Thyroid Disease Is Associated with Higher Age-Related Macular Degeneration Risk: Results from a Meta-Analysis of Epidemiologic Studies

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Keywords

Thyroid hormone · Thyrotropin · Thyroid medication · Age-related macular degeneration · Meta-analysis

Abstract

Background: Although epidemiologic studies have suggested that thyroid disease may be a risk factor for age-related macular degeneration (AMD), this finding is still controversial. **Objectives:** The aim of this meta-analysis was to investigate whether an association exists between thyroid disease and medication and AMD in epidemiologic studies. **Methods:** We searched PubMed, EMBASE, and Google Scholar from their inception to March 2020 for cross-sectional, case-control, and cohort studies that assessed thyroid function and AMD risk. Data from selected studies were extracted, and a meta-analysis was performed using fixed-effects or random-effects models. The statistical heterogeneity (I^2) among studies and the possibility of publication bias were evaluated. If $I^2 > 50\%$, a significant heterogeneity existed among studies, and a random-effects model was used to calculate the pooled RR. Otherwise, a fixed-effects model was performed. **Results:** A total of 13 epidemiologic studies that consisted of 7 thyroid disease and 7 thyroid medication studies were included. Statistically significant heterogeneity

was observed in the study results ($I^2_{\text{thyroid disease}} = 80.1\%$; $I^2_{\text{thyroid medication}} = 69.0\%$). A significant positive association was found between thyroid disease and AMD, with an overall relative risk (RR) of 1.25 (95% CI: 1.02, 1.54). However, there was no statistical association between thyroid medication and AMD risk (pooled RR 1.26 [95% CI: 0.92–1.72]). Egger's test indicated that there was no significant publication bias for thyroid disease ($p = 0.889$) or thyroid medication ($p = 0.226$). **Conclusions:** Our findings indicate that thyroid disease is associated with higher AMD risk. Thyroid disease prevention strategies may have a significant effect on the prevention of AMD and warrant further evaluation.

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Introduction

Age-related macular degeneration (AMD) is a prevalent disease leading to blindness and involves the loss of a person's central field of vision. Globally, the prevalence of AMD, which is the leading cause of irreversible loss of vision among elderly individuals, is expected to increase with population aging, ranking third as a cause of blindness after cataract and glaucoma [1]. AMD is a complex multifactorial disease accounting for 8.7% of cases of

blindness worldwide, and its prevalence is increasing and spreading [2]. The global population is expected to grow to approximately 9.5 billion by 2050, and it was estimated that there were nearly 2.4 billion people ≥ 60 years in 2050 [3]. The prevalence of AMD was 2.4% in African Americans, 4.2% in Hispanics, 5.4% in Whites, and 4.6% in Chinese individuals aged 45–85 years, and the estimated total prevalence of any AMD was 4.2% [4]. The pathophysiological mechanisms leading to AMD are not fully understood, but genetic tendencies and environmental factors, including the use of tobacco and nutritional factors, are believed to play an important role [5]. Recently, thyroid hormone (TH) signaling has been implicated in the pathogenesis of AMD [6].

Human retinal pigment epithelial cells express TH receptors and seem to be a direct target for TH [7]. Population studies have revealed that high serum thyrotropin levels are associated with retinal arteriolar narrowing [8]. Animal studies have demonstrated that moderate levels of pre- and postnatal TH insufficiency lead to alterations in visual function in adult rats [9]. These findings highlight the important role of TH in regulating various visual functions.

Ma et al. [10] reported that suppressing TH preserves cone photoreceptors in mice with retinal degeneration, while administering active TH deteriorates cones, which are known to be important factors for the development and progression of AMD. A Rotterdam study found that higher serum-free thyroxine values were associated with an increased risk of AMD [11]. Furthermore, some studies have demonstrated an association between the use of thyroid medication and the risk of AMD [12].

Previous studies have shown some evidence of a relationship between TH and AMD in the general population, although the findings have been inconsistent. In light of the above, the objective of the present meta-analysis is to evaluate the available studies related to thyroid disease and medication and AMD. Our meta-analysis analyzes relevant information published in the literature to more accurately assess the association between thyroid disease and medication and AMD.

Methods

Literature Retrieval

We performed a literature search regarding the association of thyroid disease and medication with AMD; epidemiologic studies published from inception to March 2020 were examined. An electronic search was performed using EMBASE, PubMed, and Google Scholar. The articles were searched using the following keywords

Fig. 1. References searched and selection of studies for inclusion in the meta-analysis.

in English. The following medical subject headings were used: (“thyroid function” OR “hyperthyroidism” OR “hypothyroidism” OR “thyroid disease”) AND (“age-related macular degeneration” OR “AMD” OR “ARMD” OR “age-related macular disease” OR “age-related maculopathy” OR “ARM”). Searches were restricted to human studies, and all references of the selected articles were searched manually to identify relevant original studies and citations.

Inclusion Criteria

The inclusion criteria for the literature were as follows: (1) had a cross-sectional, case-control, or cohort design; (2) evaluated the association between thyroid medication or thyroid function and AMD risk; (3) performed with human subjects; and (4) had adequate data for extraction or calculation, which may be presented as the odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI). The exclusion criteria were as follows: (1) duplicate articles and (2) articles with incomplete data.

Data Extraction and Quality Assessment

The systematic review was conducted by 2 investigators who independently reviewed the titles and abstracts of all studies identified, and disagreements were resolved by consensus. We used a unified data form. The following information was recorded for each study: year, region, study design, sample size, population characteristics, main results, and matched or adjusted variables in the study design or data analysis.

Statistical Methods

The pooled RRs with corresponding 95% CIs were considered for the effect size analysis in all analyses. When studies had multiple adjustment models, we extracted those reflecting the greatest extent of adjustment for potential confounders. Some studies separated risk estimates according to the different types of AMD (ear-

Table 1. Characteristics of epidemiologic studies of thyroid disease and medication and AMD included in the meta-analysis

Authors	Year	Region	Study design	Sample size	Population characteristics	Covariate adjustment	Main results
Friedman et al. [14]	1988	USA	Case-control study	54	29 patients with ARMD (incident thyroid disease 20 patients), 25 no ARMD (incident thyroid disorder 20 patients)	None	An increased scleral rigidity may be a significant risk factor for the development of the disorder
None [12]	2000	Maryland	Case-control study	118	Geographic atrophy (at least 1 eye has definite geographic atrophy) group has 118 participants, OR: 1.99 (1.08–3.05)	None	The increased use of TH in persons with geographic atrophy
Klein [20]	2001	USA	Cohort study	2,819	In 28 subjects exposed to thyroid hormones desiccated ($n = 2819$), 6 developed ARM, the OR and 95% CI are 2.32 (0.89–6.07)	Adjusted for age and sex	Many different medication use had no striking associations with the 5-year incidence of early ARM
van Leeuwen et al. [21]	2003	The Netherlands	Cohort study	8,649	Beaver dam eye study ($n = 3,012$), Rotterdam study ($n = 3,434$), Blue mountains eye study ($n = 2203$). In model 2 of the pooled cohort, OR: 1.20 (0.8–1.80)	Adjusted for systolic blood pressure, diastolic blood pressure, total and high-density lipoprotein cholesterol, body mass index, and smoking	Pooled data from 3 population-based studies showed no strong associations between medication use and the incidence of early ARM
Seddon et al. [22]	2004	USA	Case-control study	930	Group 1 (no druse, $n = 183$); group 2 (intermediate drusen, $n = 200$); group 3 (large drusen or intermediate AMD, $n = 325$); group 4 (geographic atrophy or neovascular AMD–advanced AMD, $n = 222$). Using thyroid hormones were 92 participants totally	None	CRP level is an independent risk factor for AMD and may implicate the role of inflammation in the pathogenesis of AMD
Douglas et al. [23]	2007	United Kingdom	Case-control study	104,176	18,007 participants with a diagnosis of AMD (1,077 participants used thyroid hormones in the past) and 86,169 controls (4,487 participants used thyroid hormones in the past); mean age: 77.4 yr	Adjusted for consultation rate, observation time, diabetes, heart failure, hyperlipidemia, cardiovascular drugs, atherosclerosis, hypertension, body mass index, aspirin, hormone replacement therapy, alcohol consumption, and smoking	No association was detected between short- and medium-term use of antithyroids, TH, and thiazide diuretics and the risk of AMD
Bromfield et al. [15]	2011	USA	Cross-sectional	9,677	The 2008 National Health Interview Survey (NHIS) served as the data source for this study, participants with AMD were 356. OR: 1.59 (1.10–2.30)	Adjusted for age, sex, and race	Literature indicates a possible relationship between AMD and hypothyroidism
Park et al. [16]	2014	Korea	Cross-sectional	14,352	14,352 subjects, early ARMD patients (6.02%) have 50 patients with thyroid disease and no ARMD group has 631 patients with thyroid disease; late ARMD patients (0.060%) have 2 patients with thyroid disease and no ARMD group has 631 patients with thyroid disease	None	Nonoverweight status and higher HDL levels, generally assumed as positive health indicators, as well as anemia and hepatitis B infection had harmful associations with AMD in our study
Chaker et al. [11]	2015	The Netherlands	Cohort study	5,572	816 patients with thyroid disorder (incident ARMD 109 patients), 4,756 euthyroid subjects (incident ARMD 696 patients)	None	It indicated an intrinsic deleterious effect of TH on AMD, and TH could even play a role in the early stage of development of AMD

Table 1 (continued)

Authors	Year	Region	Study design	Sample size	Population characteristics	Covariate adjustment	Main results
Tsai et al. [17]	2015	Taiwan, China	Case-control study	29,958	4,993 patients with ARMD (incident thyroid disorder 177 patients), 24,965 no ARMD (incident thyroid disorder 673 patients)	None	This study provides large-scale, population-based evidence that AMD, especially nonexudative AMD, is independently associated with an increased risk of subsequent AD or senile dementia development
Gopinath et al. [18]	2016	Australia	Cohort study	900	73 patients with thyroid disorder (incident ARMD 28 patients), 827 euthyroid subjects (incident ARMD 216 patients); 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)	None/adjusted for smoking, fish consumption, and CFH and ARMS2 SNPs	Overt hyperthyroidism was independently associated with an increased risk of incident AMD
Reitmeir et al. [24]	2016	Germany	Cross-sectional	822	Among all 822 participants, 465 participants (56.6%) reported the presence of cataracts, glaucoma, corneal, or retinal disorders. Associate AMD with thyroid therapy. OR: 0.35 (0.14–0.87)	None	The significantly higher risk for glaucoma in males were treated with thyroid hormones
Abdelkader and Abass [19]	2019	Egypt	Cross-sectional study	1,480	950 patients with thyroid disorder (incident ARMD 255 patients), 63.6±5.1 yr; 530 euthyroid subjects (incident ARMD 80 patients), 65.8±5.2 yr	None	There was an increase in ARMD incidence in patients with abnormal T4 and T3 and in patients using thyroxine
TH, thyroid hormone; AMD, age-related macular degeneration.							

ly AMD, advanced AMD, and dry AMD), and any report of AMD effect was included. The heterogeneity test was performed by using Cochran's Q and I^2 statistics [13]. Statistical significance for heterogeneity was considered if p value was <0.05 or I^2 was $>50\%$, and the summary estimate on the basis of the random-effects model is presented; otherwise, a fixed-effects model was performed. Publication bias was estimated using funnel plot graphics and Begg's and Egger's tests.

Results

Characteristics of Studies

According to the inclusion and exclusion criteria, a total of 13 studies were included in our systematic literature search. A flow diagram that shows how we located relevant studies is presented in Figure 1. Table 1 summarizes

the baseline characteristics of the included studies. Seven [11, 14–19] studies involved thyroid disease, and 7 [12, 18, 20–24] studies involved thyroid medication. It is worth noting that data for both thyroid disease and medication were extracted from 1 article [18].

Thyroid Disease and the Risk of AMD

Seven studies with a total of 61,993 patients reported the relationship between thyroid disease and AMD. The presence of thyroid disease was associated with a 25% increase in the risk of AMD in humans (summary RR: 1.25; 95% CI: 1.02, 1.54) (Fig. 2). Statistically significant heterogeneity was observed in the study results ($I^2 = 80.1\%$, $p < 0.001$).

Fig. 2. Forest plot for the association between thyroid disease and AMD. AMD, age-related macular degeneration.

Fig. 3. Forest plot for the association between thyroid medication and AMD. AMD, age-related macular degeneration.

Thyroid Medication and the Risk of AMD

Seven studies with a total of 118,420 patients reported the relationship between thyroid medication and AMD. The random-effects model was used for meta-analysis, and the results showed a pooled RR (95% CI) for the association between thyroid medication and AMD of 1.26 (0.92–1.72), which was heterogeneous ($I^2 = 69.0\%$, $p = 0.004$), as shown by the forest plots (Fig. 3).

Publication Bias

Egger's test was used to evaluate publication bias. There was no indication of a publication bias for the thyroid disease ($p = 0.889$) or thyroid medication ($p = 0.226$) results, as shown by the funnel plots (Fig. 4, 5).

Fig. 4. Funnel plot for the association between thyroid disease and AMD. AMD, age-related macular degeneration.

Fig. 5. Funnel plot for the association between thyroid medication and AMD. AMD, age-related macular degeneration.

Fig. 6. Sensitivity analyses for the association between thyroid disease and AMD. AMD, age-related macular degeneration.

Fig. 7. Sensitivity analyses for the association between thyroid medication and AMD. AMD, age-related macular degeneration.

Sensitivity Analysis

In sensitivity analyses, we recalculated the combined results by excluding 1 study per iteration. Overall, the results of the sensitivity analysis were similar to those of the original analysis, and the RR estimate did not change drastically in the meta-analysis of thyroid disease, thyroid medication, and AMD (Fig. 6, 7).

Discussion

TH signaling has been reported to regulate cell proliferation, differentiation, and metabolic homeostasis and to be involved in different visual functions, such as the function of specific cone subtypes in human retinal organoids [25]. Thyroid dysfunction and subclinical thyroid dysfunction are common in the general population, and the mean prevalence of total thyroid dysfunction in Europe was found to be 3.82% [26].

However, the mechanisms that link thyroid disease and AMD are currently unclear. It can be speculated that elevated TH levels can accelerate oxidative metabolism by inducing mitochondrial enzymes [27]. The retina is particularly susceptible to oxidative stress, and oxidative damage is thought to be one of the multiple components of the complex molecular mechanism of AMD [28]. In addition, thyroid dysfunction is related to vascular function, lipids, and atherosclerosis [29], which are known predisposing factors for the development and progression of AMD [30]. Population studies have revealed that rs943080 in the VEGF-A gene is associated with AMD and is significant in thyroid-stimulating hormone genome-wide association studies [11]. A possible explanation may be that susceptibility genes have been found in inflammation and oxidative stress pathways. Our findings suggested that thyroxine medication use also appears to play a role in influencing the risk of incident AMD. A population-based study in the region of Augsburg reported a significantly higher risk for other ophthalmic diseases in males treated with TH [24].

The results of the present meta-analysis were based on 7 articles and indicated that the prevalence of thyroid disease was associated with AMD (pooled RR [95% CI]: 1.25 [1.02–1.54]). In addition, there was no statistical association between thyroid medication and AMD risk. This is the first study investigating the putative association between thyroid function and AMD in the general population.

Notwithstanding these numbers, it is difficult to evaluate what the clinical consequences of this heterogeneity

may be for future settings. Therefore, we estimate the prediction interval for the RR [31]. The resulting prediction interval for RR of thyroid disease and the risk of AMD, ranging from 0.253 to 2.25, can be interpreted as the 95% range of true RR to be expected in similar studies. The prediction interval contains values above 1 which means that the presence of thyroid disease was associated with an increase in the risk of AMD. But, it also contains values below 1 which means that the presence of thyroid disease may decrease the risk of AMD. Consequently, the result in a new study may be even the exact opposite to the estimate of the meta-analysis. On the other hand, we estimate the prediction interval for the RR of thyroid medication and the risk of AMD, ranging from 0.19 to 2.33. The prediction interval is similar to the 95% range of RR.

There are several limitations in our study. First, a thyroxine drug effect on AMD requires a long period of exposure, and this study had insufficient information in this regard. Second, some studies adjusted for potential confounders. There was no distinction between adjusted and nonadjusted when combining effect values. Last, too few studies have reported AMD type, and consequently, it was not possible to conduct subgroup analyses according to AMD type. Further studies are needed to validate our findings and to better elucidate the influence of TH and medication use on the development of AMD.

Conclusions

Our results indicate that there was an increased incidence of AMD in patients with thyroid disease. Thyroid disease prevention strategies may have a significant effect on the prevention of AMD and warrant further evaluation.

Supplementary Information

The PRISMA guidelines are given in online suppl. material 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000515273).

Statement of Ethics

All analyses were based on previous published studies, and thus no ethical approval and informed consent are required. Nonetheless, the study adhered fully to the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.T. conceived the study. M.Z. and Q.Z. performed and checked the available information from eligible articles in this meta-analysis. Z.X. analyzed the data and wrote the main manuscript text. T.X. reviewed and revised the manuscript. All authors read and approved the final manuscript.

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