The association between blood vitamins D and E with age-related macular degeneration: A pilot study

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Abstract: *Background:* This study was aimed to evaluate the association of serum vitamins D and E level with age-related macular degeneration (AMD). *Methods:* This pilot study was performed in two groups of 15 patients in treatment group and 15 patients in control group. Measurements of blood factors [such as C-reactive protein (CRP) and high-density lipoprotein (HDL)] were performed after 12 h of fasting. To measure vitamins D and E, the serum was isolated from 5 cc blood samples. *Results:* HDL was higher in the control group as compared with the AMD group. However, no significant difference was found between the two groups ($p = 0.08$). On the other hand, serum vitamin E in the AMD group was remarkably higher as compared to the control group ($p < 0.002$). However, no significant difference was found in serum vitamin D levels between the two groups ($p = 0.662$). Our findings also revealed that there was no statistically significant relationship between BMI and AMD. Moreover, no significant correlation was determined between serum CRP and AMD ($p = 0.96$). *Conclusions:* Our data indicated that none provides evidence for associations between AMD and serum vitamin D levels. The association between vitamin D and AMD requires further investigations in a large population studies, to elucidate whether vitamin D deficiency can be an important risk factor for AMD.

Keywords: vitamins D and E, serum, healthy lifestyles, blood factors, age-related macular degeneration

Introduction

Age-related macular degeneration (AMD) is a progressive disease that may be associated with blurred or no vision in the center of the visual field [1]. Macular degeneration causes the macula to lose its natural function. It can be damaged by several factors, such as diabetes, genetic disease, and the consumption of medications, including chloroquine and hypertension [2]. The prevalence of this disease in the United States is high, and more than 14% of people aged 80 years and older are wholly involved with it [3]. It has also been estimated in 2000 that more than 9 million people have been infected with AMD [4]. The disease is expected to double in 2020 [5]. The prevalence of this disease in a study between the ages of 40 and 65 years old was 4.7%, which is lower than the western countries and is higher than the eastern countries [6]. Common risk factors for macular degeneration include smoking [7], high blood pressure [8], obesity [9], whiteness [10], low high-density lipoprotein (HDL) and high low-density lipoprotein (LDL) [11], C-reactive protein (CRP) [12], exposed to light sunshine [13], genetics and family history, and immune and inflammatory disorders [7]. Apolipoprotein E (ApoE) is the main apolipoprotein of the CNS, which plays a role in the transmission of lipids and cholesterol in the body. Three forms E2, E3, and E4 are known for the ApoE allelic variants associated with AMD. E4 allele has anti-AMD effects, whereas E2 allele increases the risk of the disease, E3 allele does not have an effect on the chance of developing [14]. Studies have focused on the role of some nutritional compounds on macular degeneration [15–19]. Therefore, vitamins and minerals can reduce the complications of the disease and improve vision [20]. Particularly, foods rich in antioxidants, such as vitamin E, play an important role in inflammation and oxidative stress in this pathway [16, 21]. Omega-3, a member of the family of polyunsaturated fatty acids, is not synthesized in the body; therefore, the intake of this fatty acid is important. In this group, docosahexaenoic acid and eicosapentaenoic acid have beneficial effects on the body. These compounds contain a small percentage of the tissue fatty acids, but they are abundant in the retina, so their deficiency may alter the function of the retina [22, 23]. The beneficial effects of omega-3 have been implicated in inflammatory diseases [24, 25], which is also beneficial in its anti-inflammatory function in the retina. Inflammation creates a redistribution of the choroid arteries in the wet form of AMD [26]. Several studies have shown anti-inflammatory effects of vitamin D [27–29]. Therefore, it is likely that vitamin D deficiency is also related to the incidence of AMD.

If macular degeneration is not prevented, severe vision impairment or vision loss can occur, requiring various treatments, such as Avastin injection and photocoagulation laser. These treatments do not have a satisfactory result for the patient, despite the high financial burden for the patient. On the other hand, there is no disease for the dry type. Regarding the increase in the aging population of our country and the huge costs that the disease can bring to the country, it is necessary to examine the various factors that can help reduce the disease. In Iran, there is little information about dietary intake, the nutritional status of individuals, and their impact on AMD. Moreover, regarding the levels of vitamins D and E, the intake of omega-3 and lipid profiles in AMD patients has not been studied. Therefore, in this study, the relationship between serum levels of vitamins D and E, the intake of omega 3 sources, and the lipid profiles in macular degeneration have been studied in order to use this information to prevent these patients.

Materials and Methods

Ethical committee

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and informed consent was received from all the participants in the study. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

Patients study

This case–control study was conducted in two hospitals affiliated to Tehran University of Medical Sciences (Ziaeean Hospital and Farabi Hospital). People over the age of 50 have been screened for ophthalmology, patients with AMD in the case group, and those who are complaining of visual impairment and not having AMD are included in the study.

Inclusion criteria of case group:

1. Getting newly discovered AMD without treatment
2. Age over 50 years

Inclusion criteria of control group:

1. Not having AMD
2. Age over 50 years
3. People with complaints of reduced vision

Exclusion criteria:

Use of vitamin D supplementation with therapeutic doses.

From each person, general information including age, gender, history of previous illnesses, history of drug use and supplementation, history of smoking, and exposure to sunlight was obtained. The height of the people was measured in the form of standing with no shoes and with a seca wall-mounted stadiometers. The weight of subjects was measured as fasting with a minimum dress and no shoe with a seca scale and a precision of 500 g. For both the case and control groups, the Food Frequency Questionnaire was completed by a nutrition expert. In this questionnaire, 117 questions have been used to examine food intake in the elderly population of Iran by Hashemi et al. [6].

Laboratory information

All the participants were asked to come to the hospital laboratory on the next day after 12 h of fasting. In the hospital, blood sample (10 ml) was next obtained. The measurements of CRP and HDL were performed and eventually the results were reported weekly from laboratories. To measure vitamins D and E from 5 cc blood samples, the serum was isolated and maintained until use in a −20 freezer for 1 month. Serum samples are packaged into foil to measure vitamin E. The measurement of vitamin D is done using the ELISA kit and vitamin E by HPLC technique.

Method for calculating sample size

The sample size in this study was calculated to compare the mean of vitamin D levels between the two groups. If the standard deviation of vitamin D in each group is 18 (ng/ml) [30] to detect a difference of 10 ng/ml between the two groups, with a probability of 95% and a probability of committing a type I error (5%) for each group, 85 samples are required based on the following formula:

$$n=\frac{(Z_{1-\frac{\alpha}{2}}+Z_{1-\beta})^2\times 2\sigma^2}{\Delta^2}=\frac{(1.96+1.64)^2\times 2\times 18^2}{10^2}=85.$$

Statistical analyses

The *t*-test was used to compare the mean of vitamins D and E between AMD and control groups. Covariance analysis was also applied when considering the effects of confounding factors, such as the dietary intake of these compounds and the duration of exposure to sunlight.

Results

This is a pilot study and it is part of a major study

This is a pilot study conducted in two groups: treatment group with 15 subjects and control group with 15 subjects. The findings showed that HDL was higher in the control group than the other group, but there was no significant difference between the two groups ($p = 0.08$). In addition, serum vitamin E level in case group was significantly higher than control group ($p < 0.002$) *(Table I)*.

However, serum level of vitamin D did not show significant difference between the two groups ($p = 0.662$). The study also revealed that there is no statistically significant relationship between BMI and AMD. In addition, there was no significant association between serum level of CRP and AMD ($p = 0.96$) *(Table I)*.

Discussion

Our findings indicated that serum vitamin E level in AMD group was significantly higher than control group. Conversely, HDL level was higher in the control group than the AMD group, but there was no significant difference between the two groups.

In this study, there was no significant correlation between serum vitamin D level and AMD.

This result is in agreement with previous findings that indicated no significant correlation between blood 25-hydroxyvitamin D levels and advanced AMD [31], but no early AMD. Parekh has investigated the association between serum vitamin D levels and AMD on 7,752 people. The prevalence of AMD in this study was 11%, where vitamin D deficiency was determined to be inversely linked to early AMD but not advanced AMD [31].

Our finding is contrary to those of a previous study, which revealed significant correlation between blood vitamin D levels and AMD [32]. Of course, these results can be related to the low sampling rate, which is one of the limitations of this study as a pilot study and requires a comprehensive investigation. Therefore, limiting any definitive conclusions in terms of the vitamin D effects on AMD patients

A cross-sectional study was conducted in Korea to investigate the relationship between serum vitamin D

Table I Number of clinical characteristics on means 25-hydroxyvitamin D [25(OH)D] and vitamin E status and other factors in patients in subgroups of age-related macular degeneration

Blood factors	Case ($n = 15$) Mean (SD)	Control ($n = 15$) Mean (SD)	*p*
Vitamin E	17.7 (4.9)	11.34 (4.6)	<0.002
Vitamin D	37.04 (12.6)	41.34 (17.7)	0.662
BMI	26.7 (5.03)	30.53 (29.82)	0.735
CRP	1.07 (0.25)	1.07 (0.26)	0.960
ESR	17.87 (11.7)	13.50 (11.75)	0.581
FBS	102.13 (29.30)	122.79 (53.70)	0.038
LDL	110.20 (34.82)	91.92 (16.12)	0.031
HDL	42.67 (11.78)	50.85 (8.84)	0.086
CHOL	189.13 (50.33)	168.71 (19.40)	0.002
TG	130.0 (49.85)	122.0 (62.79)	0.405

SD: standard deviation; BMI: body mass index; CRP: C-reactive protein; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ESR: erythrocyte sedimentation rate; FBS: fasting blood sugar; TG: triglyceride; CHOL: cholesterol levels and AMD. About 17,045 people who referred to the hospital during the period from 2008 to 2012 were enrolled. Therefore, after measuring the serum levels of vitamin D, they were subjected to eye examinations and imaging. Of those, 1,163 were diagnosed with AMD at an early stage and 115 subjects were advanced AMD patients. The mean serum vitamin D level in women was 17.5 ng/ml and in men was 20 ng/ml. The findings of mentioned survey demonstrated that AMD disease at advanced levels was significantly associated with a decrease in blood 25-hydroxyvitamin D levels in men [30, 32].

Tan et al. [33] examined the association between the intakes of fatty acids with the incidence of AMD for 10 years. In the mentioned study, 2,454 AMD patients participated in the study, which were initially evaluated after 5 years and finally after 10 years. The photos were taken from retina and the Food Frequency Questionnaire was also obtained. The results showed that the use of fish in a meal during a week reduces the risk of developing AMD. Moreover, nutrients use of 1–2 units per week resulted in a reduction in AMD [33]. Another study in 2006 evaluated the relationship between fish consumption, omega-3, and smoking among 681 twins, of which 222 were twins with AMD and 459 without AMD. The results showed that the risk of developing AMD increased by smoking, while fish consumption (at least twice a week) and omega-3 would reduce its risk [34].

As matter of fact, high level of blood 25-hydroxyvitamin D was inversely linked to late AMD in men but not women. A study in North Carolina was conducted in 2015 to compare the levels of vitamin D in neovascular AMD (146 individuals), non-neovascular AMD (260 individuals), and non-AMD control (100 individuals). This study showed that vitamin D in neovascular AMD was significantly lower than the other two groups [30], where vitamin D deficiency was more prevalent in neovascular AMD patients. A cross-sectional study in Denmark (2013) has been aimed at investigating the relationship between AMD disease and serum vitamin D levels. In the mentioned study, 129 subjects with different degrees of AMD and 49 controls were enrolled. The results showed that there is a significant difference between serum levels of vitamin D in control subjects (75.6 nmol/L) and AMD patients with grade 5 (47.3 nmol/L) [35]. Furthermore, the association of serum vitamin D level with AMD in the early stages was studied in 1,313 women with AMD and 1,287 without AMD [36]. Another study was conducted in Italy in 2002, in which 49 patients with AMD and 46 controls were included to compare vitamins C, E, and beta-cryptoxanthin levels. The results revealed a significant decrease in these compounds in the AMD group compared to the control group [37]. A study reported that serum levels of zinc and vitamin E in the AMD group were significantly lower than that of the control group [38].

In general, it should be noted that the sun exposure and food intake during the recent weeks, instead of the year, will increase the chance of random measurement error. Various factors may affect the outcome of the study, including unknown, unmeasured healthy lifestyles risk, or protective factors that are more common among people whose high levels of vitamin D have compared to low serum vitamin D levels [39, 40]

On the other hand, our data showed that serum vitamin E in the AMD group was significantly higher than the control group. In contrast with these findings, a study by Christen et al. [41] on 117 cases of AMD in the vitamin E group has reported that vitamin E treatment had no large beneficial or harmful effect on risk of advanced AMD. Furthermore, another study by Timms et al. [42] revealed that vitamin D intake decreases CRP, a marker of systemic inflammation. Moreover, the two studies by Seddon et al. [43, 44] have found associations between markers of inflammation (such as CRP) and AMD, but Klein et al. [45] have suggested that there was no statistically significant association between CRP and AMD. In parallel, our data showed that no significant correlation was determined between serum CRP and AMD. In addition, McKay et al.'s [46] study on 4,753 participants have been observed that no association was found with vitamin D and early or late AMD or neovascular AMD. There was no association between insufficient or deficient status with early or late AMD. This is in agreement with our finding.

In conclusion, this study conducted in a small sample as pilot study of the Iran population and none provides evidence for associations between AMD and serum vitamin D levels. In addition, this study does not show any relationship between serum CRP and AMD levels. Our results warrant reconsidering the existence of an association between vitamin D and the occurrence and progression of AMD using a large population.

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