Thyroid eye disease in New Zealand: interaction between ethnicity and smoking status

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ABSTRACT

AIM: This study was conducted to describe the epidemiology of thyroid eye disease (TED) in New Zealand.

METHODS: One hundred and sixty-one subjects with TED seen over a 14-year period in Auckland, from a combined ophthalmology-endocrinology clinic, had data extracted from clinical notes.

RESULTS: Median age at onset was 47.0±15.1 years and 77.6% were female. Crude yearly incidence of TED (per 1,000,000) was 12.6 in non-smokers and 67.3 in smokers (p<0.001). On univariate analysis, female gender, Māori ethnicity and smoking were associated with incidence of TED. On multivariate analysis, female gender and smoking status were associated with risk of TED, and the difference in ethnicity was explained by smoking status. Māori subjects with TED were more likely to be current smokers (72.7%) compared to European (39.2%), Pacific Peoples (33.3%), Asian (8.3%) and Other (12.5%). Māori ethnicity and current smokers were associated with a higher clinical activity score at presentation (p=0.049 and p=0.027).

CONCLUSION: A strong association was demonstrated with female gender and smoking status and rate of TED. Māori have increased rates of TED; however, this difference was explained by smoking. Eliminating smoking would result in at least a 28.1% reduction in TED incidence in New Zealand.

Thyroid eye disease (TED), also known as thyroid-associated orbitopathy or Graves’ orbitopathy, is an inflammatory condition resulting in cicatricial effects within the orbit. It is the most common orbital disorder in adults and occurs most often in association with autoimmune thyroid disease (most frequently, Graves’ hyperthyroidism). However, the condition is also seen in euthyroid individuals, or occasionally in subjects with hypothyroidism or Hashimoto’s thyroiditis. Most cases are mild, but in 3–5% of subjects severe orbitopathy may lead to loss of vision and/or major cosmetic disfigurement with associated psychological sequelae. Spontaneous improvement is seen in a large proportion of subjects over time; however, with regression of inflammation, fibrosis develops, and the orbital tissues seldom return to the pre-morbid state. General management principles include restoring the euthyroid state, especially in subjects who have become hypothyroid following radio-iodine treatment to reduce the risk of progression of orbitopathy, smoking cessation, supportive therapies and selenium supplementation for subjects with mild disease, targeted immunosuppressive treatments and occasionally urgent surgery for subjects with active and/or severe disease. Surgical rehabilitation is suggested for subjects with stable, inactive disease. Early disease intervention with immunosuppressive therapy such as corticosteroids and radiotherapy diminish disease progression and peak severity. Specific and targeted disease-modifying agents are still lacking although progress with the IGF-1 inhibitory antibody, teprotumumab has shown promising results.

New Zealand has a unique population including the indigenous Māori, European descendants as well as Pacific People. This diversity is ever-widening and includes
arrivals over recent years from other parts of the world, notably Asian countries. There have been many studies on risk factors for TED in European populations but none with the New Zealand population. Response to treatments among subjects with TED in different populations may vary according to the presence of different risk elements. The aim for this study was to assess the epidemiology of TED in New Zealand, compare global risk factor rates to our own and to assess whether our population is indeed reflective of previous studies, focusing on Māori ethnicity.

Methods
Subjects with TED seen over a 14-year period (2004–2018) in a combined ophthalmology-endocrinology clinic in Auckland were selected. All subjects were de-identified once data was collected and placed into our database. This is a retrospective study which adheres to the guidelines of the Declaration of Helsinki and ethics approval was granted.

TED was defined as diagnosis from the ophthalmologist in TED clinic. Subjects who were not diagnosed with thyroid eye disease but were seen in clinic as outliers or emergency oculoplastic appointments were excluded from this study. Subjects who were only seen in the inactive phase with late sequelae were excluded.

We looked at age, gender, smoking status and ethnicity. We grouped ages into categories of five-year periods paralleling New Zealand census data. Smoking status was grouped into current, ex and non-smokers. This information was collected through ophthalmic clinical notes and using Concerto (New Zealand national health index database) to look back at smoking status noted during previous hospital stays or clinic letters. Gender was self-reported by subjects. We had no transgender subjects in our population. Current smokers are defined as having had one or more cigarettes in the last 28 days with an established history of smoking. Ex-smokers are defined as subjects that have an established history of smoking but have not touched a cigarette for a period of greater than 28 days with the intent to quit smoking. Non-smokers are defined as never having smoked a cigarette or total exposure of <10 cigarettes in their life, with nil use in the last year.

We collected specific ethnic data and then collated it in to the six ethnic categories as per the 2013 New Zealand census data: European, Māori, Pacific, Asian, MELAA (Middle Eastern Latin American and African) and Other. Ethnicity was obtained through clinical notes with subjects self-identifying or through Concerto (which is also self-identified). As per Ministry of Health guidelines, subjects who identify with several ethnicities were categorised according to hierarchical classification.

Population data on smoking rates per ethnicity, health insurance rates and ethnic population was taken from the 2013 New Zealand Census and applied or compared to our database. Data was entered into an Excel spreadsheet and analysed in STATA version 15. Normally distributed variables are reported as mean ± standard deviation if normally distributed and median (interquartile range [IQR]) if skewed distribution. Categorical variables are reported as n (%). Continuous variables are compared between groups with t-test or Mann-U Whitney as appropriate, and categorical variables with chi-square. Crude rates of thyroid eye disease were calculated in reference to the Auckland and Waitematā District Health Board population and adjusted rates were calculated by adjusting for health insurance coverage by ethnicity and age distribution of the Auckland population. Rates were compared with Poisson regression analysis and incident rate ratio (IRR) calculated. All tests were two tailed and a p value of <0.05 was considered statistically significant.

Results
One hundred and sixty-one subjects were included in the study. Clinical characteristics are reported in Table 1. Age at onset was 47.0±15.1 years and 125 subjects (77.6%) were female. The median clinical activity score (CAS) was 1 (IQR 0–3). Figure 1 shows the number of current smokers per ethnicity.

Rates of disease by ethnicity are reported in Table 2. Ethnicity values were adjusted for age, private health insurance cover and current smoking status. These adjustment values were based on the most recent 2013 Census data to ensure more accurate representation of the population.
Table 1: Clinical characteristics of subjects with thyroid eye disease.

<table>
<thead>
<tr>
<th></th>
<th>N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>47.0±15.1 years</td>
</tr>
<tr>
<td>Female</td>
<td>125 (77.6%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>80 (50.6%)</td>
</tr>
<tr>
<td>Māori</td>
<td>22 (13.9%)</td>
</tr>
<tr>
<td>Pacific People</td>
<td>12 (7.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>36 (22.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5.1%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>72 (45.3%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>32 (20.1%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>55 (34.6%)</td>
</tr>
</tbody>
</table>

Table 1 shows clinical characteristics of subjects in this study, where N is the total number of subjects.

On univariate analysis, female gender, Māori ethnicity and smoking were associated with incidence of TED (Table 3). There was no significant difference in CAS (p=0.692) and no difference in age of onset (p=0.2445) between genders. Māori ethnicity and current smokers were associated with a higher clinical activity score at presentation (p=0.049 and p=0.027 respectively).

On multivariate analysis, female gender and smoking status were associated with risk of TED, and the difference in ethnicity was explained by smoking status. Māori subjects with TED were significantly more likely to be current smokers (72.7%) compared to European (39.2%), Pacific Peoples (33.3%), Asian (8.3%) and Other (12.5%).

Figure 1: Current smokers per ethnicity in our data population.
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**Discussion**

One hundred and sixty-one subjects in Auckland, New Zealand’s data was collected and analysed. Included in these subjects are native Māori and Pacific People, not before studied regarding thyroid eye disease. Our data confirmed known global risk factors as well as solidifying the impact of smoking on TED in New Zealand. Our data specifically showed that Māori have twice the rates of TED compared to other ethnicities. However, when gender and smoking status was taken into consideration, this increased rate was due to smoking status. Māori were twice as likely to be smokers compared to other ethnicities.

**Age and gender**

According to known TED data, the average age of onset is middle age and females are 3–4 times more likely to develop TED than males. The pathophysiology of increased occurrence in females is not well understood. It may be linked to the unexplained increased rates of autoimmune disease in females. The median age at onset of our population was 47.0±15.1 years and females were three times more likely to get TED than males. Our data showed no significant difference between male and female severity, as measured via CAS and no significant difference in the age of onset between males and females in our study. These results agree with the current literature, although there are some studies that show that at older age or higher severity, the ratio can reverse.

**Ethnicity**

There have been very few studies specifically looking at ethnic differences within TED and none that consider Māori. Edmunds et al looked at 343 subjects in the wider Birmingham area and found a statistically significant difference between socioeconomic status but no significant difference between ethnicities within the UK. There have been no studies defining the risk of TED in Māori subjects. We found that on multivariate analysis, Māori have significantly higher rates of TED. When we adjusted this data for smoking rates, there was no significant difference. This suggests that the difference in rates of TED is due to higher rates of smoking within the Māori population and that there is no genetic component.

**Table 2:** Rate of thyroid eye disease by ethnicity.

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Crude incidence</th>
<th>Adjusted(^a)</th>
<th>Adjusted(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>9.7</td>
<td>14.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Māori</td>
<td>21.1</td>
<td>36.9</td>
<td>21.8</td>
</tr>
<tr>
<td>Pacific Peoples</td>
<td>9.5</td>
<td>15.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Asian</td>
<td>12.5</td>
<td>21.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Other</td>
<td>19.0</td>
<td>52.5</td>
<td>64.8</td>
</tr>
</tbody>
</table>

Table 2 shows the rate of thyroid eye disease by ethnicity. Rates given per 1,000,000 population/year.

\(^a\) rate adjusted for age and health insurance cover.

\(^b\) rate adjusted for age, health insurance cover and current smoking status.

**Table 3:** Population risk factors for developing thyroid eye disease.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>P value</td>
</tr>
<tr>
<td>Female</td>
<td>3.181</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Māori</td>
<td>2.161</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>4.455</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3 shows the population risk factors for developing thyroid eye disease. Rates calculated from ADHB population and smoking status from Census 2013. Rates are compared with poisson regression analysis. IRR = incidence rate ratio.
Smoking status

Smoking is a well-known risk factor of TED. Smokers are 4–8 times more likely to develop TED than non-smokers. In our study, current smoking was associated with a 4.7-times increased risk of TED on multivariate analysis. Ethnicities varied in rates of smoking, with Māori having significantly increased rates of smoking compared to all other ethnicities. The present study found increased in rates of TED in Māori was attributable to smoking.

Recently, indigenous peoples who smoke have been focused on in greater detail targeting the unique experiences of indigenous smoking behaviour. There have been ongoing health disparities along with other inequalities that colonisation brings such as reduced access to healthcare, reduced health literacy and effects on socioeconomic status.

Higher rates of smoking in Māori worsen the discrepancy in health outcomes between Māori and non-Māori. Conversely, this study reveals that smoking cessation would disproportionately benefit Māori individuals, and eliminating smoking would likely result in a decline in TED rates in Māori subjects compared to non-Māori. Public health policies to decrease smoking has the opportunity to reduce inequality in health outcomes in Māori and non-Māori.

Severity between smokers and non-smokers has previously been studied with varied response. We found no significant difference in CAS between smokers and non-smokers in our population. Prummel et al found no association with number of cigarettes smoked or the duration of smoking with severity, but that smokers did have a significant increased risk of severity compared to non-smokers.

Limitations

This study has some limitations given the size of the population and the restrictions that apply with a retrospective study. This is a small-to-moderate sized population which has provided statistically significant results; however, is a sample of the New Zealand population. We included only Auckland subjects belonging to Auckland and Waitāmatā District Health Boards and excluded Manukau District Health Board, which may have provided more data on Māori and Pacific subjects.

Retrospective studies are limited with data able to be collected. Non-standard and variable clinic notes can be difficult to interpret. Data such as ethnicity or smoking status are not always clearly stated in notes and have required searching for on subject databases (Concerto).

Accurately representing the Auckland population could potentially have been limited by public healthcare access only. We adjusted our data with healthcare insurance rates to try and accommodate those subjects in private healthcare and create a more representative sample.

Future insights

This study has highlighted the huge impact smoking has on the Māori population with respect to TED and may guide future management. We have developed strong arguments for the impact of smoking, and this may help in advocating cessation among subjects on a clinical level but also on a political level. This research can be distributed among medical centres and aid in the campaign against smoking.
Competing interests:
Nil.

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