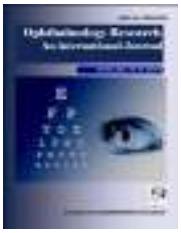

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# Risk Factors for the Development of Ophthalmopathy in Patients with Hashimoto's Thyroiditis

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***Authors' contributions***

*This work was carried out as collaboration between all authors. Author JRW Director of the Thyroid Research Group was responsible for the ideas behind the study, data interpretation, responses to the reviewers (Rev 01, 02 and 03) and preparation of the final draft of the manuscript. Author IEK prepared the data base for the study, collated and analyzed the data, carried out the statistical tests and analyses and wrote the first draft of the paper. Author BC contributed to the intellectual aspects of the study and its design helped write the final drafts of the paper and contributed to the "responses to reviewers" for REV 01 and 02 and the literature searches. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background**: Ophthalmopathy, or thyroid eye disease (TED), is more often associated with Graves' hyperthyroidism than Hashimoto's thyroiditis. In the latter disorder, the pathogenesis of the eye signs may be different and the influence of well-known risk factors for the development of eye signs in patients with Graves' hyperthyroidism, such as smoking, age and gender, have not been studied in patients with Hashimoto's thyroiditis. The aim of our study was to identify the risk factors which might influence the development of ophthalmopathy in patients with Hashimoto's thyroiditis.
**Methods**: A retrospective cross sectional study included 105 patients with Hashimoto's thyroiditis with and without ophthalmopathy and investigated 6 potential risk factors namely; age, gender, smoking, vitamin D deficiency, serum TSH and serum levels of antibodies to thyroid peroxidase (TPO) and thyroglobulin (Tg). A binary logistic regression test was used to determine whether one or more of the factors were predictive for i) ophthalmopathy ii) upper eyelid retraction (UER), often the only sign in patients with

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Hashimoto's thyroiditis iii) the type of ophthalmopathy (congestive ophthalmopathy, ocular myopathy or both) or iv) the activity of the eye disease assessed as Clinical Activity Score (CAS), in patients with Hashimoto's thyroiditis.

**Results**: Our analyses showed a protective effect of ageing on the development of ophthalmopathy in patients with Hashimoto's thyroiditis, the risk decreasing by 5.4% for each additional year and a detrimental effect of smoking, with a risk of ophthalmopathy 5.5 times greater in smokers. Increased serum TSH was not shown to be a risk factor for ophthalmopathy or its severity. High serum levels of TPO antibodies were found to be protective against the development of UER but not ophthalmopathy. None of the tested factors seemed to influence the risk of any ophthalmopathy subtype namely, congestive ophthalmopathy, ocular myopathy or mixed disease. However, gender has an effect on the activity of ophthalmopathy, men with Hashimoto's thyroiditis related eye disease being 18 times more likely to develop active ophthalmopathy than women.

**Conclusions**: Because the risk of ophthalmopathy in patients with Hashimoto's thyroiditis decreases with age, but 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. Hashimoto's thyroiditis-related ophthalmopathy is more active in male patients who should therefore be monitored more closely. The mechanism for the observed risk reduction of UER development in the presence of high levels of TPO antibodies could be studied to help with our understanding of the pathophysiology of ophthalmopathy and the development of new therapies.

*Keywords: Hashimoto's thyroiditis, ophthalmopathy, smoking, vitamin D, autoantibodies, upper eyelid retraction.*

## 1. INTRODUCTION

The pathogenesis of thyroid eye disease (TED) or endocrine ophthalmopathy has been thoroughly investigated. It has been suggested that fibroblasts, rather than myocytes are the main targets of the autoimmune attack. Focal infiltrations of lymphocytes in the orbit are similar in structure to those found in the thyroid gland of patients with auto-immune thyroiditis, the so-called thyroid associated lymphoid tissue (TALT) phenotype [1]. TALT is thought to be involved in a local production of thyroid autoantibodies and generation of auto reactive T cells, which starts in the draining lymph nodes. Because the eye muscles share their draining lymph nodes with the thyroid [2], this notion of redistribution of lymphocytes expressing thyroid specific homing receptors (addressins) from lymph nodes to thyroid [3] may similarly involve the eye muscles. The pathophysiology of ophthalmopathy could thus be explained by recognition of a shared autoantigen such as a TSH-receptor peptide(s), heat shock proteins or the "64kDa protein" by a specific homing pattern of the thyroid-reactive lymphocytes to the eye muscles (shared addressins/adhesion molecules) [1].

With progression of the eye disease and over production of ground substance and collagen in the endomysium and perimysium, the muscle fibres become progressively compressed and finally atrophie [1]. This muscle fibre destruction is thought to be followed by the production of eye muscle autoantibodies as occurs following cardiac infarction which leads to the production of autoantibodies to heart muscle cells [1]. The main eye muscle antigen appears to be calsequestrin although the corresponding serum antibodies are detected in only a third of patients with active ophthalmopathy, in one study but more often in others [4]. The notion that ophthalmopathy is triggered by eye muscle autoantibodies appears unlikely and the ophthalmopathy seems more closely related to the "thyroiditis" than being an

independent entity [5]. Thus, ophthalmopathy should logically be associated with both Graves' disease and Hashimoto's thyroiditis. Indeed, there is good evidence that orbitopathy does occur in patients with Hashimoto's thyroiditis [1,6], although less often and when present, the eye changes are usually less severe, often manifest as upper eyelid retraction (UER) only.

Age, gender and smoking have been clearly associated with the presence of ophthalmopathy in patients with Graves' disease, but these associations were not investigated in patients with Hashimoto's thyroiditis [7]. Age and gender were found to influence the severity of ophthalmopathy in a cohort of 101 patients attending a thyroid-eye clinic, which included 9 patients with Hashimoto's thyroiditis [8]. Graves' disease was shown to be milder and Hashimoto's thyroiditis less prevalent in aged patients, probably because of a reduced responsiveness of the aged thyrocyte to autoantibodies [9]. Several other studies confirmed that male patients with Graves' disease were more at risk for a severe ophthalmopathy [10].

The effect of smoking in patients with Hashimoto's thyroiditis is controversial, mainly because only a few studies are available [11-13]. More recent studies suggest that smokers with either Graves' disease or Hashimoto's thyroiditis are more at risk for ophthalmopathy [6,14]. Some studies have been reported to imply an association between smoking and negative thyroid peroxidase (TPO) antibodies in patients with Hashimoto's thyroiditis [11] while negative TPO antibodies in patients with Graves' hyperthyroidism was found to be a risk factor for ophthalmopathy [15]. The greater severity of Graves' disease in male and young patients has been suggested by their low rate of remission, requiring a more aggressive management [16]. Moreover, higher titres of circulating thyroid autoantibodies were found in elderly patients with Graves' disease compared to young patients [17]. Finally, serum TSH has been shown to be a risk factor for progression of ophthalmopathy in patients with Graves' ophthalmopathy [18]. This study is the first to investigate all the various known and possible risk factors for ophthalmopathy in patients with Hashimoto's thyroiditis.

## 2. CLINICAL SUBJECTS AND METHODS

### 2.1 Clinical Subjects

The study was a retrospective analysis of data from medical records of patients who attended the endocrinology clinics at Nepean Hospital (Kingswood, NSW, Australia) between 2007 and 2012. All records of thyroid clinic patients were examined and only patients with a confirmed and recent diagnosis of Hashimoto's thyroiditis who were either not treated with thyroxin or treated for less than 3 months, were selected. Only data from the first visit were used and only complete data sets were included for the analysis. This was a retrospective audit which was approved by the Nepean Hospital Human Ethics committee. Informed written consent was not required and there were no consent forms.

### 2.2 Eye Assessment

The ophthalmopathy was assessed as; i) Nunery type 1 (without restrictive myopathy) or type 2 (with restrictive myopathy) [19] ii) a modified Clinical Activity Score (CAS) (0-12) of Mourits et al. [20] which is a measure of disease activity iii) Werner's NOSPECS classes [21] and iv) upper eyelid margin-reflex distance (MRD) which is the distance between the centre of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze, as a

measure of eyelid retraction; an MRD of > 5mm is taken as significant UER, from which an UER score of 0 – 12 is calculated [22]. The degree of proptosis (mm) was measured using a Hertel exophthalmometer where a positive reading was defined as > 18mm in either eye or > 2 mm difference between the eyes. For the purpose of the study; i) "ophthalmopathy" was taken as a NOSPECS class ≥ 1 having ruled out other causes of UER such as hyperthyroidism, anxiety, contact lenses and allergies, regardless of the CAS ii) severe ophthalmopathy was taken as a NOSPECS class of ≥ 3 and including any patient with ocular myopathy, i.e. Nunery 2, even if eye muscle dysfunction was the only manifestation of the ophthalmopathy and iii) "more active" ophthalmopathy was defined as a CAS of > 3.

### 2.3 Measurement of Serum Vitamin D, TSH and Thyroid Antibodies

All laboratory results were generated by the same institution namely, Barratt and Smith Pathology Sydney using commercial kits. A patient with a serum level of vitamin D below 51nmol/l was considered as having a vitamin D deficiency (lab normal range: 51-140nmol/l). Patients who received vitamin D supplementation before their first visit were excluded from the study. The laboratory cut off titres for TPO antibody was < 10 IU/ml (range 0-120) and for TG antibody, < 20 IU/ml (range 0-90). The normal range for TSH was 0.4-4.0 mIU/L.
Statistical analysis

For continuous variables, means and standard deviations or medians and interquartile ranges were computed. Normality was tested using the Kolmogorov Smirnov and the Shapiro Wilks tests. Binary logistic regression analysis was performed to identify the predicting factors. Four separate logistic regression calculations were performed to identify risk factors for 1) ophthalmopathy and 2) UER. A p value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics version 19 was used for all analyses.

## 3. RESULTS

### 3.1 Demographics of the Study Population

The number of patients included in this study is 105, comprising 97 women and 8 men with Hashimoto's thyroiditis of whom 29 (27%) had eye signs and 76 had no eye signs at the first visit. Patients were examined at the first thyroid clinic visit and data from any follow up were not included in this analysis. Of these, only those patients with complete data sets, including full eye examination, were included in the analyses. The lowest age of the studied cohort was 14 years and the highest was 82. The median age was 48. The patients were then categorised as "old" or "young" when their age was above or equal/below 50. Among the selected patients, 25% were smokers, 89.2% were positive for TPO antibodies, 45.7% were positive for TG antibodies and 46% were vitamin D deficient. The calculated median value of TG and TPO serum levels was approximately 400 IU/ml in our cohort. This value was then chosen as a threshold to categorise patients as having low or high TPO or TG serum levels. Those details are summarised in Tables 1 and 2.

### 3.2 Risk Factors for Ophthalmopathy in Patients with Hashimoto's Thyroiditis

After exclusion of patients with incomplete data set, 86 patients were included in the binary logistic regression analysis. Ageing has a statistically significant protective impact against the development of ophthalmopathy in patients with Hashimoto's thyroiditis. Each additional

year of age decreases the risk for ophthalmopathy by 5.4%. On the other hand, smoking has a statistically significant negative effect, exposing patients with Hashimoto's thyroiditis to a 5.5 times higher risk for ophthalmopathy. Gender, vitamin D deficiency and serum levels of TPO and TG antibodies were not predictive for ophthalmopathy in patients with Hashimoto's thyroiditis (Table 3).

**Table 1. Contingency table for the investigation of risk factors for ophthalmopathy and upper eyelid retraction in patients with Hashimoto's thyroiditis**

| | [1]TED | No TED | Total | [2]UER | No UER | Total |
|---|---|---|---|---|---|---|
| Age > 50 yr | 9 | 38 | 47 | 13 | 22 | 35 |
| Age < 50 yr | 20 | 38 | 58 | 25 | 25 | 50 |
| Men | 3 | 5 | 8 | 5 | 3 | 8 |
| Women | 26 | 71 | 97 | 33 | 44 | 77 |
| Smoker | 9 | 12 | 21 | 8 | 8 | 16 |
| Non smoker | 20 | 64 | 84 | 30 | 39 | 69 |
| Vitamin D deficiency | 10 | 31 | 41 | 12 | 18 | 30 |
| No vitamin D deficiency | 15 | 33 | 48 | 23 | 23 | 46 |
| [3]TPO Ab titre > 400 | 15 | 43 | 58 | 15 | 31 | 46 |
| TPO Ab titre < 400 | 11 | 22 | 33 | 16 | 11 | 27 |
| Negative TPO Abs | 3 | 8 | 11 | 6 | 3 | 9 |
| [4]TG Ab titre > 400 | 6 | 15 | 21 | 3 | 11 | 14 |
| TG Ab titre < 400 | 9 | 18 | 27 | 10 | 12 | 22 |
| Negative TG Abs | 14 | 43 | 57 | 25 | 24 | 49 |

*[1]TED = thyroid related eye disease (NOSPECS class 1 or more)*
*[2]UER=upper eyelid retraction*
*[3]TPO = thyroid peroxidase (Ab = antibody, Abs = antibodies)*
*[4]TG = thyroglobulin*

**Table 2. Contingency table for the investigation of risk factors for ophthalmopathy subtypes and severity in patients with Hashimoto's thyroiditis**

| | [1]Nunery 1 | Nunery 2 | Total | [2]CAS 1, 2 | CAS 3-5 | Total |
|---|---|---|---|---|---|---|
| Age >50 yr | 10 | 0 | 10 | 28 | 4 | 32 |
| Age < 50 yr | 25 | 3 | 28 | 38 | 10 | 48 |
| Men | 5 | 1 | 6 | 3 | 4 | 7 |
| Women | 30 | 2 | 32 | 63 | 10 | 73 |
| Smoker | 7 | 1 | 8 | 12 | 4 | 16 |
| Non smoker | 28 | 2 | 30 | 54 | 10 | 64 |
| Vitamin D deficiency | 13 | 0 | 13 | 20 | 7 | 27 |
| No vitamin D deficiency | 18 | 2 | 20 | 38 | 6 | 44 |
| [3]TPO Ab titre > 400 | 19 | 1 | 20 | 38 | 6 | 44 |
| TPO Ab titre < 400 | 13 | 1 | 14 | 20 | 5 | 25 |
| Negative TPO Abs | 3 | 1 | 4 | 6 | 3 | 9 |
| [4]TG Ab titre > 400 | 7 | 0 | 7 | 13 | 1 | 14 |
| TG Ab titre < 400 | 12 | 0 | 12 | 18 | 2 | 20 |
| Negative TG Ab | 16 | 3 | 19 | 35 | 11 | 46 |

*[1]Nunery 1 = congestive ophthalmopathy, Nunery 2 = ocular myopathy [19]*
*[2]CAS = Clinical Activity Score [20]*
*[3]TPO = thyroid peroxidase (Ab = antibody)*
*[4]TG = thyroglobulin*

**Table 3. Identification of predicting variables for ophthalmopathy in patients with Hashimoto's thyroiditis**

| Variables | [1]*p*Value | Exp (B) | 95% C.I. for EXP (B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | .014 | .946 | .904 | .989 |
| Smoking | .010 | 5.515 | 1.500 | 20.269 |
| Gender | .217 | 3.028 | .521 | 17.579 |
| Vitamin D | .635 | 1.005 | .984 | 1.027 |
| [2]TPO Abs | .569 | 1.000 | 1.000 | 1.000 |
| [3]TG Abs | .616 | 1.000 | 1.000 | 1.000 |

*[1]Statistical analyses refer to comparison between groups Binary logistic regression analysis was performed to identify the predicting factors. A p value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics version 19 was used for all analyses.*
*[2]TPO = thyroid peroxidase (Abs = antibodies)*
*[3]TG = thyroglobulin*

## 3.3 Risk Factors for UER in Patients with Hashimoto Thyroiditis

After exclusion of patients with incomplete data set, 73 patients were included in the binary logistic regression analysis (Table 4). Age, gender, smoking and vitamin D deficiency did not appear to contribute to the development of UER in patients with Hashimoto's thyroiditis. The risk for UER is significantly decreased when patients have high serum levels of TPO antibodies. A similar trend was observed with high serum levels of TG antibodies but this was not statistically significant.

**Table 4. Identification of predicting variables for upper eyelid retraction in patients with Hashimoto's thyroiditis**

| Variables | [1]*p*Value | Exp (B) | 95% C.I. for EXP (B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | .118 | .965 | .923 | 1.009 |
| Smoking | .167 | 2.683 | .662 | 10.866 |
| Gender | .396 | 2.189 | .359 | 13.357 |
| Vitamin D | .836 | 1.002 | .982 | 1.022 |
| [2]TPO Abs | .010 | .258 | .091 | .726 |
| [3]TG Abs | .130 | .290 | .059 | 1.440 |

*[1] Statistical analyses refer to comparison between groups Binary logistic regression analysis was performed to identify the predicting factors. A p value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics version 19 was used for all analyses.*
*[2] TPO = thyroid peroxidase (Abs = antibodies)*
*[3] TG = thyroglobulin*

## 3.4 Risk Factors for Severe Ophthalmopathy in Patients with Hashimoto's Thyroiditis

After exclusion of patients with incomplete data set, 33 patients were included in the binary logistic regression analysis. Type 2 ophthalmopathy as defined in the Nunery classification [19] (ocular myopathy) was observed in only 3 of our patients. Taking a NONSPECS class of ≥ 3 as a more severe ophthalmopathy, we compared these patients with those with milder

eye disease (NOSPECS classes 1 or 2); none of the investigated risk factors were found to influence the development of a more severe ophthalmopathy (Table 5).

**Table 5. Identification of predicting variables for severe ophthalmopathy in patients with Hashimoto's thyroiditis**

| Variables | [1]*p*Value | Exp (B) | 95% C.I. for EXP (B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | .642 | .968 | .843 | 1.111 |
| Smoking | .332 | 8.272 | .116 | 589.361 |
| Gender | .999 | [2]** | ** | ** |
| Vitamin D | .299 | 1.072 | .940 | 1.223 |
| [3]TPO Abs | .987 | .973 | .038 | 24.718 |
| [4]TG Abs | .999 | ** | ** | ** |

*[1]Statistical analyses refer to comparison between groups Binary logistic regression analysis was performed to identify the predicting factors. A p value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics version 19 was used for all analyses.*

*[2]** = Value could not be calculated*

*[3]TPO = thyroid peroxidase (Abs = antibodies)*

*[4]TG = thyroglobulin*

*Severe ophthalmopathy was defined as a NOSPECS class of ≥ 3 and includes all 3 patients with Nunery 2 disease (ocular myopathy)*

## 3.5 Risk Factors for more Active Ophthalmopathy in Patients with Hashimoto's Thyroiditis

After exclusion of patients with incomplete data set, 69 patients were included in the binary logistic regression analysis (Table 6). Among the investigated risk factors, only gender showed a statistically significant influence on the activity of ophthalmopathy in patients with Hashimoto thyroiditis. Male patients are indeed 18 times more at risk for a highly active ophthalmopathy, defined as a Clinical Activity Score (CAS) of > 3. However, it has to be noted that men are relatively underrepresented in our cohort, although it is well known that autoimmune thyroiditis is more prevalent in women than in men with a ratio up to 10:1 [3].

**Table 6. Identification of predicting variables for highly active ophthalmopathy in patients with Hashimoto's thyroiditis**

| Variables | [1]*p*Value | Exp (B) | 95% C.I. for EXP (B) | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Age | .314 | .969 | .912 | 1.030 |
| Smoking | .082 | 4.19 | .836 | 21.04 |
| Gender | .013 | 18.173 | 1.852 | 178.289 |
| Vitamin D | .229 | .981 | .951 | 1.012 |
| [2]TPO Abs | .376 | .543 | .140 | 2.101 |
| [3]TG Abs | .208 | .182 | .013 | 2.572 |

*[1]Statistical analyses refer to comparison between groups Binary logistic regression analysis was performed to identify the predicting factors. A p value < 0.05 was considered statistically significant. The statistical software IBM SPSS Statistics version 19 was used for all analyses.*

*[2]TPO = thyroid peroxidase (Abs = antibodies)*

*[3]TG = Thyrobliobulin*

*Highly active disease was defined as a CAS of > 3*

### 3.6 Serum TSH as a Possible Risk Factor for Ophthalmopathy or UER in Patients with Hashimoto's Thyroiditis

Initial serum TSH levels were correlated with the presence of ophthalmopathy or UER in patients with Hashimoto's thyroiditis. These results are summarised in Table 7. Overall, there were no significant differences in the prevalence of ophthalmopathy or UER in patients with Hashimoto's thyroiditis with either increased (>3.0) TSH or normal (0.4-3.0 mU/L) TSH at the initial study visit, suggesting that serum TSH was not a risk factor for eye disease or UER in patients with Hashimoto's thyroiditis (Table 7).

**Table 7. Serum TSH as a possible risk factor for ophthalmopathy and upper eyelid retraction in patients with Hashimoto's thyroiditis**

| | Ophthalmopathy | No ophthalmopathy | [1]UER | No UER |
|---|---|---|---|---|
| Increased TSH(>4.0 mIU/L) | 15 | 22 [2]p = NS | 9 | 26 p = NS |
| Normal TSH(0.4-4.0 mIU/L) | 25 | 20 p = NS | 17 | 27 p = NS |

*[1] UER = upper eyelid retraction*

*[2]analyses refers to differences between increased TSH and normal TSH determined using Fisher's exact test*

## 4. DISCUSSION

In patients with Hashimoto's thyroiditis, ophthalmopathy has the same general demographics, clinical characteristics and severity and activity scores as in patients with Graves' disease [3]. It is therefore not surprising that in our cohort the observed effect of age, gender, smoking and TPO antibodies on the eye signs in patients with Hashimoto's thyroiditis is similar to those reported for Graves' disease [7,10,16,17,23,24].

There is a general agreement on the existence of so-called immunosenescence involving mainly the T cells [25-27]. Interestingly, it has been demonstrated experimentally that the efficiency of self-tolerance is reduced in young individuals, who are therefore more susceptible to the development of multiple sclerosis after exposure to an environmental trigger [28]. It has also been demonstrated that the proportion of regulatory T cells, which maintain peripheral tolerance by suppressing auto-reactive T cells [7], increases with age [29]. It would be interesting to compare the proportion of regulatory T cells for both Graves' disease and Hashimoto's thyroiditis.

In men, autoimmune thyroiditis is less prevalent, but is associated with a greater risk to develop more severe ophthalmopathy than in women [8,10]. This greater risk for severe autoimmunity in men was explained, in the case of systemic lupus erythematosus, by a higher cumulative genetic load required for men to develop the disease [30]. An amino acid change in the HLA-DR β1 chain, from glutamine into arginine at position 74, was shown to confer a strong risk for both Graves' disease and Hashimoto's thyroiditis [31]. It was demonstrated that this amino acid change results in a unique structure of the HLA-DR pocket which becomes able to bind auto-antigenic peptides and present them efficiently to T cells. A variant of the thyroglobulin gene (W1999R) was found to have a strong genetic interaction with HLA-DRβ-Arg74, which increases the susceptibility to Graves' disease. Most of these susceptibility genes were shown to have individually a weak effect and it has been estimated that more than 20 different variants are required to develop autoimmune thyroiditis

[32]. It would be interesting to compare the genetic load required for men to develop Hashimoto's thyroiditis and ophthalmopathy compared to women.

TPO and TG antibodies are markers for Hashimoto's thyroiditis and may play a pathogenetic role. TPO antibodies are detected in more than 90% of the patients with Hashimoto thyroiditis, while TG antibodies are detected in a lower proportion. TPO antibodies production was shown to be genetically determined [33]. We postulate that the observed association between high levels of circulating TPO and the absence of UER is more likely to be due to shared genetic determinants which are still to be identified and would regulate both features in an opposite manner.

Vitamin D deficiency was shown to have a role in the development of autoimmune diseases [type1 diabetes and Addison's disease [34] whereas the stimulation of vitamin D receptor (VDR), which is expressed by tolerogenic dendritic cells, promotes self-tolerance. An association between VDR gene polymorphisms and Hashimoto's thyroiditis has been identified in different populations [35]. In our cohort, vitamin D deficiency does not influence ophthalmopathy.

TSH has also been implicated in the development of ophthalmopathy or its worsening, following radioiodine therapy in patients with Graves' disease, presumably as a result of its tropic action on the orbital inflammation. This was not observed in our patients with Hashimoto's thyroiditis, possibly because their TSH levels were normal or only mildly elevated at presentation at the thyroid clinics in the majority of cases.

The detrimental effect of smoking on ophthalmopathy is well established for Graves' ophthalmopathy (GO). It increases by 4 times the risk for developing or worsening GO. We observed a similar effect of smoking on the development of ophthalmopathy in patients with Hashimoto's thyroiditis. Several mechanisms have been suggested as an explanation for the adverse effect of cigarette smoking on GO. One of these mechanisms is tissue hypoxia which induces the secretion of large amounts of glycosaminoglycans (GAGS) by cultured orbital fibroblasts. The accumulation of these GAGS in orbital tissues contributes to the swelling of extraocular muscles and orbital fat [36]. We think that these mechanisms could also apply for Hashimoto's associated eye disease.

## 5. CONCLUSION

As in the case of Graves' disease, ophthalmopathy in patients with Hashimoto's thyroiditis is less frequent with aging, more active in men and more prevalent in smokers. For the first time, we found an association between high levels of TPO antibodies and the absence of UER which is often the main eye symptom in these patients. This finding may lead to new research avenues to investigate the genetic determinants and the pathophysiology of UER.

## CONSENT AND ETHICAL APPROVAL

Ethics; this was a retrospective audit, which was approved by the Nepean Hospital Human Ethics committee. Informed written consent was not required and there were no consent forms.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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