International Journal of Frontiers in Medicine
ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

Association Between Circulating Vitamin D Concentration and early AMD in Shanghai Public Institution Population

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***ABSTRACT. AIM**: To explore the relationship between serum 25-hydroxyvitamin D and early AMD. **Methods**. This study involved a total of 3,352 subjects older than 45 years who participated in physical examination in East China sanatorium from January to September in 2019.All participants underwent fundus photographs, evaluation of blood 1-25-hydroxyvitamin D levels and comprehensive physical examination.The t-test,variance analysis and logistic regression was used to access the date in statistical way by using SPSS 25.0 statistical software. **Results.** The incidence of AMD in population who older than 45 years was 10.35%. The incidence of AMD Levels of serum vitamin D were negatively correlated with early AMD.The odds ratio (OR) and 95% confidence interval for early AMD among subjects in the lowest vs highest quintile of serum vitamin D was 1.48(95% CI,1.07-2.12). 25-VD, gender,age, hypertension, smoking were independent risk factors of AMD. **Conclusion.**This study shows that vitamin D may have a protective effect on early AMD.Further studies are needed to confirm their association.*

***KEYWORDS:** vitamin D, early age-related macular degeneration, shanghai*

1. Introduction

Age-related macular degeneration (AMD) is a degenerative disease that can cause central vision loss, which can seriously affect life quality of patients. AMD is the first blinding eye disease among the aged over 50 in the world [1, 2]. According to statistics, the prevalence of AMD in is about 3% to 5%, and the prevalence of AMD in people over 75 years old is as high as 22.4% [3]. The prevalence is even higher in Asia, at 6.8% [4]. In recent years, with the aggravation of the aging of the population in China, the prevalence of AMD shows a trend of gradual increase.

The pathophysiology of AMD is unclear. Inflammatory, genetic, nutritional, metabolism and environmental may contribute to the occurrence of AMD [5]. However, some studies show that lifestyle modifications appear to slow the

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

progression of AMD, including improving diet, increasing physical activity and avoiding smoking [6]. Vitamin D was first reported as a possible protective factor for AMD in 2007 [7]. Since then, large epidemiological studies have been conducted in European and korea, but the results are contradictory [5, 8, 9].

Vitamin D is an important immune function regulator with anti-inflammatory [10, 11] and anti-oxidative stress effects [12]. The retina is vulnerable to oxidative damage. Vitamin D can protect cells from oxidative stress damage by inhibiting the production of superoxide anion free radicals and inducing the production of NO [12]. Meanwhile, active vitamin D can improve the activity of glucose-6-phosphate dehydrogenase (G6PD) and the content of glutathione by inducing the transcription of G6PD [13]. In oxidative stress, G6PD is activated and catalyzes the formation of NADPH to maintain intracellular REDOX balance and protect cells from oxidative stress.

In this study, large sample cross-sectional investigation was conducted in Chinese population to evaluate the correlation between early AMD and vitamin D and lay the foundation for later basic experiments.

2. Subjects and methods

This study involved a total of 3,352 subjects older than 45 years who participated in physical examination in East China sanatorium from January to September in 2019. Inclusion criteria:the subjects should over 45 years old and volunteer participate in this research.Exclusion criteria: (1) the participants who had history of severe eye disease, including corneal disease, eye trauma, and severe cataract, which can affect the clarity of fundus photographs. (2) Missing relevant information. A total of 3,352 people were enrolled in the study. The age range from 45 to 92, including 1838 men and 1514 women. This study was authorized by the Medical Ethics Committee of east China sanatorium. Each volunteer signs an informed consent.

Fundus photographs were obtained using fundus camera (NW4000, Toyko, Topcon). A 45° digital retinal image was obtained for each eye (two images per person). All subjects have undergone questionnaire surveys and comprehensive physical examinations. Including age, past medical history, smoking, alcohol consumption,family history, height, weight, body mass index, waist circumference, hip circumference, waist-to-hip ratio, blood pressure. The blood pressure is monitored using a standard mercury blood pressure meter. The subject needs to be rest for more than 5 minutes before testing. Repeat the measurement 3 times, and take the average value. All subjects were tested by fasting venous blood, including triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein, uric acid, creatinine, urea nitrogen, heart rate, fasting blood glucose, glycerogelatin hemoglobin, vitamin D. All subjects underwent detailed eye examinations, including general vision examination, optometry, intraocular pressure, diopter, fundus examination.Based on the digital fundus photographs, patients were

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

graded as early AMD and late AMD using the AREDS (Age-Related Eye Disease Studies)grading system [14].

3. Statistical Analysis

All results are expressed as the mean±SEM.Data were analyzed either by unpaired t test or by ANOVA, and the analysis of covariance is used to correct confounding factors.Values of $P<0.05$ were considered statistically significant. All statistical analyses were performed with the software package SPSS 25.0 (IBM, USA) for Windows.

4. Result

A total of 3534 people whose age older than 45 years participated in the physical examination,the fundus photograph was examined in 3352 (94%). Reasons for exclusion include corneal disease (19), eye trauma (9), severe cataract (147), missing laboratory tests (28). The incidence of AMD in people older than 45 years was 10.35%. Among case group,early AMD was 323 (90.7%). Late AMD was 33 (9.27%). There ere significant gape between different ages. (Figure 1)

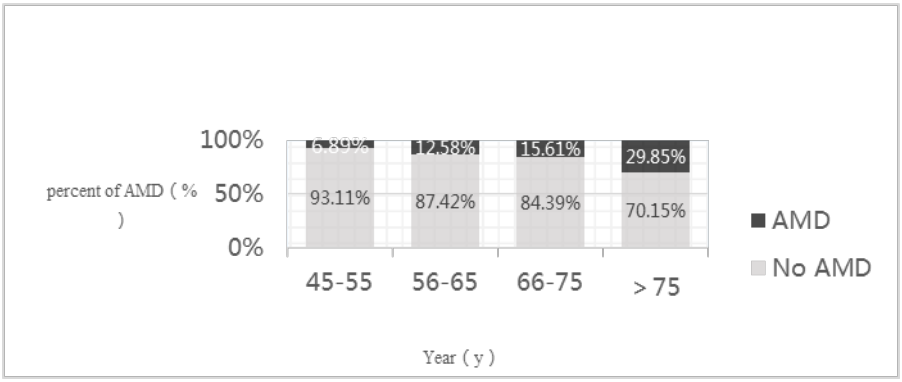

Figure. 1 The age distribution of AMD and No AMD

Table 1 shows the demographic characteristics of Participation classified by AMD statue.The early AMD were more likely to be male or smoker ($p<0.001$), have older age, higher systolic blood pressure and triglycerides ($p<0.05$), higher rate of hypertension ($p<0.05$), have lower concentrations of 25(OH)-D than those without AMD.

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

Table 1 Demographic and Clinical Characteristics, According to No AMD and Early-AMD status and Participation Status

Characteristics	No AMD 0.0(n=2996)	Early AMD 1.0(n=323)	t/x^2	P	Participation Status (n=3352)
Age	56.18±7.78	60.08±9.26	-7.538	0.000**	56.58±8.034
Systolic blood pressure	123.44±16.38	125.49±16.85	-2.203	0.028*	123.656±16.44
Diastolic blood pressure	73.91±10.64	73.21±10.54	1.166	0.244	73.839±10.634
Waist to hip ratio	0.93±1.92	0.89±0.07	0.283	0.778	0.922±1.823
BMI	24.68±3.12	24.79±3.12	-0.43	0.667	24.694±3.119
25- hydroxyvitamin D,ng/ml	20.12±7.94	19.01±7.70	2.514	0.012*	20.004±7.921
TCH	5.17±0.97	5.15±0.98	0.365	0.715	5.168±0.97
LDL	3.15±0.82	3.21±0.78	-1.278	0.201	3.157±0.818
HDL	1.41±0.41	1.39±0.41	0.735	0.462	1.405±0.409
UA	353.55±92.93	347.07±99.91	1.233	0.218	352.863±93.7
CREA	72.99±15.35	73.34±18.20	-0.39	0.696	73.03±15.671
BUN	5.80±1.25	5.88±1.30	-1.103	0.27	5.807±1.252
Blood glucose	5.92±1.32	5.83±1.24	1.195	0.232	1.791±1.461
TG	1.67±1.16	1.81±1.49	2.018	0.044*	5.912±1.315
Sex(male%)	43.69%	56.31%	24.45	0.000**	54.86%
Alcohol consumption,%	47.90%	47.88%	5.679	0.017*	47.22%
Smoking status(never%)	37.20%	58.62%	59.66	0.000**	39.49%
hypertension	17.70%	22.73%	4.669	0.031*	22.2%

Data are expressed as weighted means or weighted frequency (%) with standard errors

Abbreviation:BMI,Body Mass Index.25(OH)D,25- hydroxyvitamin D.

TCH, Total cholesterol. LDL, Low-density lipoprotein. HDL, High density lipoprotein. UA, Uricacid. CREA, Creatinine. UA, Urea Nitrogen. TG, Triglycerides. BUN, Urea Nitrogen.

*p<0.05 **p<0.01

Table 2 shows the demographic characteristics of Participation classified by 25(OH)-D quintiles.As 25(OH)D levels increased, participants were more likely to be male (P<0.001), older (P<0.001), nondrinker (P<0.001), nonsmokers (P<0.001), hypertensive (P =0.002), have high HDL, UA, CREA (P< 0.001).

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

Table 2 Demographic and Clinical Characteristics, According to concentration of 25(OH)D quintiles

Characteristics	25(OH)D				F/X^2□	p□
	1.0(n=850)	2.0(n=824)	3.0(n=824)	4.0(n=820)		
Age	56.26±8.47	56.23±8.03	56.62±7.85	57.22±7.73	2.749	0.041*
Systolic blood pressure	122.91±16.98	123.64±16.93	123.64±16.01	124.44±15.78	1.185	0.314
Diastolic blood pressure	72.88±10.85	74.10±10.72	74.14±10.50	74.26±10.42	3.079	0.026*
Waist to hip ratio	1.03±3.67	0.88±0.06	0.89±0.06	0.88±0.07	0.818	0.484
BMI	24.48±3.29	24.69±2.78	24.96±3.23	24.63±3.14	2.088	0.1
Blood glucose	5.85±1.25	5.99±1.54	5.88±1.10	5.93±1.33	1.756	0.153
TG	1.71±1.49	1.81±1.59	1.79±1.32	1.86±1.43	1.393	0.243
TCH	5.22±1.00	5.19±0.95	5.10±0.98	5.15±0.95	2.249	0.081
LDL	3.19±0.85	3.18±0.80	3.13±0.83	3.12±0.79	1.611	0.185
HDL	1.40±0.40	1.39±0.40	1.38±0.40	1.45±0.43	5.349	0.001**
UA	338.21±90.98	352.17±95.74	362.33±92.06	359.20±94.33	11.188	0.000**
CREA	70.20±14.70	73.38±15.79	74.68±15.88	73.95±15.96	13.61	0.000**
Sex(male%)	476(55.67%)	378(45.60%)	321(38.58%)	333(40.36%)	1508(45.14%)	0.000**
Alcohol consumption%	151(17.60%)	176(21.13%)	195(23.41%)	222(26.81%)	744(22.2%)	0.000**
Smoking status(never%)	315(37.28%)	398(48.36%)	432(52.30%)	420(51.22%)	1565(47.22%)	0.000**
hypertension	285(34.30%)	321(39.88%)	353(43.26%)	328(40.64%)	1287(39.49%)	0.002**

Data are expressed as weighted means or weighted frequency (%) with standard errors

*p<0.05 **p<0.01

Table 3 shows the sex difference of blood Vitamin D levels (ng/mL) of male and female according to age group and other quantity. 25(OH)D levels of male were higher than female (p<0.001), AMD in male had lower level of 25(OH)D(p=0.022*), which had no difference in female.

Table 3 Sex difference of blood Vitamin D levels (ng/mL) of male and female according different quantity.

	Blood 25–Hydroxyvitamin D Level, ng/ml					
Characteristics	Male,n=1833	P	Female,n=1508	P	Total	P
All Participant	20.86±7.99		18.97±7.72	0.000**	20.04±7.91	
Age group		0.001**		0.003**		0.000**
45-54	20.14±7.26		18.29±7.04		19.41±7.33	
55-64	21.36±8.03		19.87±8.54		20.78±8.40	
65-74	21.92±9.50		19.12±7.47		20.54±8.75	
≧75	19.21±8.43		17.64±7.54		19.12±8.07	
AMD		0.022*		0.530		0.012*
No AMD	20.98±7.97		19.01±7.77		20.12±7.94	
AMD	19.40±8.13		18.64±7.41		19.01±7.70	
Hypertension		0.000**		0.000**		0.000**
Hypertension	20.42±7.82		22.03±8.32		19.67±7.81	
No Hypertension	22.03±8.32		18.89±7.74		21.17±8.19	
Drinker		0.023*		0.663		0.000**
Drinker	20.17±8.09		19.20±7.51		20.83±7.88	
Non-drinkers	22.03±8.32		18.96±7.80		19.29±7.90	
Smoker		0.397		0.151		0.016*
Smoker	21.05±8.38		18.14±7.69		20.41±7.73	
Non-smoker	20.72±7.69		19.07±7.69		19.73±7.98	

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*p<0.05 **p<0.01

Data are expressed as weighted means or weighted frequency (%) with standard errors

Table 4 Shows the levels of serum vitamin D were negatively correlated with early AMD.The odds ratio (OR) and 95% confidence interval for early AMD among subjects in the lowest vs highest quintile of serum vitamin D was 1.48(95% CI,1.07-2.12).

Table 4 Prevalence and Adjusted OR of Early and Late AMD, Stratified According to Quintile Categories of Blood 25-Hydroxyvitamin D

Quintile Blood 25–VD Level, ng/mL	>25.50 n=663	20.70-25.50 n=669	16.9-20.70 n=659	13.5-16.9 n=665	<13.5 n=663	p
Prevalence	9.4	8.4	10.2	11.9	13.1	0.01*
Crude OR(95% CI)	1.00 (reference)	0.88 (0.60-1.28)	1.09 (0.76-1.57)	1.29 (0.91-1.84)	1.44 (1.02-2.03)	0.04*
Adjusted OR#(95% CI)	1.00 (reference)	0.91 (0.72-1.35)	1.12 (0.79-1.63)	1.33 (0.93-1.87)	1.48 (1.07-2.12)	0.04*

*p<0.05

#Adjusted for age, sex, smoking, hypertension.

Table 5 Shows 25-VD,gender,age,hypertension,smoking were independent risk factors of AMD

Table 5 Multivariable logistic regression of AMD

Variables	p	OR	OR(95% CI)
25VD	0.036*	0.981	0.964 ~ 0.999
Gender	0.016*	3.745	2.545 ~ 5.511
AGE	0.013*	1.066	1.049 ~ 1.083
HBP	0.001*	0.49	0.340 ~ 0.705
Smoking	0.035*	5.856	4.137 ~ 8.289

5. Dissusion

According to statistics, the prevalence of AMD in is about 3% to 5%, and the prevalence of AMD in people over 75 years old is as high as 22.4% [3]. The prevalence is even higher in Asia, at 6.8% [4]. Our study show the prevalence of AMD was 10.6% in people older than 45 years old,early AMD was 323(9.6%), late AMD was 33(1%). From the above data, it can be seen that the prevalence of AMD in different populations varies to different degrees, which may be related to differences in the genetic genes, basic demographic characteristics, economic conditions, climate, and regional environment of the investigated population. Possible reasons: First, the average life expectancy in developed regions may be higher than in developing countries. Second, there may be differences in genetic

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

factors among different races. Third, the limitations of detection methods affect the early diagnosis of AMD. In addition, the different inclusion and exclusion criteria in the study, as well as the different diagnostic methods for AMD also caused this difference.

In the analysis of relevant risk factors in all studies, the increase in age proved to be the most relevant risk factor for AMD [15-16]. Along with the growth of the age.The number of cells continues to decrease, and lipofuscin, which can cause oxidative damage, continues to increase, making the synthesis and secretion of retinal pigment cells impaired, and ultimately affecting the normal physiological functions of the retina, leading to the formation of AMD.In our study,there were significant gape between different ages.From 6.89% in 45-55 years old to 29.85％in people older than 75 years old.

The incidence of AMD in men (13.08%) is higher than in women (7.9%). Which was similar to previous research [17-18]. Japanese reports proved that gender may be related to early AMD at the genetic level,and the Incidence of early AMD was 12.3% and 10.3% respectively in male and female [17]. A report on Chinese Americans in the United States shows that AMD is more common in male than female [18]. speculate that the reason may be the difference in genetic susceptibility and lifestyle between male and female.

Vitamin D was first linked to AMD in 2007 [19]. Since then, several studies have been carried out in various countries to explore the relationship between vitamin D and AMD. Some studies suggest that levels of serum vitamin D are not associated with AMD progression, which carried out in Isreai [20], France [21], Iran [22] and Europe [23]. Some cross-sectional studies in United States and Korea showed that high levels of serum vitamin D have a protective effect on AMD, especially on advanced AMD [24]. However, the results of studies are vary. Eun Chul Kim et al found that Vitamin D plays a different role in different genders [25]. Amy E. Millen et al found that Vitamin D plays a different role in different types of AMD [26]. In summary, the role of levels of serum vitamin D in AMD remains controversial internationally. The current study showed that the prevalence of early AMD have statistically negative correlation to 25-hydroxyvitamin D levels.This difference may be caused by difference of ethnic,latitude and dietary structure.On the other hand, Due to different, people who from different dimensions may had different basic vitamin D concentrations. As shown in Table 3,Mean±Standard error blood 25(OH)-D level in our study was 20.04±7.91ng/ml, which is lower than those from the US research(23.0±0.1ng/ml).[18]. It is reported that serum vitamin D levels are lower in Asians than Caucasians [27].

Some studies have shown that 25(OH)D can protect against cancer, infection, cardiovascular disease [28-29]. A large number of vitro and in vivo studies indicate that vitamin D can prevent the development of AMD [30-31]. Drusen,which is a manifestation of local inflammatory events, plays an important role in the pathogenesis of AMD.Drusen is mainly composed of amyloid beta protein (Aβ). Lee V etal found that Aβ increases the expression of VEGF in human RPE cells [32-34]. On the other hand, vitamin D can clean Aβ deposits and improve the function of

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

retinal through injected in aged mice [35]. These results indicate that vitamin D can protect against early AMD.Inflammation was confirmed to be the key pathogenic factors in AMD through damage protein,degeneration of RPE [36]. Vitamin D was proved to anti-inflammation in AMD,as reviewed by Hewison et al [37]. It is well known that angiogenesis plays a major role in the development of AMD. Saeb S et al shown that vitamin D can interruption the angiogenesis signaling pathway in cancer cells [38]. Amir S et al found that 1,25(OH)D inhibit the transcription of hypoxia-inducible factor (HIF-1)-VEGF pathway to anti-angiogenic in various human cancer cells [39].

6. Conclusions and Future Perspectives

In conclusion, Our study provides population-based epidemiologic evidence of a relationship between blood 1,25(OH)D with early AMD in a representative population in Shanghai.Since our research objects come from enterprises and institutions, considering mostly of them work interior, they had less sunshine time.One the other hand,they have a stronger awareness of health care. Therefore this population may can not respect China crowd.On the other hand,although cross-sectional studies are useful for exploring a possible association between AMD and vitamin D, they are not designed to determine causality. For this reason, prospective studies are preferable and avoid issues related to assessment of vitamin D levels after the development of advanced disease. We will study the causal relationship between vitamin D and AMD in terms of cells and animal models in future study.

Acknowledgments

Fund project: East China sanatorium fund (201805), Shanghai Municipal Health Commission Fund (20194Y0437).

References

[1] Zou M, Zhang Y, Chen A, Young CA, Li Y, Zheng D, Jin G. Variations and trends in global disease burden of age-related macular degeneration: 1990-2017. Acta Ophthalmol 2020.

[2] Erke MG, Bertelsen G, Peto T, Sjolie AK, Lindekleiv H, Njolstad I. Prevalence of age-related macular degeneration in elderly Caucasians: the Tromso Eye Study. Ophthalmology 2012, 119 (9): 1737-1743.

[3] Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cachulo ML, Khawaja AP, Cougnard-Gregoire A, Merle BMJ, Korb C, Erke MG et al. Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. Ophthalmology 2017, 124 (12): 1753-1763.

[4] Kawasaki R, Yasuda M, Song SJ, Chen SJ, Jonas JB, Wang JJ, Mitchell P, Wong TY. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. Ophthalmology 2010, 117 (5): 921-927.

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

[5] McKay GJ, Young IS, McGinty A, Bentham GC, Chakravarthy U, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F et al. Associations between Serum Vitamin D and Genetic Variants in Vitamin D Pathways and Age-Related Macular Degeneration in the European Eye Study. Ophthalmology 2017, 124 (1): 90-96.

[6] Merle BMJ, Silver RE, Rosner B, Seddon JM. Associations Between Vitamin D Intake and Progression to Incident Advanced Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 2017, 58 (11): 4569-4578.

[7] Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. Arch Ophthalmol 2007, 125 (5): 661-669.

[8] Annweiler C, Drouet M, Duval GT, Pare PY, Leruez S, Dinomais M, Milea D. Circulating vitamin D concentration and age-related macular degeneration: Systematic review and meta-analysis. Maturitas 2016, 88: 101-112.

[9] Kim EC, Han K, Jee D. Inverse relationship between high blood 25-hydroxyvitamin D and late stage of age-related macular degeneration in a representative Korean population. Invest Ophthalmol Vis Sci 2014, 55 (8): 4823-4831.

[10] Liu Y, Chen L, Zhi C, Shen M, Sun W, Miao D, Yuan X. 1,25(OH)2D3 Deficiency Induce Colon Inflammation via Secretion of Senescence-Associated Inflammatory Cytokines. PLoS One 2016, 11 (1): e0146426.

[11] Lee V, Rekhi E, Hoh Kam J, Jeffery G. Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. Neurobiol Aging 2012, 33 (10): 2382-2389.

[12] Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, Squarzanti DF, Cisari C, Molinari C. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. J Clin Endocrinol Metab 2014, 99 (4): 1367-1374.

[13] Bao BY, Ting HJ, Hsu JW, Lee YF. Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int J Cancer 2008, 122 (12): 2699-2706.

[14] Bird, A.C., et al., An international classification and grading system for age-related maculopathy and age-related macular degeneration. Survey of Ophthalmology, 1995. 39 (5): p. 367.

[15] Klein, R., Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology, 1992. 99.

[16] Se Joon Woo, Jeeyun Ahn, Margaux A Morrison, et al. Analysis of Genetic and Environmental Risk Factors and Their Interactions in Korean Patients with Age-Related Macular Degeneration. 2017, 10 (7).

[17] Sasaki, M., et al., Gender-specific association of early age-related macular degeneration with systemic and genetic factors in a Japanese population. Sci Rep, 2018. 8 (1).

[18] Varma, R., et al., Prevalence of Age-Related Macular Degeneration in Chinese American Adults: The Chinese American Eye Study. Jama Ophthalmology, 2014. 134 (5).

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

[19] Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D andage-related macular degeneration in the Third National Health and Nutrition Ex amination Survey, 1988 through 1994. Arch Ophthalmol 2007, 125 (5): 661-669.

[20] Golan S, Shalev V, Treister G, Chodick G, Loewenstein A. Reconsidering the connection between vitamin D levels and age-related macular degeneration. Eye 2011, 25 (9): 1122-1129.

[21] Cougnard-Gregoire A, Merle BM, Korobelnik JF, Rougier MB, Delyfer MN, Feart C, LeGoff M, Dartigues JF, Barberger-Gateau P, Delcourt C. Vitamin D Deficiency in Community-Dwelling Elderly Is Not Associated with Age-Related Macular Degeneration. J Nutr 2015, 145 (8): 1865-1872.

[22] Hashemi R, Bandarian M, Abedi-Taleb E, Khojasteh H, Khedmat L, Asadollahi E, Beytollahi M, Jelodar AM. The association between blood vitamins D and E with age-related macular degeneration: A pilot study. Interv Med Appl Sci 2018, 10 (3): 127-132.

[23] McKay GJ, Young IS, McGinty A, Bentham GC, Chakravarthy U, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F et al. Associations between Serum Vitamin D and Genetic Variants in Vitamin D Pathways and Age-Related Macular Degeneration in the European Eye Study. Ophthalmology 2017, 124 (1): 90-96.

[24] Merle BMJ, Silver RE, Rosner B, Seddon JM. Associations Between Vitamin D Intake and Progression to Incident Advanced Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci 2017, 58 (11): 4569-4578.

[25] Kim EC, Han K, Jee D. Inverse relationship between high blood 25-hydroxyvitamin D and late stage of age-related macular degeneration in a representative Korean population. Invest Ophthalmol Vis Sci 2014, 55 (8): 4823-4831.

[26] Millen AE, Voland R, Sondel SA, Parekh N, Horst RL, Wallace RB, Hageman GS, Chappell R, Blodi BA, Klein ML et al. Vitamin D status and early age-related macular degeneration in postmenopausal women. Arch Ophthalmol 2011, 129 (4): 481-489.

[27] Parekh, Niyati. Association Between Vitamin D and Age-Related Macular Degeneration in the Third National Health and Nutrition Examination Survey, 1988 Through 1994 [J]. Archives of Ophthalmology, 2007, 125 (5): 661.

[28] Matthew S. Seasonal, ethnic and gender variations in serum vitamin D3 levels in the local population of Peterborough [J]. Bioscience Horizons, 3, 2 (2010-5-3) (2): 124-131.

[29] Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014 Mar 20; 21 (3): 319-29. doi: 10.1016/j.chembiol.2013.12.016. Epub 2014 Feb 13. PMID: 24529992; PMCID: PMC3968073.

[30] H, W. and H. ME, Regulation of signaling events involved in the pathophysiology of neovascular AMD. Molecular vision, 2016. 22: p. 189-202.

[31] F, P., et al., Mechanism of inflammation in age-related macular degeneration. Mediators of inflammation, 2012. 2012: p. 546786.

ISSN 2706-6819 Vol.2, Issue 3: 16-26, DOI: 10.25236/IJFM.2020.020303

[32] T, Y., et al., The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. The Journal of clinical investigation, 2005. 115 (10): p. 2793-800.
[33] Wang, J., K. Ohno-Matsui and I. Morita, Elevated amyloid β production in senescent retinal pigment epithelium, a possible mechanism of subretinal deposition of amyloid β in age-related macular degeneration. Biochemical & Biophysical Research Communications, 2012. 423 (1).
[34] Anderson, D.H., et al., Characterization of β amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. Experimental Eye Research, 2004. 78 (2): p. 243-256.
[35] V, L., et al., Vitamin D rejuvenates aging eyes by reducing inflammation, clearing amyloid beta and improving visual function. Neurobiology of aging, 2012. 33 (10): p. 2382-9.
[36] KM, G., et al., Age-related macular degeneration--emerging pathogenetic and therapeutic concepts. Annals of medicine, 2006. 38 (7): p. 450-71.
[37] M, C., et al., Immune activation in retinal aging: a gene expression study. Investigative ophthalmology & visual science, 2010. 51 (11): p. 5888-96.
[38] S, S., et al., 9-cis-Retinoic Acid and 1,25-dihydroxy Vitamin D3 Improve the Differentiation of Neural Stem Cells into Oligodendrocytes through the Inhibition of the Notch and Wnt Signaling Pathways. Iranian journal of medical sciences, 2018. 43 (5): p. 523-532.
[39] M, B., et al., 1alpha,25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. Molecular cancer therapeutics, 2007. 6 (4): p. 1433-9.