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PART 1:

Journal Name:	<u>Ophthalmology Research: An international Journal</u>
Manuscript Number:	2013_OR_4562
Title of the Manuscript:	Identification of risk factors for the development of ophthalmopathy in patients with Hashimoto's thyroiditis
Type of the Article	Research paper

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- This form has total 7 parts. Kindly note that you should use all the parts of this review form.



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PART 2: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	1. Hashimoto's thyroiditis is a very frequent disease. Therefore, I would expect significantly higher number of patients included in the period between 2007 and 2012. Why is the number of patients so low?	1. Indeed, large numbers of patients with Hashimoto's thyroiditis are seen at the thyroid clinics at Nepean Hospital. All patient details from 2007 - 2012 were archived, however only those with complete data sets e.g. only patients who received full eye examination, are included in the study details are missing - such as smoking status or biochemical tests or treatment for > 3 months, these patients were later excluded. The number that we finally studied reflects those patients seen in this period in whom complete data sets were obtained and for the purposes of this retrospective study. To summarise; all patients were included in the archives / database initially, but by the time we had excluded those in whom full data sets were not available, the number left with complete data sets, some of whom had eye disease and some of whom did not have eye disease, were included. We studied patients with Hashimoto's thyroiditis, with and without ophthalmopathy. This has been clarified in the manuscript

	2. From the manuscript, it is not clear how authors established the patient cohort (consecutive patients? randomly selected patients? patients with TED?). 2. Again, referring back to point No. 1, data from <u>all</u> patients in the thyroid clinics have been recorded in an extensive data base. We decided to access all patients with Hashimoto's thyroiditis from 2007 – 2012 and to include, in the present study only those in whom complete data sets were obtained, as described, thus the starting point were all patients, not randomly selected and not just patients with above thyroid eye disease.
	3. Authors should specify the hormonal status of the patients. Were they hypothyroid, euthyroid or hyperthyroid? They should include data on TSH and thyroid hormones. 3. The patients were typical of a cohort of patients with Hashimoto's thyroiditis. Most patients were first seen and included in the study at the time when the TSH was increased and they were hypothyroid. Some patients were euthyroid and referred because of previously high TSH and /or high levels of thyroid antibodies and two patients were included who were hyperthyroid initially. The latter is a rare manifestation of Hashimoto's thyroiditis and none of the patients studied were hyperthyroid at the onset of their disease, or subsequently. We have now re-grouped patients according to TSH status and



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	4. Why authors included also treated patients and not only untreated patients? They should explain the impact of treatment on the presentation of TED emphasising the role of TSH concentration on the activity of TED.	thyroid function at the time of study i.e. at the first visit, as shown in new Table 7. We studied patients at the first visit only, with no follow-up for Vitamin D treatment. The aim of the project was to determine risk factors for the development of ophthalmopathy in these carefully selected patients with typical Hashimoto's thyroiditis. However, the influence of hormonal status (TSH, T4) on the development of TED in patients with Hashimoto's thyroiditis is indeed an interesting question that will be addressed in a separate paper, as it has been done very recently for Graves' associated ophthalmopathy 4. We are aware of the possible role of TSH in ophthalmopathy and thus of thyroxin treatment of patients with ophthalmopathy. However, TSH appears not to be a risk factor for the development of ophthalmopathy in our patients, as shown in new table 7. We did not wish to determine the effects of vitamin D treatment on eye signs. We only wanted to identify risk factors for ophthalmopathy in patients with Hashimoto's thyroiditis seen at the thyroid clinics by a single investigator early in the
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	course of their illness, whether euthyroid or hypothyroid. Patients included were either not treated (with thyroxin) or treated for < 3 months. We have not followed up our patients, but are studying any effects of treatment in our other studies.
5 . It is not clear, if all patients were TSH-receptor antibodies negative and they did not have Graves' disease.	5. All patients had Hashimoto's thyroiditis as defined from the usual well known criteria. TSH receptor antibodies are not measured routinely in these patients. Where measured, these antibodies were always negative. The patients had Hashimoto's thyroiditis according to classical criteria abnormal thyroid function in many of them, positive thyroid antibodies and information obtained from real-time ultrasonography carried out by the senior author who can determine with great accuracy the stage of inflammation in these patients. No patients with Graves' disease were included in the study.
6. I was surprised by the high portion of patients with TED among patients with Hashimoto's thyroiditis. In my clinical experience (I see around 100 thyroid patients weekly) TED is very rare in patients with Hashimoto's thyroiditis. Is there a possibility, that some of the patients included	6. We have published showing that about 25% of patients with Hashimoto's thyroiditis have ophthalmopathy, if looked for. The eye signs are usually mild but definite. A few patients had more severe disease with double vision, proptosis and



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	actually had Graves' disease? This is not clear from the manuscript.	eye muscle damage, but the majority have eye lid signs and symptoms including itchiness, grittiness, watery eyes, eye lid swelling and upper eye lid retraction and lag. The latter signs are clearly identifiable if the clinician actually studies the eyes. A typical patient with Hashimoto's thyroiditis is a young female with positive thyroid antibodies, family history of thyroid autoimmunity, a goitre and white eyes above the iris due to upper eye lid retraction. No patients with Graves' disease were included in the study. Graves' eye disease is quite different and these patients are hyperthyroid with positive TSH receptor antibodies, diffuse goitre and the classical clinical features and biochemical abnormalities. Our patients were very carefully characterised and selected with full clinical information obtained including eye assessment by experts who study eye disease on a day by day basis, real-time thyroid ultrasonography, biochemical testing and thyroid antibody testing.
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	7. Authors should include data on TSH-receptor antibodies (second generation). Otherwise, the whole manuscript is questionable.	7. This is not true. Hashimoto's thyroiditis is a different disease and the eye signs were carefully assessed as described. Where measured TSH receptor antibodies are always negative and no patient included had Graves' disease (which is a very different disease). Whilst it is true that TSH receptor antibodies could be considered a risk factor for the eye changes of Hashimoto's thyroiditis this assessment was not included in the study because the antibodies are not measured routinely in patients with Hashimoto's thyroiditis (there is no reason to do so) and because they are negative. Antibodies were measured in about 10% of patients, and were always negative (where tested for) and these patients were representative of the whole cohort of Hashimoto's patients.
	8. It is not clear, how and by whom the activity and the severity of TED have been established. Have all patients been examined by an ophthalmologist?	8. All patients were examined by one observer, Jack R Wall senior author, who has carried out research into thyroid eye disease for 30 years. Patients were only referred to an ophthalmologist where necessary i.e. in the rare case where patients had severe progressive disease. All patients at the thyroid clinic at Nepean Hospital are studied using a single protocol



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		for assessment of eye signs associated with thyroid autoimmunity. These are standard criteria developed by the authors over decades, and incorporating, for the major assessments, the standard NOSPECS, Clinical Activity Scores, Nunery 1 and 2 and the author's upper eye lid retraction score (since the aforementioned classifications do not recognise mild eye and eye lid changes which are common in patients with Hashimoto's thyroiditis).
<u>Minor</u> REVISION comments	Page 4, line 76: instead of "is triggered is" please correct into "is triggered"	In addition to this error we have made multiple small changes to the manuscript to improve its presentation. We have checked for typos and made the tables and text consistent.
<u>Optional/General</u> comments		