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Retrospective analysis of the progression of early dry age-related macular degeneration in patients receiving versus not receiving a multi-component nutraceutical for four years

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Purpose: *To retrospectively analyze the optical coherence tomography (OCT) changes in retinal morphology and progression in these changes in patients with early dry age-related macular degeneration (AMD) receiving versus not receiving a multi-component nutraceutical daily for four years.*

Material and Methods: *We retrospectively analyzed disease progression in 52 patients (98 eyes) with early dry AMD who had been regularly followed up for four years. Group 1 was comprised of 24 patients (98 eyes) who had been receiving vitamin and mineral tablets containing the AREDS2 formulation plus resveratrol and vitamin D daily for four years. Group 2 was comprised of 28 patients (53 eyes) who had not been receiving any nutritional supplement. Retinal morphology was assessed by OCT and OCT angiography.*

Results: *In group 1, best-corrected visual acuity (BCVA) did not change after completion of the 4-year observation period compared to baseline (0.6 ± 02, p = 0.72). In group 2, BCVA was 0.6 ± 0.2 at baseline and decreased to 0.2 ± 0.2 in four years (p ≤ 0.001). In patients with a low to moderate risk of progression in groups 1 and 2, the four-year progression rate was 15.4% and 45.4%, respectively, which corresponds to an annual progression rate of 3.8% and 11.3%, respectively. In patients with a high risk of progression in groups 1 and 2, the four-year progression rate was 26.3% and 80%, respectively, which corresponds to an annual progression rate of 6.5% and 20%, respectively. Patients who had early dry AMD eyes with a low to moderate risk of progression (and a high risk of progression) at baseline and were not taking the nutritional supplement, had 4.58 greater odds (95% CI, 1.291 – 16.267; p = 0.018) [and 11.2 greater odds (95% CI, 2.505 – 50.081; p = 0.0016)] of having AMD progression than those receiving the nutritional supplement daily for four years.*

Conclusion: *A regular intake of tablets containing the AREDS2 formulation plus resveratrol and vitamin D slows the progression of early dry AMD, especially in eyes with a high risk of disease progression, and contributes to the preservation of visual function.*

Keywords:

age-related macular degeneration, nutraceutical, progression, optical coherence tomography, changes in retinal morphology

Introduction

Age-related macular degeneration (AMD) is the most common chronic retinal degenerative disease leading to visual function loss. It accounts for 5% of all cases of global blindness, is a major cause of blindness among adults aged ≥50 years in developed countries, and the incidence of the disease exponentially increases every ten years after the age of 50 [1,2,3]. Dry AMD is more common and is accompanied by pigment epithelial atrophy and drusen development without exudative manifestations or neovascularization [4].

In recent decades, studies have been aimed at investigating AMD mechanisms and identifying AMD risk factors. Retinal pigment epithelium (RPE) cell degeneration is one of the central hallmarks in the pathogenesis of AMD. Age-related alterations in RPE cells are contributed by accumulation of lysosomal lipofuscin and extracellular drusens. Oxidative stress is believed to be another key factor in AMD pathogenesis and a trigger of RPE damage in AMD. High oxygen consumption, long periods of exposure to light, involvement in lipid peroxidation, and the anatomic location close to photoreceptors evoke oxidative stress to RPE cells. In addition, oxidative stress is associated with dysfunction of autophagy, an important lisosomal protective mechanism that regulates age-related changes in tissues and contributes to AMD [5].

Thorough investigation of the pathogenetic mechanisms of AMD has enabled an improved understanding of treatment for the disease. The goal of treatment of dry AMD is to slow disease progression. So far, the best evidence for preventing progression to non-neovascular AMD comes from the Age-Related Eye Disease Studies (AREDS) I and II, multicenter, randomized double-masked studies. The efficacy of carotenoids (lutein, 10-12 mg; zeaxanthin, 1-2 mg), vitamin C, vitamin E, zinc oxide (10-20 mg) and selenium (40 mg) for the prevention of the development and progression of AMD has been demonstrated. Besides the minerals and antioxidants whose clinical efficacy for the conservative treatment of dry AMD has been established, there are promising options (other mineral and vitamin supplements) for prophylaxis against age-related retinal changes which require further research [6, 7]. The current study addresses these topical issues as our research interest concerns regular and long-term intake of these multicomponent supplements and their effects on AMD progression. This is why we believe it was feasible to use a retrospective design to conduct an extended and thorough review of the results obtained without a placebo-control simulation during COVID-19 pandemic.

The purpose of the study was to retrospectively analyze the optical coherence tomography (OCT) changes in retinal morphology and progression in these changes in patients with early dry AMD receiving versus not receiving a multi-component nutraceutical daily for four years.

Material and Methods

We retrospectively reviewed the medical records of 900 patients (1800 eyes) with dry AMD who were under observation during September 2022 to February 2023. Of these, we selected 273 patients who were under observation since 2018. Fifty-two patients (98 eyes) conforming to the inclusion criteria and having follow-up OCT visits were included in a subsequent analysis.

This was a retrospective study without a control group. The study was conducted at the facilities of the Zaporizhzhia Regional Clinical Hospital. Inclusion criteria were the presence of early dry AMD at the beginning of the observation period and either receiving oral tablets containing the AREDS2 formulation plus resveratrol and vitamin D daily for four years (group 1; 24 patients, 45 eyes) or receiving no daily supplement (group 2; 28 patients, 53 eyes). Exclusion criteria included poor adherence to daily supplementation schedule, changing the recommended preparation, inadequate OCT image quality, any previous or concomitant ophthalmological condition that could confound the interpretation of AMD features on imaging, or evidence of late AMD in the fellow eye.

This paper is a part of the department's research program entitled Optimization of Eye Disease Diagnosis, Treatment and Follow-up with Ocular Coherence Tomography and Angiography (registration number № 0119U101932). This study included human participants, was approved by the local bioethics committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was not obtained as this was a retrospective study. This study did not include animal experiments.

On completion of the four-year observation period, patients were assessed for progression from early dry AMD to advanced dry or wet AMD. OCT changes in retinal morphology were assessed as per the NG82 National Institute for Health and Care Excellence (NICE) AMD Classification [8]. The following biomarkers, if any were identified: hyperreflective inclusions associated with pigmentary abnormalities, reticular pseudodrusen, early signs of geographic atrophy, hypertransmission of light through the RPE, drusen with subretinal fluid, and patterns of drusen heterogeneity in the form of OCT–reflective drusen substructures. In addition, OCT drusen measurements were obtained. Risk of disease progression was determined on the basis of this analysis. Eyes with early dry AMD were classified as those with (a) low risk of progression if they had medium drusen (≥63 μm and <125 μm) or pigmentary abnormalities; (b) medium risk of progression if they had large drusen (≥125 μm) or reticular drusen or medium drusen with pigmentary abnormalities; and (c) high risk of progression if they had large drusen (≥125 μm) with pigmentary abnormalities or reticular drusen with pigmentary abnormalities, or pseudovitelliform without significant visual loss (best-corrected acuity better than 0.3), or atrophy smaller than 175μm and not involving the fovea.

Changes in the AMD stage were analyzed separately for eyes with a low risk of progression, eyes with a medium risk of progression, and eyes with a high risk of progression. In group 1, 26 eyes had a low to medium risk of progression and 19 eyes, a high risk of progression. In group 2, 33 eyes had a low to medium risk of progression and 20 eyes, a high risk of progression.

Optical coherence tomography angiography (OCTA) was used to exclude the presence of subretinal neovascular membranes (SNM) either at the baseline and throughout the observation period or, in case of AMD progression, throughout the observation period.

Patients received a comprehensive eye examination including visual acuity, perimetry, tonometry, OCT and OCTA of the posterior segment. The AngioVue OCTA system (RTVue XR OCT Avanti, Optovue, Inc., Fremont, CA) was used for split-spectrum amplitude-decorrelation angiography (SSADA) measurements with OCT and OCTA. Retinal OCT was performed using Cross Line, Retina Map, and 3D Widefield scans. The AngioRetina 6 × 6 mm scan protocol was used to perform OCTA in the macular area. Angiography was assessed using manual and automatic segmentation modes.

Statistical analyses were conducted using Statistica 10.0 (StatSoft, Tulsa, OK, USA) software. Continuous variables are presented as mean ± standard error of mean (SEM), and categorical variables are presented as percentages. Categorical variables were compared using Pearson chi-square test. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the

relationship between AMD progression and nutraceutical intake [9].

Results

Fifty-two patients (98 eyes) with early dry AMD were included in the analysis. Demographic characteristics of the observation groups are presented in Table 1.

In group 1, best-corrected visual acuity (BCVA) did not change after completion of the 4-year observation period compared to baseline (0.6 ± 02, p = 0.72). In group 2, BCVA was 0.6 ± 0.2 at baseline and decreased to 0.2 ± 0.2 in four years ($p \leq 0.001$).

Because modern classifications take into account the risk of AMD progression, changes in the AMD stage were analyzed separately for eyes with a low or medium risk of progression (Table 2), and eyes with a high risk of progression (Table 3).

At baseline, there was no significant difference between observation groups in terms of age, gender or number of patients (Table 2). Over the 4-year observation period, there was a gradual increase in the stage of dry AMD, and 15% of eyes became eyes a high risk of progression, in group 1. In addition, in group 2, 33% of eyes and 12% of eyes became eyes a high risk of progression, and eyes with late AMD, respectively. Therefore, the four-year progression rate was 15.4% in group 1, and 45.4% in group 2, which corresponds to an annual progression rate of 3.8% in group 1, and 11.3% in group 2.

Our retrospective analysis found that, although at baseline, there was no significant difference between groups, in four years, 26.3% of eyes in group 1 and as much as 80% of eyes in group 2 progressed to late AMD. Therefore, the four-year progression rate was 26,3% for group 1 and 80% for group 2, which corresponds to a one-year progression rate of 6.5% in group 1, and 20% in group 2.

Odds ratios were calculated to assess the relationship between AMD progression and nutraceutical intake (Table 4). Patients who had early dry AMD eyes with a low to moderate risk of progression at baseline and were not receiving the nutritional supplement, had 4.58 greater odds of having AMD progression than those receiving the nutritional supplement daily over four years. Patients who had early dry AMD eyes with a high risk of progression at baseline and were not receiving the nutritional supplement, had 11.2 greater odds of having AMD progression than those receiving the nutritional supplement daily over four years.

Discussion

Since AMD is a major cause of vision loss among the elderly, it is important to develop and implement effective techniques to prevent the development or progression of

Table 1. Demographic characteristics of the observation groups

Characteristic	Group 1	Group 2	p
Number /percentage of women	14/58%	14/50%	0.72
Number /percentage of men	10/42%	14/50%	0.84
Number of patients/ eyes	24/45	28/53	0.68
Age (M ± m), years	74 ± 7.2	72 ± 6.4	0.62

Note: p, significance of difference; M, mean value of the characteristic; m, standard error of mean

Table 2. Age-related macular degeneration (AMD) in eyes with a low to moderate risk of disease progression at baseline and four years after

Characteristic	Early dry AMD			Late AMD, n/%
	Low risk of disease progression, n/%	Moderate risk of disease progression, n/%	High risk of disease progression, n/%	
Baseline				
Group 1 n=26	13 / 50%	13 / 50%	0	0
Group 2 n=33	16 / 48%	17 / 52%	0	0
p	0.91			
Four years after				
Group 1 n=26	9 / 35%	13 / 50%	4 / 15%	0
Group 2 n=33	8 / 24%	10 / 30%	11 / 33%	4 / 12%
p	0.00046			

Note: n, number of eyes; p, significance of difference (Pearson χ^2)

Table 3. Age-related macular degeneration (AMD) in eyes with a high risk of disease progression at baseline and four years after

Characteristic	High risk of disease progression in early dry AMD, n/%	Late AMD, n/%
Baseline		
Group 1	19/100%	0
Group 2	20/100%	0
p≥0,05		
Four years after		
Group 1	14/73,7%	5/26,3%
Group 2	4/20%	16/80%
p=0.001		

Note: n, number of eyes; p, significance of difference (Pearson χ^2)

Table 4. Odds ratios for the progression of age-related macular degeneration (AMD) in patients who had early dry AMD eyes with a low to moderate risk of progression (and a high risk of progression) at baseline and were not taking the nutritional supplement compared to those who were taking the nutritional supplement daily for four tears

Characteristic	Low to moderate risk of progression	High risk of progression
OR	4.583	11.200
95% CI	1.291– 16.267	2.505 – 50.081
P	0.018	0.0016

the disease. Administering nutraceuticals is an effective method for preventing AMD progression. Lutein and zeaxanthin dietary supplements have been demonstrated to raise macular pigment density and serum concentrations of these carotenoids in humans [10, 11]. A European survey on the opinion and use of micronutrition in AMD has shown that general ophthalmologists and retinal specialists are generally of the opinion that nutritional supplements are effective in slowing disease progression in early/intermediate-stage AMD. Nutritional supplements are considered to have the most beneficial symptomatic effects on visual acuity contrast vision [12]. There is a wide spectrum of opinions regarding the most important components for nutritional supplements. The most important spontaneous answers are lutein (77%), omega-3 (72%), and zeaxanthin (68%). Resveratrol is considered to be a very important component by 26%, and vitamin D, by 10% of ophthalmologists. Given the recent data on the role of resveratrol and vitamin D in the function of the human body in general and visual system in particular [13,14], we have selected as the subject of our study a nutritional supplement containing the original AREDS formulation plus lutein and zeaxanthin (at a ratio of 5:1), resveratrol and vitamin D. What makes the current study different from ones done previously is that it was a retrospective study that reviewed the medical records after the patients were questioned on their adherence to the recommended supplement taking regimen for four years, and the results were compared to other studies. Patients that reported poor adherence with the recommended supplementation were excluded from the current study.

Other studies conducted analyses of various risk factors and AMD progression and investigated the relationships between taking various nutraceuticals and AMD progression. The results of these studies were, however, inconsistent or contradictory because they varied in AMD classifications used. In the Cardiovascular Health and Age-related Maculopathy Study (CHARM) [15], the progression rate of early AMD ranged between 3.4 and 4.67% per annum depending upon the definition used. Progression rates over 7 years for early AMD were 24% for definition 1, 32% for definition 2, and 33% for definition 3. Brandl and colleagues [16] reported that when the 65-year-old and the 85-year-old had early AMD, their 3-year risk to progress to late AMD was 7% and 21%, respectively. In the current study, the AMD progression rate was 6.5% for early dry AMD patients receiving the nutritional supplement and 20% for those not receiving the supplement. Such a high AMD progression rate in controls is likely to be partially explained by variations in patient age, presence of concomitant conditions and risk factors, since the analysis was performed retrospectively.

Odds ratio is an important indicator of how large the likelihood of an outcome (e.g., AMD progression) is for one group of patients compared to the other. Patients who had early dry AMD eyes with a high risk of progression at baseline and were not taking the nutritional supplement, had 11.2 greater odds of having AMD progression than those receiving the nutritional supplement daily for four years. Age, smoking, sex, cholesterol level and genetic risk score have been reported to be associated with increased odds for progression to late AMD [16, 17]. There was an unadjusted OR of 47.2 for the 18-year cumulative progression to late AMD comparing individuals with baseline early AMD with those AMD-free and an OR of 35.0 (95% CI 7.4 to 166.0, p value < 0.0001) when adjusting for age and follow-up time. Robman and colleagues [18] reported that family history of AMD and smoking (ever vs never) have been associated with increased odds for AMD progression (OR 4.8, 95% CI 1.46–15.68 and OR 2.06, 95% CI 1.14–3.71, respectively).

A major feature of the current study was that we did not investigate individual risk factors, and did not define narrow inclusion criteria, but tried to include the general population with early dry AMD which is usually followed by an ophthalmologist. Therefore, we retrospectively analyzed the longitudinal changes in early dry AMD in patients receiving and not receiving daily oral tablets containing the AREDS2 formulation plus resveratrol and vitamin D for four years. This analysis demonstrated that (1) patients who had early dry AMD eyes (especially those with a high risk of progression) at baseline and were not receiving the nutritional supplement, had greater odds of having AMD progression than those receiving the nutritional supplement daily for four years, and (2) a regular intake of these tablets contributed to the preservation of visual function.

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Ethics Statement. *This study included human participants, was approved by the local bioethics committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was not obtained as this was a retrospective study. This study did not include animal experiments.*

Abbreviations: *AREDS, Age-Related Eye Disease Studies; AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CI, confidence interval; NICE, National Institute for Health and Care Excellence; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; OR, odds ratio*