Original Article

Thyroid Dysfunction as a Modifiable Risk Factor for Wet Type Age-Related Macular Degeneration: A Case–Control Study

Mohsen Farvardin[1], Seyed Esmaeil Mousavi[1], Kamran Zare[1], Somaye Bazdar[1], Zahra Farvardin[1], Mohammadkarim Johari[1]

[1]Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine,Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Purpose: To investigate possible links between thyroid dysfunction and prevalence of wet age-related macular degeneration (AMD).

Methods: The present case–control study enrolled a total number of 90 patients with wet AMD and 90 sex-, and age-matched controls through a convenient sequential sampling method. Thyroid hormones were profiled in serum assay. Statistical measures were done to compare means between groups.

Results: Our findings showed a significant difference in free T4 levels between wet AMD and control groups (P = 0.002), but the mean values of total T3 and Thyroid-stimulating hormone levels were similar between the two groups. In addition, there were no differences in serum lipid profile between groups. Although no significant difference in the history of hypertension and hyperlipidemia between wet AMD and control groups was found, the history of smoking was higher in controls (P = 0.039).

Conclusion: Thyroid hormone abnormalities may be associated with wet AMD.

Keywords: Age-related macular degeneration, Dyslipidemia, Thyroid dysfunction

Address for correspondence: Mohammadkarim Johari, Poostchi Eye Research Center, Poostchi St, Shiraz, Iran.
E-mail: mkjoharii@gmail.com
Submitted: 01-Nov-2020; **Revised:** 24-Jul-2021; **Accepted:** 28-Jul-2021; **Published:** 06-Jan-2022

Introduction

Age-related macular degeneration (AMD) is considered amongst the main causes of irreversible vision loss, which is the underlying cause of 8.7% of blindness cases worldwide.[1] Although the definite etiopathophysiological underpinnings of AMD are yet to be identified, some factors such as genetics, diet, inflammation, and oxidative stress are of etiological significance in AMD.[2]

Clinically, AMD is classified into the following two types: geographic atrophy (dry AMD) and neovascular or exudative AMD (wet AMD).[3] It has been estimated that 10–15% of all AMD cases fit into the wet classification.[4] Wet AMD is characterized by choroidal neovascularization (CNV) that consequently leads to severe vision loss.[5,6]

Although aging, the white race, having fair-colored irises, and obesity are among the well-described risk factors for AMD, the contributing role of some other factors such as gender and hypertension in the prevalence of AMD has remained controversial across studies yet.[7] Among all the risk factors known for AMD, obesity, smoking, and hyperlipidemia are generally considered the modifiable risk factors.[8]

Some recently performed studies have proposed that thyroid dysfunction may also be considered a modifiable risk factor for AMD.[9-12] In fact, thyroid dysfunction predisposes the individual to other risk factors such as dyslipidemia, atherosclerosis, and hypertension. Moreover, recent investigations in this regard have reported that the suppression of thyroid hormone

Access this article online

Quick Response Code:

Website: www.jcurrophthalmol.org

DOI: 10.4103/joco.joco_174_20

How to cite this article: Farvardin M, Mousavi SE, Zare K, Bazdar S, Farvardin Z, Johari M. Thyroid dysfunction as a modifiable risk factor for wet type age-related macular degeneration: A case–control study. J Curr Ophthalmol 2021;33:449-52.

signaling was associated with cone photoreceptors preservation in mouse models.[9]

Considering hyperthyroidism as an independent controversial risk factor for AMD and few studies regarding the association of thyroid hormones and wet type AMD, the present study attempted to assess an association between thyroid dysfunction and wet type AMD in Fars province, Southern Iran.

Methods

This research was a case–control study performed in Poostchi Ophthalmology Center, Shiraz, Iran from January 2014 to December 2014. The study participants were selected from wet AMD patients and cataract surgery candidates who were referred to these two university-affiliated ophthalmology clinics.

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (approval code: IR.SUMS.REC.1395.s227). In addition, each participant signed a written informed consent after being briefed about the purpose and method of the current study.

A total number of 90 patients with unilateral wet AMD were included in the case group using a sequential sampling method. Patients with bilateral wet AMD or sub-foveal geographic atrophy in fellow eye were excluded. The diagnosis of wet AMD was performed based on the clinical findings, optical coherence tomography, fluorescein angiography, and the presence of CNV. The control group (n = 90) subjects were recruited from sex-, age-matched cataract surgery candidate patients using a convenient sequential sampling method. Subjects with any stage of dry or wet type of AMD were excluded. The exclusion criteria for both study groups were as follows: the presence of any other retinal or choroidal vascular problems, diabetic retinopathy, retinal and choroidal dystrophy, hypertensive retinopathy or choroidopathy, autoimmune diseases, diabetes mellitus, renal disease, liver disease, different types of cancer, rheumatoid diseases, and the current use of thyroidal or glucocorticoid hormones.

All the individuals' demographic data as well as any past history of hypertension, hyperlipidemia, and smoking were recorded in data collection forms with their blood samples that were referred to the clinic's laboratory. Blood sampling (5 ml clot) was done for the fasting patients at 9:00 AM, and total levels of T3, free T4, Thyroid-stimulating hormone (TSH), and lipid profile were measured. Thereafter, thyroid function test was done through enzyme-linked immunosorbent assay (ELISA) technique. Moreover, for wet AMD patients, the number of intravitreal anti-vascular endothelial growth factor injections were asked and then recorded in their data collection forms.

Statistical analysis

Quantitative and qualitative data were described by mean ± standard deviation and frequency (percent), respectively. At first, normal distribution of the study population was confirmed, and then, to compare the means in quantitative data (thyroid hormones blood levels, and lipid profile) between the case and control groups, independent t-test was employed. Mann–Whitney U test was used for ordinal data. All statistical analyses were done using the SPSS statistical software (version 18, Company, country), and $P < 0.05$ was considered statistically significant.

Results

A total number of 90 patients with wet AMD and 90 controls who were candidates for cataract surgery were enrolled in this study. Both the study groups were sex-matched (45.6% of the wet AMD subjects and 51.1% of the controls were men, $P = 0.12$). The mean age in the wet AMD and control groups was 76.04 ± 17.64 and 72.45 ± 15.42 years old, respectively ($P = 0.41$).

The results of our statistical analyses revealed that the free T4 level was significantly different between the wet AMD and control groups ($P = 0.002$). Although the mean TSH level was observed to be lower in the AMD group, no statistically significant differences were found in total T3 and TSH levels between the wet AMD and control groups [Table 1]. In addition, the comparison of lipid profile between the wet AMD and control groups showed no statistically significant differences [Table 1]. The comparison of the past medical history of the wet AMD patients and controls also revealed no statistically significant differences in terms of hypertension and hyperlipidemia. However, there was a significant difference between the wet AMD patients and controls regarding their past history of smoking (which was higher in the controls) [$P = 0.039$, Table 2].

Table 1: The mean values of thyroid hormones blood levels and lipid profile in wet age-related macular degeneration and normal groups

	Group	*n*	Mean±SD	*P*+
TSH (mint/lit*)	Wet AMD	90	1.92±1.98	0.819
	Normal	90	2.57±2.80	
Total T3 (nmol/l**)	Wet AMD	90	1.44±1.06	0.152
	Normal	90	1.27±0.28	
Free T4 (ng/dl***)	Wet AMD	90	2.78±1.32	0.002
	Normal	90	1.66±0.26	
Triglycerides (mg/dl)	Wet AMD	90	138.68±25.60	0.126
	Normal	90	154.83±19.71	
LDL (mg/dl)	Wet AMD	90	108.58±51.12	0.141
	Normal	90	116.25±48.14	
Cholesterol (mg/dl)	Wet AMD	90	187.95±14.74	0.236
	Normal	90	195.77±19.10	
HDL (mg/dl)	Wet AMD	90	52.51±9.14	0.265
	Normal	90	57.71±7.51	

*Milli-international units per liter, **Nanomoles per liter, ***Nanograms per deciliter, +t-test P value. SD: Standard deviation, AMD: Age-related macular degeneration, TSH: Thyroid stimulating hormone, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, T3: Triodothyronine, T4: Thyroxine

In addition, we evaluated the relationship between the total number of intravitreal injections and the serum level of thyroid hormones. No relationship was found between these parameters [Table 3].

Discussion

The current study attempted to find any association between the prevalence of wet AMD and thyroid dysfunction, which is a modifiable risk factor. Too few studies have reported the association of thyroid hormones and AMD subtype. The main advantage of our study is to evaluate the association of thyroid dysfunction and wet type AMD. Our findings revealed that free T4 serum level has a direct relationship with wet AMD, while no statistical relationship was observed between TSH serum level and wet AMD. Gopinath *et al.* demonstrated that overt hyperthyroidism (low TSH and high free T4 levels) in older cases is independently associated with a 3-fold increase in the risk of AMD development (dry and wet types); however, they did not verify any significant positive association between serum free T4 levels and the incident AMD observed in their study.[11] Xu *et al*., in their meta-analysis (conducted on 13 epidemiologic studies) also found a significant positive association between thyroid disease and AMD. In this study, no statistical association was reported between thyroid medication and AMD risk, although they could not conduct subgroup analyses according to AMD type.[12]

Table 2: Past medical history of hyperlipidemia, hypertension, and smoking in wet age-related macular degeneration and normal groups

	Groups		Total	*P*+
	Wet AMD	Normal		
Smoking history				
No	79	66	145	0.039
Previously	8	9	17	
Currently	2	10	12	
Total	89	85	174	
Past medical history of hyperlipidemia				
Yes	19	9	28	0.050
No	70	77	147	
Total	89	86	175	
Past medical history of hypertension				
Yes	22	20	42	0.755
No	67	68	135	
Total	89	88	177	

+Mann–Whitney U-test. AMD: Age-related macular degeneration

Table 3: Comparison of the mean values of serum thyroid hormones levels between wet age-related macular degeneration cases that had more than three total number of intravitreal bevacizumab (IVB) injections and three or less IVB

	IVB_OD	*n*	Mean±SD	*P*+
TSH (mint/lit*)	≤3	34	2.45±1.79	0.329
	>3	15	3.14±2.13	
T3 (nmol/L**)	≤3	34	1.50±1.11	0.471
	>3	15	1.81±1.88	
Free T4 (ng/dL***)	≤3	33	2.29±2.75	0.291
	>3	15	3.80±2.01	

*Milli-international units per liter, **Nanomoles per liter, ***Nanograms per deciliter, +Mann–Whitney U-test. SD: Standard deviation, TSH: Thyroid stimulating hormone, T3: Triodothyronine, T4: Thyroxine, IVB: Intravitreal bevacizumab

Regarding dry type AMD as an earlier stage of AMD, several studies reported similar findings of free T4 and TSH serum levels in these patients. In addition, the above-mentioned study highlighted an adverse relationship between high free T4 serum level and pigmented retinal epithelium alteration.[9,10] Several studies have also shown a positive association between the usage of both synthetic and desiccated thyroid hormones and the risk of AMD.[13,14]

Indeed, it was indicated that the elevated level of serum thyroid hormones can augment the basic metabolic rate and oxidative metabolism that potentially induces mitochondrial activities, which consequently result in an increased hypermetabolic state in reactive oxygen species. This condition was found to occur in patients with Graves' disease.[15] In addition, thyroid dysfunction is related to vascular function and atherosclerosis.[16] Oxidative stress and vascular dysfunction when combined together could predispose chorioretinal tissue for the development and progression of AMD.

Correspondingly, the TSH serum level was shown to be decreased in healthy elderly controls potentially due to the diminished TRH level of secretion from the pituitary gland.[17] Although the decreased TSH level results in diminished T4 secretion, total T4, and free T4 levels would not be altered.[18] Nevertheless, the T4 level decreases with aging and free T4 de-iodination, and its conversion to T3 would subsequently diminish. Therefore, the free T4 level would not be changed by aging.[19] The above-mentioned insights were in agreement with our results, denoting that although AMD risk increases with aging, there is no relationship between aging and the increased free T4 level.

In another investigation by Woo *et al.*, it was shown that age, smoking, hyperlipidemia, spherical equivalent, and education are the important environmental factors for AMD.[20] Accordingly, smoking is known as a risk factor strongly linked with AMD.[21] Inconsistent with this finding, in the current study, we reported that the smoking rate was higher in the control group than in the AMD cases.

This disparity in results may be due to recruiting the control subjects from cataract surgery candidates because smoking has been previously documented among the most considerable risk factors for cataract development by exposing the lens to oxidation.[22]

On the other hand, in several studies, hyperlipidemia and hypertension are controversially regarded as risk factors for

AMD. Some studies have proposed that a high dietary intake of docosahexaenoic fatty acid could consequently reduce the risk of neovascular AMD by increasing mitochondrial activity through the anti-oxidative, anti-inflammatory, anti-apoptotic, and anti-angiogenic effects.[23] Although there have been studies claiming that no definite relationship exists between hypertension and AMD, other studies reported hypertension as a risk factor due to its effect on the choroidal circulation.[24] In this regard, the present study revealed that although thyroid function has a close relationship with cardiovascular diseases such as vascular disorders, hyperlipidemia, and hypertension, no associations exist between hyperlipidemia or hypertension and wet AMD.[25]

Although we excluded patients who used thyroidal or glucocorticoid hormones from the study, multiple drugs used by patients such as (anti-hypertensive and fat-lowering drugs or multivitamins supplements used for AMD treatment) in both control and wet AMD groups could potentially affect patients' thyroid tests and should be considered in interpreting conclusion. This is the main limitation of this study. Other limitations include a small sample size and the absence of a control group of patients dry AMD.

In conclusion, the effect of thyroid hormone derangements on retina should not be neglected. In other words, checking thyroid hormones and consulting with endocrinology service may be included as parts of the overall health examinations in elderly subjects with wet AMD. However, further studies should be conducted on this topic to substantiate the above statements and describe underlying structural and ultra-structural mechanisms of thyroid dysfunction regarding the pathogenesis of AMD.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: A meta-analysis. Ophthalmology 2012;119:571-80.
2. Liu F, Ding X, Yang Y, Li J, Tang M, Yuan M, *et al.* Aqueous humor cytokine profiling in patients with wet AMD. Mol Vis 2016;22:352-61.
3. Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, *et al.* Clinical classification of age-related macular degeneration. Ophthalmology 2013;120:844-51.
4. McKibbin M, Devonport H, Gale R, Gavin M, Lotery A, Mahmood S, *et al.* Aflibercept in wet AMD beyond the first year of treatment: Recommendations by an expert roundtable panel. Eye (Lond) 2015;29 Suppl 1:S1-11.
5. Yuan J. Role of inflammatory factors in the effects of aflibercept or ranibizumab treatment for alleviating wet age-associated macular degeneration. Exp Ther Med 2019;17:4249-58.
6. Garc-58ddMedo A, Cabrera-Labrz F, Garczra-LMed J, Arias-Barquet L, Ruiz-Moreno JM. Early and intermediate age-related macular degeneration: Update and clinical review. Clin Interv Aging 2017;12:1579-87.
7. Lambert NG, ElShelmani H, Singh MK, Mansergh FC, Wride MA, Padilla M, *et al.* Risk factors and biomarkers of age-related macular degeneration. Prog Retin Eye Res 2016;54:64-102.
8. Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): Associations with cardiovascular disease phenotypes and lipid factors. Eye Vis (Lond) 2016;3:34.
9. Chaker L, Buitendijk GH, Dehghan A, Medici M, Hofman A, Vingerling JR, *et al.* Thyroid function and age-related macular degeneration: A prospective population-based cohort study – The Rotterdam Study. BMC Med 2015;13:94.
10. Abdelkader M, Abass N. The relation between age related macular degeneration and thyroid disorders. IJOVS 2019;4:101-5.
11. Gopinath B, Liew G, Kifley A, Mitchell P. Thyroid dysfunction and ten-year incidence of age-related macular degeneration. Invest Ophthalmol Vis Sci 2016;57:5273-7.
12. Xu Z, Zhang M, Zhang Q, Xu T, Tao L. Thyroid disease is associated with higher age-related macular degeneration risk: Results from a meta-analysis of epidemiologic studies. Ophthalmic Res 2021;64:696-703.
13. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-related eye disease study report number 3. Ophthalmology 2000;107:2224-32.
14. Klein R, Klein BE, Jensen SC, Cruickshanks KJ, Lee KE, Danforth LG, *et al.* Medication use and the 5-year incidence of early age-related maculopathy: The Beaver Dam Eye Study. Arch Ophthalmol 2001;119:1354-9.
15. Tsai CC, Kao SC, Cheng CY, Kau HC, Hsu WM, Lee CF, *et al.* Oxidative stress change by systemic corticosteroid treatment among patients having active graves ophthalmopathy. Arch Ophthalmol 2007;125:1652-6.
16. Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2000;45:115-34.
17. van Coevorden A, Laurent E, Decoster C, Kerkhofs M, Neve P, van Cauter E, *et al.* Decreased basal and stimulated thyrotropin secretion in healthy elderly men. J Clin Endocrinol Metab 1989;69:177-85.
18. Barbesino G: Thyroid Functi on Changes in the Elderly and Their Relati onship to Cardiovascular Health: A Mini-Review. Gerontology 2019; 65:1-8.
19. Herrmann JH, Kröll HJ, Rudorff KH, Krüskemper HL. Thyroid function and thyroid hormone metabolism in elderly people low T 3-syndrome in old age. Klin Wochenschr 1981;59:315-23.
20. Woo SJ, Ahn J, Morrison MA, Ahn SY, Lee J, Kim KW, *et al.* Analysis of genetic and environmental risk factors and their interactions in Korean patients with age-related macular degeneration. PLoS One 2015;10:e0132771.
21. Paetkau ME, Boyd TA, Grace M, Bach-Mills J, Winship B. Senile disciform macular degeneration and smoking. Can J Ophthalmol 1978;13:67-71.
22. Taseer Z KM, Afzal S, Gillani SA, Sarwar S. Cataract; diabetes and smoking as a major risk factor for cataract in the community population of residents of lahore cantt. Prof Med J 2019;26. DOI:https://doi.org/10.29309/TPMJ/2019.26.02.3085.
23. Querques G, Merle BM, Pumariega NM, Benlian P, Delcourt C, Zourdani A, *et al.* Dynamic drusen remodelling in participants of the nutritional AMD treatment-2 (NAT-2) randomized trial. PLoS One 2016;11:e0149219.
24. Waring AC, Arnold AM, Newman AB, B wman1 P, Hirsch C, Cappola AR. Longitudinal changes in thyroid function in the oldest old and survival: The cardiovascular health study all-stars study. J Clin Endocrinol Metab 2012;97:3944-50.
25. Biondi B, Bartalena L, Cooper DS, Hegedre L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. Eur Thyroid J 2015;4:149-63.