Thyroid Dysfunction and Ten-Year Incidence of Age-Related Macular Degeneration

Bamini Gopinath, Gerald Liew, Annette Kifley, and Paul Mitchell

Center for Vision Research, Department of Ophthalmology and The Westmead Institute, University of Sydney, Sydney, New South Wales, Australia.

Correspondence: Bamini Gopinath, Centre for Vision Research, Westmead Hospital, Westmead, NSW 2145, Australia; bamini.gopinath@sydney.edu.au.

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Purpose. Epidemiologic evidence of a relationship between thyroid dysfunction and age-related macular degeneration (AMD) is inconsistent and unclear. We aimed to assess the prospective associations between serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) measurements, as well as thyroid dysfunction (hyperthyroidism and hypothyroidism) and incidence of AMD.

Methods. Categories of thyroid dysfunction were defined according to a serum TSH screen followed by serum FT4 assessment, and were available in 906 participants (aged 55+ years) at risk of AMD incidence (from 1997–1999 to 2007–2009). Continuous serum FT4 measures were available regardless of TSH screening results in 583 participants at risk of AMD incidence. Age-related macular degeneration was assessed from retinal photographs.

Results. Participants with overt hyperthyroidism compared to those with normal thyroid function at baseline had increased risk of developing any incident AMD, after adjusting for age, sex, smoking, fish consumption, and variants in AMD susceptibility genes (*CFH* and *ARMS2*): odds ratio (OR) 3.51 (95% confidence interval [CI] 1.16–10.65). Participants who reported current use of thyroxine ($n = 67$; 7.3%) versus those who were not current users ($n = 839$) had a 68% increased risk of incident AMD, multivariable-adjusted OR 1.68 (95% CI 1.01–2.82). Similarly, participants who had ever been on thyroxine medication ($n = 77$; 8.4%) compared to those who had never been on thyroxine ($n = 829$) also had a higher risk of any AMD, multivariable-adjusted OR 1.91 (95% CI 1.18–3.09).

Conclusions. Overt hyperthyroidism was independently associated with an increased risk of incident AMD. Thyroxine usage in older adults was also positively associated with incidence of AMD.

Keywords: Blue Mountains Eye Study, thyroid dysfunction, age-related macular degeneration, older adults, incidence

Age-related macular degeneration (AMD) is the leading cause of blindness and visual impairment among older adults.[1] While there have been recent significant advances in the understanding of AMD, knowledge of the pathophysiology underlying the development and progression of this disease remains incomplete. Current treatment options are limited to patients with late-stage neovascular AMD or intermediate AMD.[2,3] For the majority of the population with no AMD or early AMD, there is no strategy for disease prevention except the avoidance of cigarette smoking[4,5] and use of antioxidant supplements.[6,7] Other potential risk factors include other nutritional factors, cardiovascular diseases, and genetic markers, including genes that regulate complement, lipid, angiogenic, and extracellular matrix pathways.[8,9]

Thyroid disease has been implicated as a risk factor for AMD, although inconsistently so.[10,11] Cross-sectional data from the National Health Interview Survey found increased odds of AMD in participants with self-reported hypothyroidism.[10] Recently, the Rotterdam Study found that higher serum free thyroxine (FT4) values were associated with increased risk of AMD, even in older euthyroid individuals.[11] Further, some studies have shown that the use of thyroid hormones is associated with AMD[12,13] while another study did not establish any such relationship.[14]

Given the lack of population-based cohort studies that have prospectively examined the relationship between thyroid dysfunction and incidence of AMD, as well as the equivocal nature of the existing literature in this area, we conducted an exploratory study involving a relatively large cohort of older adults to establish the temporal association between serum thyroid-stimulating hormone (TSH) and FT4 values and the 5- and 10-year incidence of AMD, independent of potential confounders; the prospective relationship between thyroid dysfunction (overt and subclinical hypothyroidism, and overt and subclinical hyperthyroidism) and risk of incident AMD over 5 or 10 years; and the role of thyroxine medication usage on the risk of developing AMD among older adults.

Methods

Study Population

The Blue Mountains Eye Study (BMES) is a population-based cohort study of age-related eye diseases and other health outcomes in a population located west of Sydney. Study

methods have been described elsewhere.[15] Baseline examinations of 3654 residents aged > 49 years were conducted during 1992 to 1994 (BMES-1; 82.4% participation rate). Surviving baseline participants (i.e., survivors) were invited to attend examinations after 5 years (1997–1999, BMES-2), 10 years (2002–2004, BMES-3), and 15 years (2007–2009, BMES-4). At BMES-2 there were 3079 survivors, of whom 2334 (75.8%) were contactable and agreed to participate; at BMES-3 there were 2544 survivors, of whom 1952 (76.7%) were contactable and agreed to participate; and at BMES-4 there were 2048 survivors, of whom 1149 (56.1%) were contactable and agreed to participate. Thyroid function measures were taken only from BMES-2 onward and thus were not collected at BMES-1. Participants who presented with normal TSH levels (0.1–4.0 mIU/L) at BMES-2 did not have serum FT4 measured at BMES-2. At BMES-3, participants had serum FT4 measures available regardless of whether serum TSH levels were in the normal range or not. The main analysis presented in this paper is on the association between thyroid function status and 10-year incidence of AMD (from BMES-2 to BMES-4); however, we also present analysis of data on thyroid function status and 5-year incidence of AMD data (from BMES-3 to BMES-4), primarily to establish the associations of serum FT4 in the full range with risk of AMD.[16] The University of Sydney and the Western Sydney Area Human Ethics Committees approved the study, and written, informed consent was obtained from all participants at each examination. All study procedures were in accordance with the Declaration of Helsinki.

Assessment of AMD

The detailed methodology of assessing for the presence of AMD has been previously reported.[17,18] Briefly, we took two 30° stereoscopic color retinal photographs of the macula of both eyes, which were graded AMD by two trained and experienced graders.[17,18] Inter- and intragrader reliability showed good agreement for grading of specific AMD lesions.[17–19] Early AMD was defined as the absence of late AMD and presence of either (1) large (>125-μm diameter) indistinct soft or reticular drusen or (2) both large distinct soft drusen and retinal pigmentary abnormalities (hyper- or hypopigmentation) in either eye.[18] Late AMD was defined as the presence of neovascular AMD or geographic atrophy in either eye.[18] Incident any AMD was defined as presence of any AMD lesions at follow-up in the absence of AMD at the first examination. A retinal specialist (PM) adjudicated all uncertain cases and confirmed all late AMD cases.

Assessment of Thyroid Dysfunction

Fasting blood was collected from participants and testing was carried out on the same day as blood collection (Institute of Clinical Pathology and Medical Research, Westmead Hospital), as previously described.[20] Serum TSH was measured using an Abbott AxSYM autoanalyzer (Abbott Park, IL, USA) with analytical sensitivity of 0.03 mIU/L and assay range of 0 to 100 mIU/L. The Abbott AxSYM system was also used to measure free T4 (FT4) with an assay range of 0 to 77.2 pM.

Normal TSH levels were defined as serum TSH 0.1 to 4.0 mIU/L and normal FT4 levels as 11.5 to 25.1 pM. Hypothyroidism was defined as TSH > 4.0 mIU/L in the presence of either normal or abnormal serum FT4.[16] We defined hyperthyroidism as TSH < 0.1 mIU/L in the presence of either normal or abnormal serum FT4. Overt hyperthyroidism was defined as serum TSH < 0.1 mIU/L and high FT4 (>25.1 pM). Overt hypothyroidism was defined as elevated TSH (>4.0 mIU/L) and low FT4 (<11.5 pM). Subclinical hyperthyroidism was defined as low TSH (<0.1 mIU/L) and normal FT4. Subclinical hypothyroidism was defined as increased TSH (>4.0 mIU/L) and normal FT4.[16]

Assessment of Covariates

Participants self-reported smoking status as either never smoked, past smoker, or current smoker. We extracted separate data on the frequency of consuming fish (e.g., salmon, tuna, and sardines) from a food-frequency questionnaire. Genotypic status was available for the complement factor H (*CFH*) single nucleotide polymorphism (SNP) *rs*1061170 in 2041 baseline participants who returned at BMES-2 and for the age-related maculopathy susceptibility gene 2 (*ARMS2*) SNP *rs*10490924 in 1893 baseline participants who returned at BMES-2. Two sources of genotypic information were used.[21] TaqMan assays (Applied Biosystems, Foster City, CA, USA) had been performed to provide specific genotyping of *rs*1061170 in 1925 individuals and *rs*10490924 in 638 individuals. In addition, BMES genotyping was also carried out for a genome-wide association study (GWAS) using a custom array (Human 670-Quad, version 1; Illumina, Inc., San Diego, CA, USA) at the Wellcome Trust Centre for Human Genetics, Sanger Institute, Cambridge, United Kingdom, as part of the Wellcome Trust Case Control Consortium 2. After quality control, genotype imputation was performed using a genetic variation catalogue (1000 Genomes, version 1, EMBL-EBI, Heidelberg, Germany) and IMPUTE software (University of Oxford, UK). Imputed genotypic status was available for *rs*1061170 in 1657 baseline participants who returned at BMES-2 and *rs*10490924 in 1802 baseline participants who returned at BMES-2. This information on genotyping status from imputed data was used where TaqMan assays were not available, for *rs*1061170 in 116 individuals and for *rs*10490924 in 1255 individuals. Concordance rates between typed and imputed SNP values were 99.6% for *rs*1061170 and 99.2% for *rs*10490924. Imputation data metrics were as follows: Imputation R^2 values were 0.968 for *rs*1061170 and 0.996 for *rs*10490924; the proportion of the sample with missing SNP information was 8.8% for *rs*1061170 and 0.5% for *rs*10490924; Hardy-Weinberg equilibrium *P* values were 0.79 for *rs*1061170 and 0.95 for *rs*10490924; minor allele frequencies were 0.39 for *rs*1061170 and 0.22 for *rs*10490924. We inspected all current medications, and participants also self-reported past medication use, which allowed us to determine whether participants were currently receiving or had used thyroxine in the past.

Statistical Analyses

SAS statistical software (SAS Institute, Cary, NC, USA) version 9.3 was used for analyses. Associations between thyroid dysfunction categories (study factor) and 10-year cumulative incidence of AMD (study outcome) were examined in discrete logistic regression models. The discrete logistic model refers to a survival model in which event times are treated as being genuinely discrete in truth rather than being on a continuous spectrum. The discrete time hazard is related to covariates by a logistic regression equation.[22] We have used its implementation in SAS in PROC PHREG, where a partial likelihood estimation method is used. Moreover, associations between thyroid dysfunction categories, quintiles of serum FT4 levels, and 5-year AMD incidence were examined using standard logistic regression models. Regression analysis first adjusted for age and sex, and then for covariates that have been found to be associated with incidence of AMD in the BMES cohort: current smoking; fish consumption; and the presence of *CFH* and *ARMS2* SNPs, *rs*1061170 and *rs*10490924, respectively. Genotype status was included as an adjustment factor in multivariable-adjusted models using three categories (no minor alleles, one minor allele only, or two minor alleles), and no minor

Table 1. Association Between Baseline Thyroid Disease and 10-Year Incidence of Any AMD, Presented as Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI)

		Incidence of Any AMD, OR (95% CI)		
Thyroid Function Status	***n* (%)**	**Age, Sex Adjusted**	**Multivariable Adjusted***	**Multivariable Adjusted *P****
Normal thyroid function, $n = 827$	216 (26.1)	1.0, reference	1.0, reference	
Hyperthyroidism				
Overt, $n = 11$	7 (63.6)	**3.65 (1.28–10.4)**	**3.51 (1.16–10.65)**	**0.03**
Subclinical, $n = 9$	2 (22.2)	0.78 (0.17–3.55)	0.80 (0.17–3.67)	0.70
Hypothyroidism				
Overt, $n = 13$	4 (30.8)	1.38 (0.45–4.25)	1.68 (0.51–5.49)	0.4
Subclinical, $n = 40$	15 (37.5)	1.45 (0.79–2.67)	1.44 (0.70–2.96)	0.3

Bold numbers indicate significant findings.
* Further adjusted for smoking, fish consumption, and *CFH* and *ARMS2* SNPs (*rs*1061170 and *rs*10490924).

alleles was used as the reference group to which each other category was compared. Findings from all analyses are expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI). We analyzed serum TSH and FT4 both as categorized (quintiles and diagnostic cut-points). Statistical significance was defined as $P < 0.05$.

Results

Thyroid Function Status and 10-Year Incidence of AMD

Of the 2334 participants examined at baseline (i.e., BMES-2 in this case), 906 had complete thyroid measures and 10-year AMD data; hence, these participants were included for longitudinal analyses. We had conducted preliminary analysis that did indeed involve analyzing any, early, and late AMD as the study outcome; however, these initial analyses revealed very small numbers when analyzing early and late AMD separately. Hence, for this reason we have chosen to focus on any AMD as the key outcome in the current report. After multivariable adjustment, having a high TSH (>4.0 mIU/L) or low TSH (<4.0 mIU/L) level at baseline versus normal TSH levels was not associated with the 10-year incidence of any AMD: OR 1.53 (95% CI 0.84–2.81), $P = 0.17$, and OR 1.68 (95% CI 0.74–3.81), $P = 0.2$, respectively. Participants with overt hyperthyroidism compared to those with normal thyroid function at baseline had 3.5-fold increased risk of developing any AMD over the 10 years, after adjusting for all potential confounders: OR 3.51, 95% CI 1.16 to 10.65 ($P = 0.03$; Table 1).

We also separately analyzed the associations between thyroxine medication use and 10-year incidence of any AMD, that is, compared risk of incident AMD among those who reported current thyroxine use versus nonusers (reference group). Participants who reported current use of thyroxine ($n = 67$; 7.3%) versus those who were not current users ($n = 839$) had a 68% increased risk of incident AMD, multivariable-adjusted OR 1.68 (95% CI 1.01–2.82), $P = 0.05$. Similarly, participants who had ever been on thyroxine medication ($n = 77$; 8.4%) compared to those had never been on thyroxine ($n = 829$) also had a higher risk of any AMD over the 10 years, multivariable-adjusted OR 1.91 (95% CI 1.18–3.09), $P = 0.01$.

Thyroid Function Status and 5-Year Incidence of AMD

After multivariable adjustment, having a high TSH ($n = 38$) versus normal TSH level ($n = 535$) at baseline was associated with a greater risk of any AMD 5 years later, OR 2.62 (95% CI 1.04–6.56), $P = 0.04$. A low TSH ($n = 10$) level versus normal TSH levels was not associated with the 5-year incidence of any AMD, OR 2.91 (95% CI 0.64–13.24), $P = 0.17$. Table 2 shows that thyroid dysfunction status categories were not associated with the 5-year incidence of any AMD. Participants who had ever been on thyroxine medication or reported current use of thyroxine did not have a higher risk of developing any AMD over the 5 years: OR 1.62 (95% CI 0.74–3.54), $P = 0.2$, and OR 1.75 (95% CI 0.79–3.86), $P = 0.17$. Table 3 shows that there was no significant association between increasing quintiles of serum FT4 levels and the 5-year incidence of any AMD.

Table 2. Association Between Baseline Thyroid Disease and 5-Year Incidence of Any AMD, Presented as Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI)

		Incidence of Any AMD, OR (95% CI)		
Thyroid Function Status	***n* (%)**	**Age, Sex Adjusted**	**Multivariable Adjusted***	**Multivariable Adjusted *P****
Normal thyroid function, $n = 535$	100 (18.7)	1.0, reference	1.0, reference	
Hyperthyroidism				
Overt, $n = 2$	0 (0.0)	ND	ND	
Subclinical, $n = 8$	3 (37.5)	2.00 (0.44–9.02)	5.09 (0.94–27.61)	0.06
Hypothyroidism				
Overt, $n = 17$	5 (29.4)	1.77 (0.58–5.39)	3.03 (0.86–10.7)	0.09
Subclinical, $n = 21$	6 (28.6)	1.83 (0.68–4.95)	2.18 (0.59–8.07)	0.20

ND, not defined.
* Further adjusted for smoking, fish consumption, and *CFH* and *ARMS2* SNPs (*rs*1061170 and *rs*10490924).

Table 3. Association Between Baseline Quintiles of Serum FT4 Levels and 5-Year Incidence of Any AMD, Presented as Adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI)

	Incidence of any AMD, OR (95% CI)			
Serum FT4, pM	No. Cases/No. at Risk	Age, Sex Adjusted	Multivariable Adjusted*	Multivariable Adjusted *P**
1st quintile	19/115	1.0 (reference)	1.0 (reference)	
2nd quintile	29/129	1.60 (0.82–3.10)	2.08 (0.94–4.60)	0.07
3rd quintile	18/117	0.95 (0.46–1.98)	1.34 (0.56–3.24)	0.50
4th quintile	28/118	1.67 (0.85–3.28)	2.03 (0.87–4.70)	0.10
5th quintile	20/104	1.14 (0.56–2.33)	1.19 (0.47–3.02)	0.71
P trend		0.75	0.77	

* Further adjusted for smoking, fish consumption, and *CFH* and *ARMS2* SNPs (*rs*1061170 and *rs*10490924).

Discussion

We provide novel epidemiologic data showing that overt hyperthyroidism was independently associated with a greater risk of developing incident AMD over 10 years. Further, thyroxine medication use at baseline was also associated with a greater risk of incident AMD. However, baseline serum TSH or FT4 levels per se were not associated with 5- or 10-year incidence of AMD.

Our exploratory study does not verify the significant positive association between serum FT4 values and incident AMD observed in the recent Rotterdam Study.[11] However, we report that overt hyperthyroidism (low TSH and high FT4 levels) in older adults is independently associated with ~3-fold increased risk of developing any AMD, and this is aligned with the Rotterdam Study findings.[11] There are several potential underlying mechanisms for our observed association with overt hyperthyroidism (i.e., an overactive thyroid and overproduction of thyroid hormones). First, elevated thyroid hormone levels can accelerate the basal metabolic rate and oxidative metabolism by induction of mitochondrial enzymes, which causes a hypermetabolic state with increased generation of reactive oxygen species.[23,24] Moreover, there is growing evidence of an imbalance between pro-oxidant–antioxidant status and increased free radical–mediated oxidative stress in patients having Graves' disease (an autoimmune disease that is the common cause of hyperthyroidism).[23–25] Cumulative oxidative damage plays an important role in the pathogenesis of AMD,[26] suggesting that this is a potential pathway by which overt hyperthyroidism could influence AMD risk. Further, there is evidence that stimulating thyroid hormone signaling could cause degeneration of cone photoreceptors[27] and thyroid hormone itself could adversely influence retinal pigment epithelial cells,[11,28] which could also partly explain the observed association between clinical hyperthyroidism and AMD.

Our finding that thyroxine usage in older adults predicted an increased risk of AMD concurs with other published studies,[12,13] including the Beaver Dam Eye Study, that reported a positive association between the use of both synthetic and desiccated thyroid hormones and risk of AMD.[12,13] While thyroxine medication use may be a surrogate for clinical hypothyroidism in previous studies, prescription of medication and adherence to the medication may not be considered equal in all instances.[10] This could explain the nonsignificant link between hypothyroidism and AMD, and why thyroxine use was positively associated with incident AMD in the BMES. However, we cannot discount the possibility that the relationship between thyroid medication use and incident AMD is a chance finding; hence, the long-term significance of this observation remains unclear and warrants further investigation in other cohort studies.

Strengths of this study include its prospective data collection and long-term follow-up of a population-based sample. Further, this study used high-quality stereoscopic retinal photography with validated grading to assess macular conditions, and a detailed side-by-side comparison of the baseline and follow-up photographs to ensure negligible misclassification of incident AMD.[29–31] However, study limitations also deserve discussion. First, we did not have measures of antithyroid antibodies and serum T3; hence, complete assessment of thyroid function was not possible in this study,[32] and we could not determine the temporal relationship between these other measures of thyroid function and incidence of AMD. Second, the number of participants who developed incident AMD was small. Third, we cannot discount the influence of residual confounding from unmeasured or unaccounted for factors (e.g., inflammatory markers). A further limitation is the use of a survivor cohort; for instance, persons with thyroid dysfunction might have developed AMD but could have been lost to follow-up or have died before the 5- or 10-year examination.

Improved knowledge of risk factors could help to develop comprehensive screening strategies for AMD, particularly given that it is a condition often diagnosed in an already advanced sight-threatening stage.[33] Our findings support some of the other cohort studies[11] by suggesting that thyroid disease could contribute to a better profiling of AMD in clinical practice. Specifically, we show that overt hyperthyroidism was associated with a greater risk of developing AMD in the longer term. Thyroxine medication use also appears to play a role in influencing risk of incident AMD. Nevertheless, we caution that further studies are needed to confirm and validate our findings and to better elucidate the influence of thyroid hormones and medication use on the development of AMD in older adults.

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