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Reconsidering the connection between vitamin D levels and age-related macular degeneration

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Learning objectives

On completion of this activity, participants will be able to:

1. Distinguish established risk factors for AMD
2. Evaluate physiological effects of vitamin D
3. Analyze the relationship between serum levels of vitamin D and the prevalence of AMD in the current study

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CLINICAL STUDY

Reconsidering the connection between vitamin D levels and age-related macular degeneration

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Abstract

Purpose **Recent evidence has suggested a correlation between reduced vitamin D levels and delayed angiogenesis and reduced inflammatory response, which are known to have a major role in the development and progression of age-related macular degeneration (AMD).**
Design **Cross-sectional study.**
Participants **Members of the Maccabi Healthcare Services (MHS, one of the four largest Israeli Health Maintenance Organization) aged $\geq$60 years, whose vitamin D levels were taken as part of routine examinations between 2000 and 2008.**
Methods **All data for this study were obtained from MHS databases that include medical information on 1.8 million subscribers.**
Main outcome measures **Serum 25-OH vitamin D levels.**
Results **The total study population comprised of 1045 members diagnosed as having AMD, and 8124 as non-AMD, for whom there was information on vitamin D levels. The mean $\pm$ SD level of 25-OH vitamin D was 24.1 $\pm$ 9.41 ng/ml (range 0.8–120) for the AMD patients and 24.13 $\pm$ 9.50 ng/ml (range 0.0–120) for the controls (P = ns). One-third (33.6%) of the AMD patients and 32.86% of the controls had a 25-OH vitamin D level $<$16 ng/ml, and the proportions of tests in which the 25-OH vitamin D level was $>$74 ng/ml were 0.19 and 0.14%, respectively (P = ns)**
Conclusions **No association was detected between vitamin D levels and the presence of AMD in this cross-sectional study. These results raise some doubt about an association between reduced vitamin D levels and the prevalence of AMD.**

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Keywords: age-related macular degeneration; serum 25-OH vitamin D; Maccabi Healthcare Services; Health Maintenance Organization

Introduction

Age-related macular degeneration (AMD) is the leading cause of legal blindness among people in the western world.[1]

High-dose antioxidants have been shown to slow progression from intermediate to late AMD.[1] Several potential risk factors for the development and progression of AMD have been identified, such as age,[2] cigarette smoking,[3] hypertension[2] and family history of the disease.[4] Other potential risk factors associated less consistently in previous studies include sunlight exposure[2,5] and diets low in lutein and zeaxanthin,[6,7] or diets high in fats.[8,9]

The pathogenesis of AMD is not fully understood, but it is well established that angiogenesis has a major role in the development and progression of AMD.[10] Inflammation has recently received some attention as a potential risk factor for AMD.[11–22] Immunological changes seemed to be related to early pathological changes in retinal pigment epithelial (RPE) and drusen formation. Immune components, including immunoglobulins, complement factors and fibrinogen, have been observed to be entrapped within drusen.[11–14,16] Evidence of inflammatory cell involvement in the later stages of AMD includes the presence of multinucleated giant cells and leukocytes in the choroid of AMD eyes[15] and in excised choroidal neovascularization.[20,22] A number of *in vitro* and *in vivo* studies have suggested an anti-inflammatory role for vitamin D.[23,24]

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It was also shown that vitamin D reduces the proliferation of cells of the immune system,[25–29] and that there is an inverse relationship between vitamin D levels and several chronic conditions associated with inflammation.[30–33] Owing to the potential causative role of inflammation in AMD development and progression, it is possible that vitamin D may protect against the occurrence and progression of AMD by virtue of its anti-inflammatory properties. Furthermore, it was recently shown that vitamin D was a potent inhibitor of angiogenesis by its effects on endothelial cells[34] and by interrupting signaling pathways that are key to angiogenesis, specifically in tumorigenesis.[35,36]

The primary purpose of this study was to examine the relationship between serum vitamin D levels and AMD. We hypothesized that individuals in the highest quintile of serum vitamin D levels would have a lower prevalence of AMD compared with those in the lowest quintile.

Materials and methods

This cross-sectional study was carried out in Maccabi Healthcare Services (MHSs), a 1.8 million enrollee health maintenance organization operating in Israel. It was approved by the MHS institutional review board. All the data were obtained from the MHS's automated databases, that were used to retrieve information on biochemistry results, and medical diagnoses using the international classification of diseases 9 (ICD-9). Included in the study were MHS members aged 60 or above, that have had their vitamin D test between 2000 and 2008 as part of a routine exam. For each eligible patient, information on age at vitamin D test, sex and past diagnoses of AMD, diabetes mellitus and hypertension were collected from the electronic medical files using a unique nine-digit personal number. AMD was identified by the presence of the following ICD-9 codes: unspecified macular degeneration (senile) of retina, non-exudative senile macular degeneration of retina, exudative senile macular degeneration of retina.

Serum data

Serum 25-hydroxyvitamin D was measured as part of the member's routine examination with no relation to suspected or confirmed AMD. The level was determined by collecting approximately 100 ml of whole blood in evacuated containers. Serum specimens were immediately frozen at −70°C and subsequently used to estimate serum vitamin D levels within 2 weeks of collection.[37] In Israel, estimation of serum 25-hydroxyvitamin D in humans is regularly carried out with the LIAISON 25 OH Vitamin D TOTAL assay[38] (now DiaSorin Inc., Stillwater, MN, USA) based on a radioimmunoassay method. Values of vitamin D are usually described in quintiles: a level of <16 ng/ml indicates deficiency, a level between 17 and 73 ng/ml is considered as being sufficient and a level ≥ 74 ng/ml is indicative of vitamin D toxicity. The standard deviation is 9% and it is calculated as coefficient of variation (CV−SD/mean × 100).

Statistical analysis

The χ^2-test for categorical variables and the *t*-test for comparing averages were performed to determine significant differences in baseline characteristics between AMD and non-AMD patients. Pearson's correlation was used to measure the association between vitamin D levels and age. Statistical significance was considered when $P<0.05$.

Results

The total study population of 9167 was comprised of 1045 AMD and 8124 non-AMD subjects, which represents 12.5% of the AMD patients and 9.5% of the non-AMD patients in MHS. The participants' characteristics are summarized in Table 1. Compared with the non-AMD study participants, AMD patients were more likely to be older (77.7 *vs* 76.0, $P<0.01$). Both study groups, had a comparable sex distribution and a similar prevalence of DM and hypertension.

Mean serum levels of 25-hydroxyvitamin D correlated negatively with age ranging from above 26 ng/ml in subjects aged 60–69 to less than 22 in elderly aged 85 or above (Figure 1), which suggest a bi-variate correlation of −0.136 ng/ml per increase of 1 year of age ($P<0.01$). Similar trends were found in men and women. The mean 25-OH vitamin D levels for the AMD patients and the controls are provided in Table 2. Vitamin D levels were

Table 1 Demographic characteristics of the study participants

	AMD (n = *1045*)	*Controls* (n = *8124*)	*Total* (n = *9167*)	P
Sex				
Female	789 (75.6%)	6172 (76%)	6961 (75.9%)	0.422
Male	254 (24.4%)	1952 (24%)	2206 (24.1%)	0.422
Mean age (SD)	77.66 (7.07)	76.04 (5.75)	76.23 (5.94)	<0.01
Hypertension				
No	160 (15.3%)	1418 (17.5%)	1578 (17.2%)	0.09
Yes	883 (84.7%)	6076 (82.5%)	7589 (82.8%)	0.09
Diabetes				
No	782 (75%)	6020 (74.1%)	6802 (74.2%)	0.543
Yes	261 (25%)	2104 (25.9%)	2365 (25.8%)	0.543

Abbreviation: AMD, age-related macular degeneration.

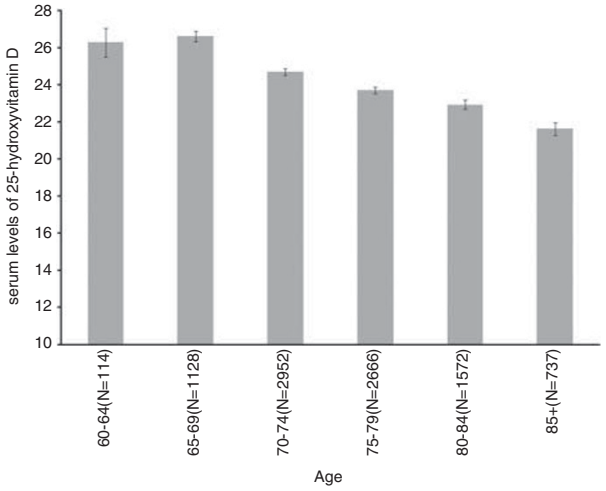

Figure 1 Mean and standard error of mean serum levels of 25-hydroxyvitamin D in ng/ml, according to age in Maccabi Healthcare Services, Israel.

Table 2 Levels of 25-OH vitamin D of the study participants

25-OH vitamin D	*AMD (n = 1045)*	*Controls (n = 8124)*	P
Mean (ng/ml), SD	24.10, 9.41	24.13, 9.50	$P = 0.925$
Proportion of tests <16 ng/ml	33.6% ($n = 351$)	32.8% ($n = 2666$)	$P = 0.642$
Proportion of tests >74 ng/ml	0.19% ($n = 2$)	0.14% ($n = 11$)	$P = 0.987$

Abbreviation: AMD, age-related macular degeneration.

24.1 ± 9.41 ng/ml for the former and 24.13 ± 9.50 ng/ml for the latter ($P = 0.925$). The proportion of tests in which the 25-OH vitamin D level was below the normal limit (<16 ng/ml) was 33.6% for the AMD patients and 32.86% for the controls ($P = 0.642$). When we examined the proportion of tests in which the 25-OH vitamin D level was higher than the normal laboratory limit (>74 ng/ml), it emerged that 0.19% of the AMD patients had vitamin D level >74 ng/ml compared with 0.14% of the controls ($P = 0.987$).

Discussion

We had hypothesized that AMD patients would have lower levels of vitamin D compared with non-AMD subjects, basing our expectations on several putative mechanisms supporting the anti-inflammatory properties of vitamin D as well as its anti-angiogenic properties. The evidence we accumulated from our data on a large number of AMD patients failed to support any association between vitamin D levels and the prevalence of AMD, as the MHS members with AMD had 25-OH vitamin D levels similar to those of non-AMD controls. The relatively large number of AMD patients in our study allowed a statistical power of 80% to detect an OR of at least 1.3 for AMD among patients with low vitamin D level, and 99% power to detect an OR of at least 1.5. Therefore, it is unlikely that our negative results are explained by type II error.

Several studies have reported that vitamin D decreases the proliferation of T-helper cells,[23] T-cytotoxic cells and natural killer cells[24] and enhances T-suppressor cell activity.[31] Other studies have reported that vitamin D also decreases the production of proinflammatory agents, such as IL-2,[25,26] IL-8,[27] IL-6[28] and IL-12.[29] One recent study demonstrated that vitamin D intake reduces C-reactive protein, a marker of systemic inflammation.[33]

Dramatic advances have been made in unraveling the biological bases of AMD, implicating chronic local inflammation and activation of the complement cascade in the pathogenesis of the condition.[16,17] A number of complement system proteins, complement activators and complement regulatory proteins were identified as molecular constituents of drusen, the hallmark extracellular deposits associated with early AMD[12,39–42] and of geographic atrophy and choroidal neovascularization, the hallmark of advanced AMD.[43] Genetic studies revealed highly significant associations between AMD and variants of several complement pathway-associated genes, including complement factor H, complement factor H-related 1 and 3, complement factor B, complement component 2 and complement component 3.[39–42,44] Associations between markers of inflammation (such as C-reactive protein) and AMD have been observed in some[45,46] but not all[47] previous epidemiological studies. Results of the Beaver Dam Eye Study indicated an association between histories of gout and emphysema, two diseases associated with inflammation, and intermediate and late stages of AMD.[31]

A comprehensive review by Zarbin[18] described several concepts relevant to the cell biology of AMD. One especially relevant concept was that in AMD (and perhaps in aging), injury to the RPE and, possibly, choriocapillaris results in a chronic inflammatory response within the bruch membrane and the choroid and that this inflammation leads to formation of an abnormal extracellular matrix (ECM), which causes altered diffusion of nutrients to the retina and RPE, possibly precipitating further RPE and retinal damage. The abnormal ECM results in altered RPE-choriocapillaris behavior, leading ultimately to atrophy of the retina, RPE, and the choriocapillaris and to choroidal new vessel growth. Inflammation clearly has a major role in AMD pathogenesis in such a sequence of events.

Vitamin D might protect against AMD by virtue of its antiangiogenic properties. Vitamin D is a potent inhibitor of angiogenesis by its effects on endothelial cells[34–36]

and by interrupting signaling pathways that are key to angiogenesis, specifically in tumorigenesis. Vitamin D is provided by some foods and is also generated endogenously on exposure to sunlight. The serum levels of 25-hydroxyvitamin D that were assessed in this study reflected the cumulative quantity of vitamin D from all sources.

Parekh *et al*[48] evaluated the associations between levels of vitamin D (25-hydroxyvitamin D) in serum and prevalent AMD in a large population based cross-sectional study. They found that levels of serum vitamin D were inversely associated with early AMD but not advanced AMD. When they evaluated associations of early and late AMD with important food and supplemental sources of vitamin D, they found that milk intake was inversely associated with early AMD (OR, 0.75; 95% CI, 0.6–0.9) and that fish intake was inversely associated with advanced AMD (OR, 0.41; 95% CI, 0.2–0.9).

Other studies evaluated the association of fish intake (a major source of vitamin D) to AMD and found that higher fish intake was associated with a lower risk of AMD development and progression.[8,9,49,50]

This cross-sectional study found that higher vitamin D levels are not associated with decreased prevalence of AMD, as expected by the above evidence.

We found that vitamin D levels were inversely associated with age (Figure 1). This finding was also demonstrated in a large cross-sectional study, investigating the association between 25(OH)D levels with all-cause, cancer and cardiovascular disease (CVD) mortality in 13 331 nationally representative adults 20 years or older from the Third National Health and Nutrition Examination Survey.[51] In cross-sectional multivariate analyses, they found that increasing age, female sex, non-white race/ethnicity, diabetes, current smoking and higher body mass index were all independently associated with higher odds of 25(OH)D deficiency (lowest quartile of 25(OH)D level $\leq$17.8 ng/ml). They found that in the general United States population, 25(OH)D deficiency (lowest quartile $\leq$17.8 ng/ml) was associated with a 26% higher risk of all-cause mortality, independent of baseline demographics, traditional and non-traditional CVD risk factors, and measures of a healthy lifestyle. The estimated association with increased risk of CVD mortality was similar, though not statistically significant. No association was found with cancer mortality or other causes of death.

Several potential limitations of our study must be considered before drawing any conclusions from the results. We did not estimate the food and supplement intake of the patients or the amount of sun exposure, the lack or excess of which could have affected the results. As in many cross-sectional studies, the recorded serum 25-hydroxyvitamin D values would reflect sun exposure and food intake over recent weeks, rather than years, a feature that would have increased the random measurement error. However, we do not believe that this potential non-differential misclassification of exposure has biased the reported associations toward the null, as a pervious study from Israel has shown that sun exposure carries only a small and insignificant effect on the variation in vitamin D levels between seasons.[52]

Cases of AMD were defined by diagnostic codes according to ICD-9 without detailed clinical data (eg, retinal pigment epithelial depigmentation, size and type of drusen and so on), which were unavailable. Therefore, no distinctions were made between early and late AMD, and we were not able to examine any associations of serum vitamin D levels and the advanced form of AMD, which are meaningful, given the antiangiogenic properties of vitamin D. Several important differences between the findings of our study and those of other population-based studies on this issue[6] may lie in the fact that we did not examine the amount of sun exposure of the patients, a factor that could have a great impact on the results measured.

Another explanation for the difference could be the level of awareness to the value of supplement intake by both the AMD patients and the controls, as we do not have any data on the percentage of AMD patients who take vitamin supplements (vitamin D in particular). Finally, our results could be influenced by a large percentage of the MHS membership who takes supplement vitamin D for other medical conditions (osteomalacia, osteoporosis and so on)

Also, the categorization values of vitamin D used to determine deficiency is not definite, although it is widely agreed that 25(OH)D $<$15 ng/ml (or $<$37.5 nmol/l) is generally considered inadequate.[53]

However, this relatively high cutoff value may have masked effects of more severe hypovitaminosis D.

In conclusion, this study, which was conducted on a large, representative sample of the Israeli population, provides no evidence for inverse associations between AMD and serum vitamin D levels, as we had expected from the findings of others. Our results warrant reconsidering the existence of an association between vitamin D and the occurrence and progression of AMD.

Summary

What was known before

- Little was known about the connection between vitamin D levels and age-related macular degeneration (AMD).

What this study adds

- No association was detected between vitamin D levels and the presence of AMD in this cross sectional study.

Conflict of interest

The authors declare no conflict of interest.

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Medscape EDUCATION

Reconsidering the connection between vitamin D levels and age-related macular degeneration

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1. You are seeing a 67-year-old woman with a chief complaint of blurry central vision. You consider whether she may have age-related macular degeneration (AMD). Which of the following variables is the most significant established risk factor for AMD?

- A Obesity
- B High levels of alcohol consumption
- C Hyperlipidemia
- D Cigarette smoking

2. You have heard that vitamin D levels might also influence the risk for AMD. Which of the following is an action of vitamin D that might explain this relationship?

- A Vitamin D promotes angiogenesis
- B Vitamin D decreases the proliferation of T-helper cells
- C Vitamin D reduces the activity of T-suppressor cells
- D Vitamin D can increase the production of most interleukins

3. Based on the results of this study, what can you advise this patient regarding vitamin D and her risk for AMD?

- A There was no association between vitamin D levels and the presence of AMD in this research
- B She should consume as much fish as possible to boost her levels of vitamin D and prevent AMD
- C She should stay in the sun for 1 h per day to boost her levels of vitamin D and prevent AMD
- D She should undergo an evaluation for 25-OH vitamin D and receive supplements to prevent AMD if her level is <20 ng/ml

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice.

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial boas.

Strongly disagree				Strongly agree
1	2	3	4	5