

Hashimoto Risk Factor Paper Revision 2

Response to Referees:

- 1) *Abstract :Your statement: “Because the risk of ophthalmopathy in patients with Hashimoto's thyroiditis decreases with age older patients should be advised not to smoke as a preventive measure against ophthalmopathy development”. This sentence has no sense. The first and second part of the sentence are not causally connected. Every patient should refrain from smoking as a preventative measure and not only older patients.*

The reviewer believes this comment makes no sense as all patients would be advised not to smoke as a preventative measure, not only in older patients. Because the risk of ophthalmopathy in patients with Hashimoto's thyroiditis is linked to smoking at all ages, patients with Hashimoto's thyroiditis should be advised not to smoke as a preventive measure against development of ophthalmopathy, regardless of their age. Many ophthalmologists use the risk of loss of sight to scare patients (with Graves' disease) into not smoking and it would be quite appropriate to point out that younger patients with Hashimoto's thyroiditis are at greater risk than older patients. This section has been changed to make better sense.

- 2) *Please replace as triggered is (Pg 4)*

We have made this correction

- 3) *Diagnosis of ophthalmopathy etc*

As the reviewer knows, it is difficult to determine who does and who does not have ophthalmopathy. One could say that patients have ophthalmopathy if they have any inflammatory changes that are not due to other causes, e.g. sun damage; such patients would be defined as having Nunery 1 i.e. ophthalmopathy but no eye muscle involvement. Of course, Nunery 2 means the patient has eye muscle involvement, or ocular myopathy, with or without congestive changes; this too is considered ophthalmopathy. Thus, we have defined ophthalmopathy, for convenience we define any ophthalmopathy a NOSPECS class of ≥ 1 (having excluded other causes for eyelid changes) regardless of the CAS (since this measures activity not severity), or Nunery class. This is subjective but it does need to be defined and this has now been clarified the manuscript (REV02).

- 4) *Explain the abbreviation UER (Pg 6)*

UER means Upper Eyelid Retraction, which indicates upper eyelid disease which is often a characteristic of patients with Hashimoto's thyroiditis, if looked for.

- 5) *Please explain expression Nunery 1 (pg 6)*

Nunery 1 is ophthalmopathy with congestive changes, without eye muscle disease. Nunery 2 is ophthalmopathy with eye muscle involvement which indicates a more severe disease which corresponds to a higher NOSPECS class. We have gone through the manuscript carefully to clarify the use of Nunery 1 and Nunery 2 what we mean by and “severe” eye disease. Nunery 4 is a clumsy expression and we have eliminated that. Of course there is no Nunery 4, just Nunery 1 and Nunery 2 as defined by Nunery (an ophthalmologist) and used by us in our publications over the past many years.

6) *“Nunery 4” (Pg 7)*

Socalled “mixed disease” comprises congestive changes plus eye muscle involvement, i.e. Nunery 2, and is a more severe disease (NOSPECS class 4). However, for the purpose of this study we have defined severe disease as a NOSPECS class of ≥ 3 , which includes the 3 patients with ocular myopathy (Nunery 2) even if they did not have congestive changes or proptosis (so called “pure ocular myopathy”).

7) *Do not explain the abbreviation CAS again (Pg 7)*

I agree it should be described once only and subsequently we have used the abbreviation CAS.

8) *Missing data (Pg 7)*

The missing data have been inserted into the manuscript.

9) *Nunery 2*

Nunery 2 was observed in 3 patients who were indeed in the group with “severe ophthalmopathy”. Patients cannot have Nunery 1 plus Nunery 2. This is an error in the way the first author analysed the patients and classified them. This has been corrected to be consistent with the description of severe eye disease as defined above.

10) *Table 1 abbreviation TPO*

TPO is the abbreviation for “thyroid peroxidase” and TPO Ab(s) is the abbreviation for TPO antibodies. We have carefully checked this throughout the manuscript and made it consistent. Other authors follow this convention.

11) *How was TED established*

This has already been addressed above and is now carefully annotated in the legend of Table 1. Any ophthalmopathy was taken as a NOSPECS of ≥ 1 .

Table 2 Patients with CAS 3 or more etc.

The referee knows that most patients with Hashimoto's thyroiditis have fairly mild disease but did not have ocular myopathy. CAS describes the activity not the severity. It is true that 14 out of 105 patients, which is not a large number, had active eye disease, but the disease is mainly mild. In patients with Graves' disease, the prevalence of active eye disease is greater than that, but again this depends on how one uses the CAS and measurements of the severity of the eye disease. Eye disease can be severe but inactive and *vice versa*.

Orbitopathy is common in Hashimoto's thyroiditis, as we have published, and continually find. I point out that one must actually look for the signs before deciding that a patient does not have eye disease and these are mainly upper eyelid retraction and lag, and the symptoms of; itchy, gritty, watery eyes with some swelling. The disease is therefore usually mild. Eye muscle involvement is not common, but occurs. The eye disease can be active and it tends to be rather chronic but is not severe.