

Serum Vitamin D Level in Different Stages of Age-related Macular Degeneration

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Received: 12 November 2018 / Received in revised form: 12 March 2018, Accepted: 20 March 2019, Published online: 25 May 2019
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Abstract

Aim: Investigate the correlation between serum Vitamin D level and patient with wet and dry AMD in the comparison with normal patients. **Methods:** A total of 204 patients were enrolled, and were divided into three groups as: The wet (early) AMD group, dry (late) AMD group, and those without any macular degeneration (normal control group). We checked serum 25-hydroxyvitamin D levels of all subjects. Serum vitamin D deficiency was defined as a serum 25-hydroxyvitamin D level below 20ng/mL. **Results:** We analyzed whole data by multiple logistic regression analysis between the normal control group, and both early and late AMD groups. Serum vitamin D deficiency showed a tendency to increase the risk of late AMD, (OR=4.36; CI 95%; P =0.012). Serum vitamin D deficiency was also significantly associated with an increased risk of early AMD (OR= 4.78; CI 95%; P=0.008). **Conclusion:** serum vitamin D deficiency may increase the risk of early and late AMD. It may also be associated with subretinal fibrosis.

Keywords: Vitamin D, Age Related Macular Degeneration, Wet AMD, Dry AMD.

Introduction

Age-related macular degeneration (AMD) is a progressive chronic degenerative disease affecting the central retina, macula and reducing central visual acuity. (Layana ET AL., 2017) AMD is one of the main causes of visual impairment and blindness in old patients worldwide. (Lim ET AL., 2012) The pathogenesis of AMD is multifactorial including; metabolic, functional, genetic and environmental factors. The leading processes of visual blindness in these patients are mostly divided in two categories: "Wet" age-related macular degeneration, and "Dry" atrophy.

In wet age-related macular degeneration (also called Neovascular AMD), choroidal neovascularisation develops into the neural retina, causing leakage of fluid, lipids, and blood into retina, and leading to fibrosis, scar formation and permanent damage. In Late Dry atrophy (also called geographic degeneration), retinal pigment epithelium, choriocapillaris, and photoreceptors leads to a progressive atrophy. (Lim ET AL., 2012) age-related macular degeneration was almost untreatable a decade ago. New pharmaceutical agents through the suppression of vascular endothelial growth factor (VEGF) have altered the process of the disease and has changed basic management of this condition. (Lim ET AL., 2012; Gragoudas ET AL., 2004) Lately, Inflammation has been established to have an important impact in the pathogenesis of AMD. (Kim & Park, 2018) Recent researches have showed that inflammation, Oxidative injuries, and angiogenesis are the leading pathogenesis in AMD, causing progressive photoreceptor loss in Macula. (Layana ET AL., 2017) In the recent studies, it's been hypothesized that, vitamin D with a counteractive inflammatory, angiogenesis and fibrosis effect have preventive role in the progression of AMD. (Kim & Park, 2018; Millen et al., 2015) While some epidemiological surveys insist on a potential role of vitamin D in AMD pathophysiology (Gola et al., 2011; Morrison et al., 2011) but its effect in the pathogenesis of AMD is controversial, (Annweiler et al., 2016; , Layana et al., 2017) in this paper we aimed to investigate the correlation between serum Vitamin D level, and patient with wet and dry AMD in the comparison with normal patients.

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Method and Material:

This study is a cross sectional case control study. Patients included in this study were all the cases who had visited Tabriz Nikookari eye hospital, Tabriz, Iran, with a complaint of a decrease in visual acuity from Jan 2015 to Oct 2017. All the patients were divided into three groups as: The wet AMD group, dry AMD group, and those without any macular degeneration (normal control group). A total of 204 patients were enrolled.

The Age-Related Eye Disease Study (AREDS) protocol was used to grade stereoscopic retinal fundus photograph. Early AMD was defined similar to AREDS Category 3,33 which means the presence of one or more large drusen (≥ 125 microns) or vast intermediate drusen (area ≥ 360 microns when soft indistinct drusen were present or ≥ 650 microns when soft indistinct drusen were absent). Unlike the AREDS Category 3, early AMD was described as pigmentation abnormalities including; an increase or decrease in pigmentation if accompanied by at least one druse ≥ 63 microns. As a matter of fact, late AMD included geographic atrophy (non-central or central), neovascularization, or exudation in the center subfield. The retinal diagnosis was made by 2 trained ophthalmologists. (Millen et al., 2015)

Fasting blood samples collected to measure serum concentrations of 25(OH) Vitamin D in Sadra Laboratory with high performance liquid chromatography (HPLC) method. The kit used for these samples were from Abzar Parseh kit company calibrated by chrome system vitamin D calibrators. All of the results were validated by biomérieux mini vidas vitamin D kit through 3 levels. After collecting blood samples and dividing patients into the Furth mentioned groups, all of the data were analysed through SPSS software version 20.0 for windows (IBM Corp, Armonk, NY). The odds ratios were estimated and the confidence intervals of 95% were determined to evaluate the association of serum vitamin D level and AMD.

Results:

A total of 204 patients who aged 69.26 ± 6.61 were enrolled in our study (normal control group: n=100, early (wet) AMD group: n=58, late (dry) AMD group: n=46). We found a significant correlation among aging and vitamin D deficiency ($P=0.006$) And our main outcomes showed no statistically significant differences were observed among the 3 groups (normal control group, early AMD group, and late AMD group) in terms of the ratio of gender ($P>0.05$) and age ($P>0.05$). P values intended using the Chi-square test. We used multiple logistic regressions to exclude the effects of perplexing factors which may have affected with the association between serum vitamin D deficiency and AMD. We analyzed whole data by multiple logistic regression analysis between the normal control group and both early and late AMD group, serum vitamin D deficiency showed a tendency to increase the risk of late AMD, (OR=4.36; CI 95%; $P=0.012$). Serum vitamin D deficiency was also significantly associated with a more risk of early AMD (OR= 4.78; CI 95%; $P=0.008$). Serum vitamin D level mean in early AMD group was 22.83 ± 12.95 , in late AMD group was 25.02 ± 12.75 and in normal group was 33.17 ± 19.50 . In the multiple logistic regression analysis, patients with early AMD had a significantly greater risk for serum vitamin D deficiency than the normal control group.

Discussions:

Our study in aspects of results and design differs from previous studies that have examined the relationship between levels of serum vitamin D and AMD. Previous studies have divided patients based on funduscopic findings, but in our study patients who visited the "Tabriz Eye hospital" were **selected using** fundus imaging, fluorescence angiography, and neovascularization (OCT). (Itty et al., 2014; Amy et al., 2011; Lee et al., 2012; Eun et al., 2014) hence, we could categorize patients more precisely; for example, patients with AMD are divided into two subgroups, depending on subretinal fibrosis in OCT images. In our study, there was no significant statistical difference between the control group and patients with AMD with subretinal fibrosis on OCT in terms of the age and gender of patients with serum vitamin D deficiency. Previous studies reported that changes to the complementary system were associated with subretinal fibrosis. (Lim ET AL., 2012; Lechner et al., 2016; Curcio et al., 2013; Coleman et al., 2008) Oxidative stress, caused by the aging process as well as environmental factors, may damage the retina cells, cause inflammation, increase the level of extracellular destructive matrix proteins, and release growth factors that seem to be associated with fibrosis. (Boonstra & Post, 2004; Buschini et al., 2011; Bhutto & Luttu, 2012) Vitamin D prevents these changes. Therefore, based on previous study, serum vitamin D deficiency may be associated with subretinal fibrosis. (Kim & Park, 2018; Lim et al., 2012) In our study, serum vitamin D deficiency was associated with an increased risk of developing AMD. A previous study showed that the prevalence of late AMD increases with 25-hydroxy vitamin D levels. (Kim & Park, 2018) It is important to note that many inflammatory cells have a receptor for vitamin D, **for example inflammatory bowel disease is associated with decreased serum vitamin D level and has increased prevalence of early AMD.** (Mouli et al., 2014; Ardizzone et al., 2011; Ardesia et al., 2015) In addition, Multiple Sclerosis is associated with an increased in vitamin D levels. (Munger et al., 2006; Mowry et al., 2010) Eventually, inflammation is induced by cytokines and immunoglobulins secreted from T cells and B cells; this inflammation is suppressed by vitamin D. (Coussens et al., 2012; Wöbke et al., 2014) In previous studies of AMD, inflammation and pathogenesis, immunological components, including immunoglobulins, complementary factors and fibrinogen

have been found. In one study, treating healthy rats using vitamin D reduced inflammation and beta-amyloid sedimentation in the retina. (Choi et al., 2011) Therefore, based on these findings and our study results, serum vitamin D deficiency may be associated with AMD.

In our study, vitamin D deficiency in serum was strongly associated with early (wet) AMD compared to late (dry) AMD. Vitamin D inhibits angiogenesis by reducing vascular endothelial growth factor, as well as inhibiting the matrix metalloproteinase type 9. (Wei et al., 2004) The results of our study showed that patients with vitamin D deficiency in the AMD group were significantly higher than the control group. However, our study had limitations. For example, we used a small study population to confirm our hypothesis. The sample cannot represent the general population. There were also differences in the ratio of male and female participants as well as the age distribution of different groups in our study. Nevertheless, our study showed an inverse relationship between serum vitamin D deficiency and AMD using multiple regression analysis. The main objection to our study was, not considering taking vitamin D by the participants, because vitamin D is obtained from ultraviolet radiation in addition to food. However, the number of patients with serum vitamin D deficiency in the AMD group was higher than the control group, although significant border differences were observed. In future studies, we must ask additional questions from patients to confirm whether they have been exposed to sunlight or not.

Conclusion

As a result, serum vitamin D deficiency may increase the risk of early and late AMD. It may also be associated with subretinal fibrosis. Other major demographic studies are needed to confirm these results and to explain the underlying mechanisms.

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