299 valuable.

300 *Biomarkers in orbital fat of TAO patients*

301 Exploring the orbital fat content in TAO patients is, to our point of view, highly
302 relevant since the disease directly affects this tissue. In orbital fat, the IL-1 β and IL-6
303 levels seem to be associated with the smoker status of TAO patients [83]. Besides, a
304 transcriptomics study performed on orbital fat reports a clear upregulation of IFN- γ in

305 TAO patients [84]. Transforming growth factor- β (TGF- β) and fibroblast growth factor
306 (FGF) are elevated in the orbital fat of TAO patients and levels of these factors are
307 correlated with the severity of the disease. In the family of growth factors, platelet-
308 derived growth factor (PDGF) is probably the most promising at this stage with a
309 central role in the TAO pathological events. Indeed, several studies have reported its
310 overexpression in orbital tissues of TAO patients [85-87], independently of the activity
311 grade of TAO. In addition, specific isoforms of PDGF improve the TSH-R expression
312 on orbital fibroblasts, amplifying the autoimmune reaction against TSH-R [85]. Drugs
313 blocking PDGF signalling allow opening new therapeutic options [87, 88]. Finally, *in*
314 *vitro* studies have also highlighted the adipogenic function of PDGF, able to induce
315 the transformation of orbital fibroblasts into adipocytes [89]. This mechanism
316 participates in the extension of orbital tissue during TAO course. Adipogenesis is also
317 induced by IL-1 β through an increase of Cyclooxygenase-2 (COX-2). This enzyme,
318 known to modulate inflammation, is anticipated to be a central element of the active
319 phase of TAO disease. Its mRNA and protein levels have been shown to be
320 overexpressed in orbital fibroblasts of TAO patients [90] and hyaluronic acid (HA)
321 seems involved in its regulation. Nevertheless, the interest of COX-2 is not
322 definitively assessed as others studies revealed no modification of its expression
323 [91]. On the other hand, at the transcript levels, TGF- β receptor, IGF-1 and insulin-
324 like growth factor binding protein-6 (IBP-6) appear to be downregulated [84].

325 *Biomarkers in tears of TAO patients*

326 But, from our point of view, the most promising fluid for TAO in the future will be
327 probably tears. Surprisingly, until now, tears and their clinical relevance have been
328 poorly studied. With the non-invasive, easy and rapid collection of samples, tear-

329 based approaches open up new routes for diagnostic methods and for understanding
330 of both ocular and systemic diseases. Tears play a key role in the correct function
331 and health of the eye. Tears are necessary for the lubrication of the eye surface that
332 ensures the appropriate optical properties and for the nutrition and protection of
333 surrounding tissues. Tears are secreted by lachrymal glands and contain
334 electrolytes, nucleotides, lipids, metabolites and proteins. But these components can
335 also be released from surrounding damaged tissues or by passive transport from
336 blood. The production and composition of tears is therefore a dynamic system that
337 depends on environmental factors, stimulus, infection or disease. Consequently, the
338 ability to measure any subtle modification targeting one or several biomarkers in tear
339 contents opens promising opportunities for screening not only ocular but also
340 systemic diseases.

341 The behaviour of the pro-inflammatory proteins in blood could be extrapolated to
342 tears. A profile similar to that observed in the blood, can be highlighted in tears with a
343 net increase of IL-1 β , IL-6 and IL-17 in active compared to inactive TAO patients [62].
344 Another important actor of inflammation, Tumor necrosis factor (TNF)- α , has been
345 measured only in tears. Its concentration is higher in inactive and active TAO patients
346 than in control ones [62]. Moreover, two polymorphisms (-1031T/C and -863C/A) of
347 TNF- α gene have been found in samples from a Japanese population with a dramatic
348 increase in patients with Graves' disease suffering from TAO in comparison to those
349 without TAO. In addition, these polymorphisms seem associated to the severity of
350 TAO [92]. Interleukin-7 has also been reported in tears and orbital fat and is
351 suspected to changes according to the different phases of the disease [93]. Finally,
352 using proteomics experiments, potential new candidates have been revealed such as
353 Proline-rich-protein members (PROL1/PRP4) involved in the modulation of the

354 microflora of the eye, and presenting protective function [94, 95], or S100 calcium
355 binding proteins (S100A8/S100A9) modulating inflammation and cell adhesion [94,
356 95].

357

358 **Conclusions**

359 The story of TAO biomarkers is just starting: efficient biomarkers used in routine for
360 TAO have still to be discovered. Ideally, they will offer a new opportunity for
361 improving early diagnosis, follow-up and treatment monitoring. Further, it could help
362 to a better understanding of pathophysiology and permit new personalized-
363 therapeutic strategies.

364 Nevertheless, to be a success story, biomarker discovery should carefully consider
365 the best source of samples in relation to the clinical question and the characteristics
366 of the TAO disease. In order to be extended on a larger scale and finally to the whole
367 population, we strongly believe that a good source of biomarkers should take into
368 account sample collection feasibility. Orbital fat or muscles, even if highly specific,
369 will not be easy to obtain and their collection is an invasive method. They can be
370 collected during a surgery of orbital decompression, which is possible only when the
371 inflammation is calming down. It means also that such samples could not be
372 extrapolated for basic diagnosis nor used as preventive tool. In these situations,
373 common biofluids such as blood seem to be more appropriate for biomarker
374 investigation. However, considering the past, whatever the disease, there has been
375 little success in translating these findings into clinical applications.

376 More unusual samples including tears have recently emerged as new global source
377 of biomarkers and could be promising and innovative clinical tests in TAO disease in
378 the near future. Because tear sampling is a non-invasive and rapid method, tear-
379 based approaches open promising avenues for diagnostic method and will allow
380 opportunities for deepening understanding of this challenging orbital disease. In
381 addition, as a complex mixture, tears offer the possibility of discovering not only
382 proteins but also RNAs, lipids, metabolites biomarkers that could interestingly
383 complement the traditional clinical tools available for ophthalmologists.

384

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389 **Author disclosure statement**

390 The authors declare that they do not have any commercial relation that might create
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399

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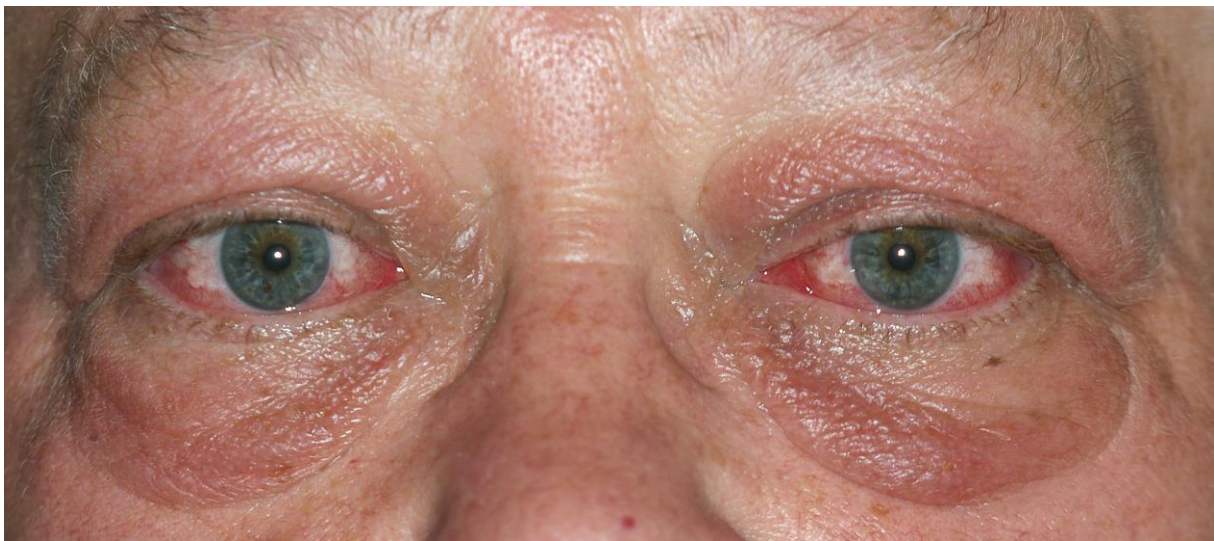
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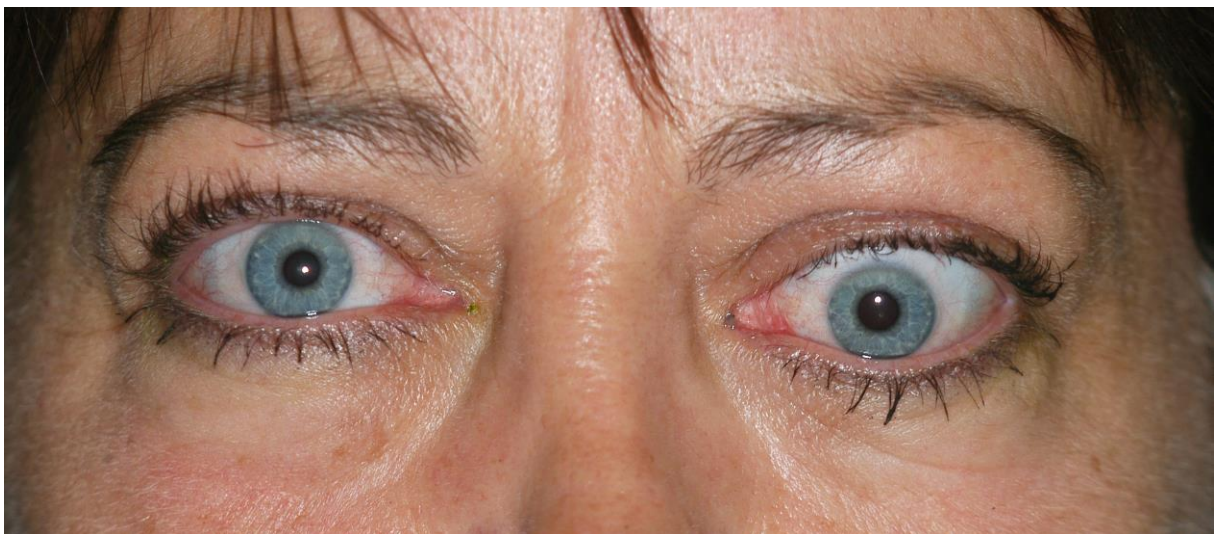
666 **Figures**

667 FIG. 1. Bilateral inflammatory Thyroid-Associated Orbitopathy with oedema and redness of
668 eyes and lids



669

670 FIG. 2. Left unilateral exophthalmos with limitation in upgaze and diplopia (double vision).



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