

Association of severity of primary open-angle glaucoma with serum vitamin D levels in patients of African descent

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Purpose: To study the relationship between primary open-angle glaucoma (POAG) in a cohort of patients of African descent (AD) and serum vitamin D levels.

Methods: A subset of the AD and glaucoma evaluation study III (ADAGES III) cohort, consisting of 357 patients with a diagnosis of POAG and 178 normal controls of self-reported AD, were included in this analysis. Demographic information, family history, and blood samples were collected from all the participants. All the subjects underwent clinical evaluation, including visual field (VF) mean deviation (MD), central cornea thickness (CCT), intraocular pressure (IOP), and height and weight measurements. POAG patients were classified into early and advanced phenotypes based on the severity of their visual field damage, and they were matched for age, gender, and history of hypertension and diabetes. Serum 25-Hydroxy (25-OH) vitamin D levels were measured by enzyme-linked immunosorbent assay (ELISA). The association of serum vitamin D levels with the development and severity of POAG was tested by analysis of variance (ANOVA) and the paired *t*-test.

Results: The 178 early POAG subjects had a visual field MD of better than -4.0 dB, and the 179 advanced glaucoma subjects had a visual field MD of worse than -10 dB. The mean (95% confidence interval [CI]) levels of vitamin D of the subjects in the control (8.02 ± 6.19 pg/ml) and early phenotype (7.56 ± 5.74 pg/ml) groups were significantly or marginally significantly different from the levels observed in subjects with the advanced phenotype (6.35 ± 4.76 pg/ml; $p = 0.0117$ and 0.0543 , respectively). In contrast, the mean serum vitamin D level in controls was not significantly different from that of the subjects with the early glaucoma phenotype ($p = 0.8508$).

Conclusions: In this AD cohort, patients with advanced glaucoma had lower serum levels of vitamin D compared with early glaucoma and normal subjects.

Glaucoma is the leading cause of irreversible blindness in the world [1]. The disease can be characterized as a progressive optic neuropathy, where gradual visual field loss eventually leads to blindness. Primary open-angle glaucoma (POAG) is the most common type of glaucoma; it is typically asymptomatic at the early stages, and it is often not diagnosed until irreversible loss of the visual field transpires. Well-known risk factors are elevated intraocular pressure (IOP), advanced age, positive family history, and African ancestry [1]. The prevalence of glaucoma has been reported

to be higher in black compared with white and mixed-race populations [2]. Similarly, the mean IOP was reported to be highest in black compared with mixed-race or white patients [3]. Currently, no reliable methods or biomarkers for the early detection of glaucoma are available.

In recent years, findings have suggested that serum 25-OH vitamin D levels are associated with glaucoma. In a study on a South Korean population, participants with low serum 25-OH vitamin D levels were found to be at a significantly elevated risk of open-angle glaucoma (OAG) [4]. More recently, in a French case-control study, POAG cases had a lower mean serum 25-OH vitamin D concentration than controls did, as well as a greater prevalence of vitamin D insufficiency [5]. Past findings have also revealed associations between vitamin D levels and various other ocular

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conditions. Serum 25-OH vitamin D deficiency was associated with a reduced ganglion cell complex in a cohort of older Caucasians [6]. Moreover, a lower serum 25-OH vitamin D concentration was associated with a high risk of myopia in a population of young adults in Australia [7]. In addition, a poorer quality of overall visual acuity was associated with vitamin D insufficiency in older adults [8]. Although the prevalence of glaucoma has been observed to be high in patients of African descent (AD), information is not available on the relationship between serum vitamin D levels and POAG in this population.

There is abundant evidence that, compared with Americans with European ancestry, African Americans display significantly lower levels of 25-OH vitamin D. Lower serum levels of 25-OH vitamin D in African American women has been attributed to a reduction in dermal synthesis [9]. Contrasting health outcomes have been observed in these studies when comparing 25-OH vitamin D levels between white and African Americans. For example, higher serum levels of 25-OH vitamin D were associated with lower cardiovascular disease (CVD) risk in white Americans, while higher serum 25-OH vitamin D in black Americans was associated with a slightly higher CVD risk. In addition, higher

25-OH vitamin D levels were associated with lower all-cause mortality in white Americans, but they were less strongly associated with all-cause mortality in black Americans [10]. However, there is limited information on the effects of 25-OH vitamin D levels on ocular abnormalities in African Americans. The aim of this study was investigating the possible association between vitamin D levels and the development of POAG, as well as the severity of POAG in a cohort of patients of AD.

METHODS

Subjects: A subset of 357 POAG patients and 178 control subjects of AD participating in the “Contribution of Genotype to Glaucoma phenotype in African Americans” study (Figure 1), commonly referred to as the AD and glaucoma evaluation study III (ADAGES III), were included in this study. The research was conducted following the tenets of the Declaration of Helsinki and with the approval of the institutional review boards of the participating institutions.

To be considered to have POAG, patients were required to have glaucomatous visual field damage or an optic disc photograph or clinical drawing clearly indicating POAG in their medical charts. Control subjects had IOP ≤ 21 mmHg,

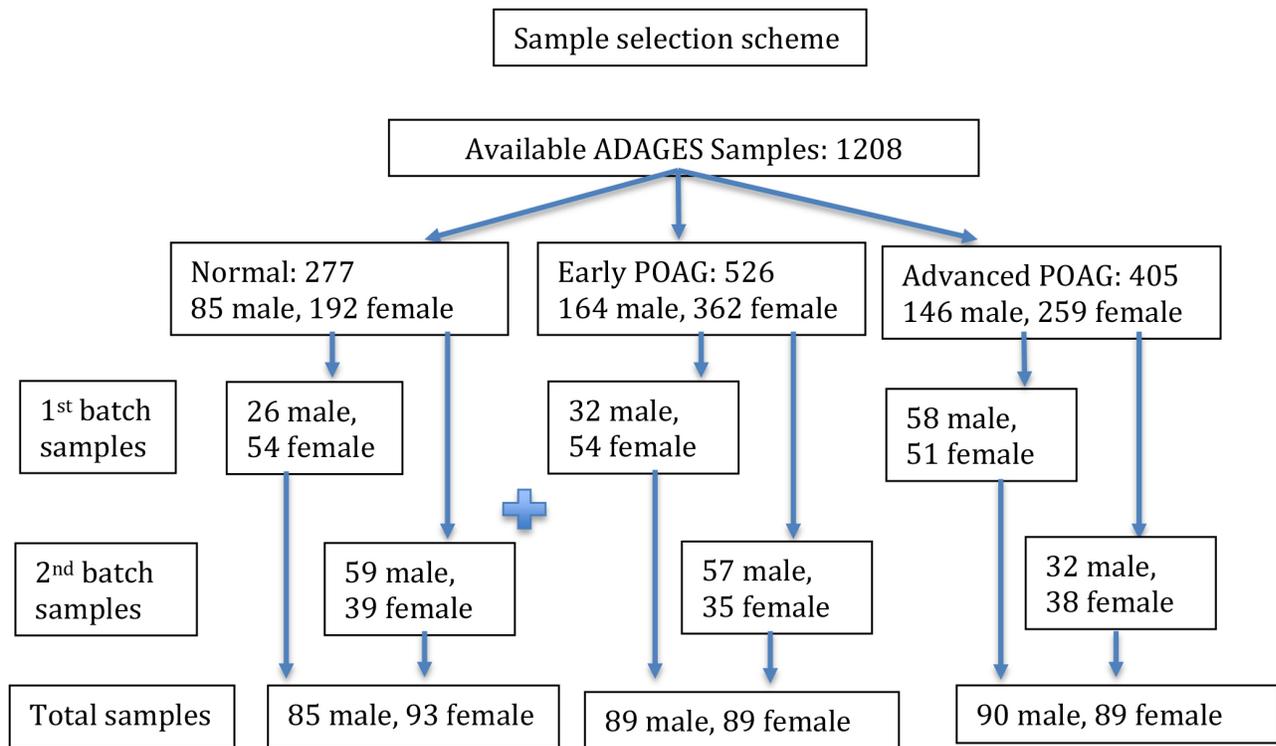


Figure 1. Sample selection scheme.

no evidence of glaucomatous optic neuropathy based on a clinical exam, and no family history of POAG in first-degree relatives. The exclusion criteria included the following: 1) ocular pathology making it difficult to determine whether there was characteristic visual field damage, 2) closed or occluded angles, 3) secondary glaucoma, 4) a history of human immunodeficiency virus or hepatitis C infection, and 5) non-African or European descent.

For this report, POAG patients were classified into “early” and “advanced” phenotypes based on the severity of their visual field damage at the time of blood sample collection; early POAG patients had a visual field MD better than -4 dB, and advanced POAG had visual field MD values ≤ -10 dB. Glaucoma patients with visual field MD between -4 and -10 dB were excluded. The three groups were matched for age, sex, and self-reported history of hypertension and diabetes.

Ocular measurements: Central corneal thickness (CCT), the mean deviation (MD) of the visual field closest to the blood draw, and the highest IOP recorded were extracted from each patient’s medical record. The mean values of both eyes were included in the analysis. IOP measurements were obtained using a Goldman Applanation Tonometer.

Body mass index: Each participant’s height and weight were measured, and the body mass index (BMI) was calculated according to standard protocols. Height and weight measurements were performed at each study center using standardized protocols and equipment. A model 213 stadiometer (Seca, Chino, CA) was used to measure the height to the eighth of an inch. A Professional Remote Digital Scale (Health-o-Meter, McCook, IL) was used to measure weight after the removal of jackets or bulky sweaters, as described previously [11].

Measurement of 25-OH vitamin D in serum: The levels of free serum 25-OH vitamin D were measured by enzyme-linked immunosorbent assay (ELISA) using a Free 25OH Vitamin D ELISA kit (Future Diagnostics and DIASource Immuno-Assays, Louvain-la-Nueve, Belgium). The methodology used for the measurement of free vitamin D has been reported to be reliable in recent studies [12,13]. Free vitamin D has also been observed as being the biologically active form [14], and for these reasons, we chose to measure levels of free 25-OH vitamin D.

Statistical analysis of data: The means and standard deviations (SDs) of serum vitamin D levels were calculated using standard methodology. A log transformation was applied to normalize the distribution, and analyses were performed on the log-transformed free vitamin D levels. Analyses of variance (ANOVAs) were used to compare the vitamin D levels

among the three POAG groups, and a post hoc Tukey’s test was used for pairwise comparisons. We also compared the demographic data among the three groups, using ANOVA for continuous data (age, BMI, MD, IOP, CCT) and the chi-square test for binary traits (gender, diabetes, hypertension) and categorical data (family history of glaucoma). To test the correlations between free vitamin D and the demographic data, we applied the Pearson correlation for continuous data (age, BMI, MD, IOP, CCT), *t*-test for binary data (gender, diabetes, hypertension), and ANOVA for categorical data (family history of glaucoma). Most of the quantitative traits in this study were normally distributed; the exception was the free vitamin D levels, which had a skewness level of 2.2973 and kurtosis of 6.2872. Thus, we applied log transformation only to the free vitamin D levels (Appendix 1).

RESULTS

The demographic, clinical, and ocular characteristics of the early POAG, advanced POAG, and controls without POAG study groups are presented in Table 1. As patients were matched for age, sex, history of systemic hypertension, and diabetes, no significant differences were found in these characteristics. BMI was significantly lower in the advanced POAG patients compared with the controls and early POAG ($p = 0.0334$ and 0.0041). There were no significant differences between controls and early POAG regarding BMI ($p = 0.7142$). Most subjects had eye measurements performed on the same day as the blood draw. Specifically, the median (interquartile range) difference in years between the blood draw and 1) visual field testing and 2) IOP measurements was small, at 0.4 (1.1) years and 0.0 (0.1) years, respectively.

Advanced glaucoma patients had a significantly higher “highest IOP” recorded ($p < 0.0001$), as well as worse visual field MD ($p < 0.0001$); moreover, they were more likely to have a family history of glaucoma ($p < 0.0001$) compared with the control group. Compared with the early POAG group, advanced glaucoma patients also had a significantly higher “highest IOP” record ($p < 0.0001$) and worse visual field MD ($p < 0.0001$; Table 1). There were no differences among the three groups in terms of CCT. Similarly, no significant differences were noted in self-reported hypertension and diabetes among the three groups.

Levels of serum 25 (OH) vitamin D in different groups and the relationship between vitamin D and progression of glaucoma: The associations of age, visual field MD, and IOP with free vitamin D were small but significantly different from zero ($r = 0.1116, 0.1236, 0.0819$ and $p = 0.01094, 0.0162, 0.0018$, respectively). No linear correlations significantly different from zero were observed between free vitamin D

TABLE 1. DEMOGRAPHIC, CLINICAL AND OCULAR CHARACTERISTICS BY STUDY GROUPS.

Information	Trait	Control (n=178)	Early POAG (n=178)	Advanced POAG (n=179)	P value*
Demographic and clinical information	Age at blood draw (SD; MIN,MAX)	67.2 (9.09; 27.8, 95.5)	65.29 (10.47; 33.3, 92.4)	67.51 (11.28; 32.2, 91.4)	0.0934
	Gender (% male)	32.6	32.6	33	0.9962
	BMI (SD; MIN,MAX)	31.0 (6.7; 17.9, 54.5)	31.6 (6.3; 19.2, 54.4)	29.2 (6.3; 16.9, 49.4)	0.0039
	Self-reported diabetes (%)	31.5	33.7	31.3	0.8615
	Self-reported hypertension (%)	73	67.4	65.9	0.3217
	**	-2.39 (3.99; -21.99, 1.2)	-1.77 (1.47; -3.98, 1.85)	-21.65 (6.53; -35.3, -10.1)	<0.0001
Ocular Information	Visual Field Mean Deviation in dB (SD; MIN,MAX)				
	Intraocular pressure in mmHg (SD; MIN,MAX)	15.9 (3.0; 8.5, 28.0)	19.7 (6.2; 9.5, 46.0)	22.7 (9.3; 8, 54.5)	<0.0001
	Central corneal thickness in um (SD; MIN,MAX)	531.3 (36.7; 450.0, 586.0)	538 (37.3; 445, 635.5)	532.4 (44.4; 330, 730)	0.3935
	Family History of Glaucoma (1 st degree relative; %)	8.4	36.2	49.6	<0.0001

* p value is the ANOVA across all 3 groups. ** Visual Field Mean was the criteria for selection, thus the significant difference is expected, #Note that the three groups have been matched on age, sex, self-reported history of diabetes and of hypertension. All 4 traits were not significant between groups by ANOVA.

and CCT ($r = 0.0377$, $p = 0.4744$) or between free vitamin D and BMI ($r = -0.0448$, $p = 0.333$; Table 2). Females had significantly higher mean levels of free vitamin D than males did (7.90 ± 5.97 vs. 6.09 ± 4.62 ; $p = 0.0002$). No significant differences in free vitamin D levels were observed in cases versus controls in terms of diabetes (7.96 ± 6.18 in diabetics vs. 7.01 ± 5.33 in controls; $p = 0.0886$) or hypertension (7.52 ± 5.80 in hypertensives versus 6.93 ± 5.26 in controls; $p = 0.2724$; Table 3).

The serum free vitamin D levels of the normal control group were in the range of 1.08–33.64 pg/ml, with a mean \pm SD of 8.02 ± 6.19 pg/ml. The free vitamin D levels of patients in the early POAG group were in the range of 0.77–33.22 pg/ml, with a mean \pm SD of 7.56 ± 5.74 pg/ml. In contrast, the advanced glaucoma group of patients had lower serum free vitamin D levels, in the range of 0.59–31.47 pg/ml, with a mean \pm SD of 6.35 ± 4.76 pg/ml (Table 4).

The ANOVA test revealed significant differences in the serum vitamin D levels among the three groups of subjects tested ($p = 0.0098$, Figure 2). In the follow-up analysis with the pairwise *t*-test, we found that both the normal and early (0 to -4) glaucoma groups were significantly or marginally significantly different from the advanced (worse than -10) glaucoma group ($p = 0.0117$ and 0.0543 , respectively), while the normal group was not significantly different from the early (better than -4) glaucoma group (Figure 2). Similar results were observed when comparing the male subjects in the three groups ($p = 0.0045$), while no significant difference was observed within female subjects ($p = 0.2986$).

DISCUSSION

Vitamin D has attained much focus over the last couple of decades as an important contributor to health, especially in the context of chronic lifestyle-related diseases. Vitamin D deficiency has been associated with a wide range of

TABLE 2. CORRELATIONS BETWEEN FREE VITAMIN D AND AGE, MD, CCT, BMI, AND IOP.

	N	Correlation Coefficient	P value
Age	519	0.1116	0.0109
MD	378	0.1236	0.0162
CCT	363	0.0377	0.4744
BMI	469	-0.0448	0.333
IOP	519	-0.0819	0.0018

TABLE 3. CORRELATION BETWEEN GENDER, DIABETES AND HYPERTENSION.

Trait	N	P value*	Category	N	Mean pg/ml	Median pg/ml	Std Dev pg/ml	Minimum pg/ml
Gender	519	0.0002	Female	349	7.9	6.28	5.97	0.77
			Male	170	6.09	4.87	4.62	0.59
Diabetes	519	0.0886	No	355	7.01	5.63	5.33	0.59
			Yes	164	7.96	6.02	6.18	1.14
Hypertension	515	0.2724	No	163	6.93	5.43	5.26	0.59
			Yes	352	7.52	5.99	5.8	0.77
Family History Glaucoma	321	0.0041	No	214	6.99	5.44	5.05	0.59
			Yes	107	5.54	4.5	3.72	0.77

* t test p value

pathologies, including osteoporosis, CVD, diabetes, cancer, autoimmune diseases, and depression in several populations, including subjects of AD [12,15]. A strong association between vitamin D levels and various ophthalmic conditions, such as age-related macular degeneration, cataract, and dry eye syndrome has been reported [8]. Specifically, the association of vitamin D levels with a risk of glaucoma has been reported in Chinese, Korean, French, and Caucasian populations [4-6,13].

In the present study on individuals of African descent, advanced glaucoma patients had significantly lower levels of serum vitamin D ($p < 0.01$) than both the normal control and early glaucoma groups did. Our findings are consistent with a larger cross-sectional study on the South Korean population that included 290 OAG cases, 410 suspected glaucoma cases, and 5,394 controls [4]. That study reported a significantly elevated risk of OAG at lower vitamin D levels, supporting the association between glaucoma and vitamin D levels. Similarly, a French study found reduced vitamin D levels in 150 moderate and severe glaucoma patients (mean VF MD -17 db) compared to 164 controls [5]. However, that study did not find a difference in serum vitamin D levels between the 99 patients with severe POAG and the 51 with moderate POAG [5]. The variation observed in the association of vitamin D with severity of glaucoma between the current study and studies on other populations could be due

to the difference in the severity of the two glaucoma groups included in the analysis. For example, in the current study, we compared vitamin D levels in early (better than -4 dB) and advanced POAG (worse than -10 dB), while the French study compared vitamin D levels in moderate (better than -12 dB) and advanced glaucoma (worse than -12 dB). In addition, the underlying genetic variation between the French population and patients of AD may also contribute to the differences observed. Analysis of a larger cohort of patients from both populations using a common set of diagnostic criteria may provide a better understanding of the association between serum vitamin D levels and glaucoma progression. Identification of genetic factors associated with glaucoma in these populations may provide further insight into the mechanism underlying the variation in findings between different populations.

It is intriguing to note that the vitamin D levels were not associated with the risk of POAG in our cohort, while a significant association was observed with advanced glaucoma (Table 4). Little is known about the specific role of vitamin D in the pathology of glaucoma, and this remains to be elucidated. However, vitamin D deficiency is reported to be associated with other neurodegenerative diseases, such as Alzheimer disease [16,17]. Specifically, supplementation of vitamin D analogs was suggested to have beneficial effects in Alzheimer disease patients [18]. It is well established that

TABLE 4. DISTRIBUTION OF SERUM FREE VITAMIN D LEVELS IN THE THREE GROUPS.

Study Group	N	Mean pg/ml	SD pg/ml	Minimum pg/ml	Maximum pg/ml	Median pg/m	Lower Quartile pg/m	Upper Quartile pg/m
Control	174	8.02	6.19	1.08	33.64	6.29	3.97	9.76
Early	170	7.56	5.74	0.77	33.22	5.99	4.17	9.14
Advanced	175	6.35	4.76	0.59	31.47	5.09	3.47	7.19

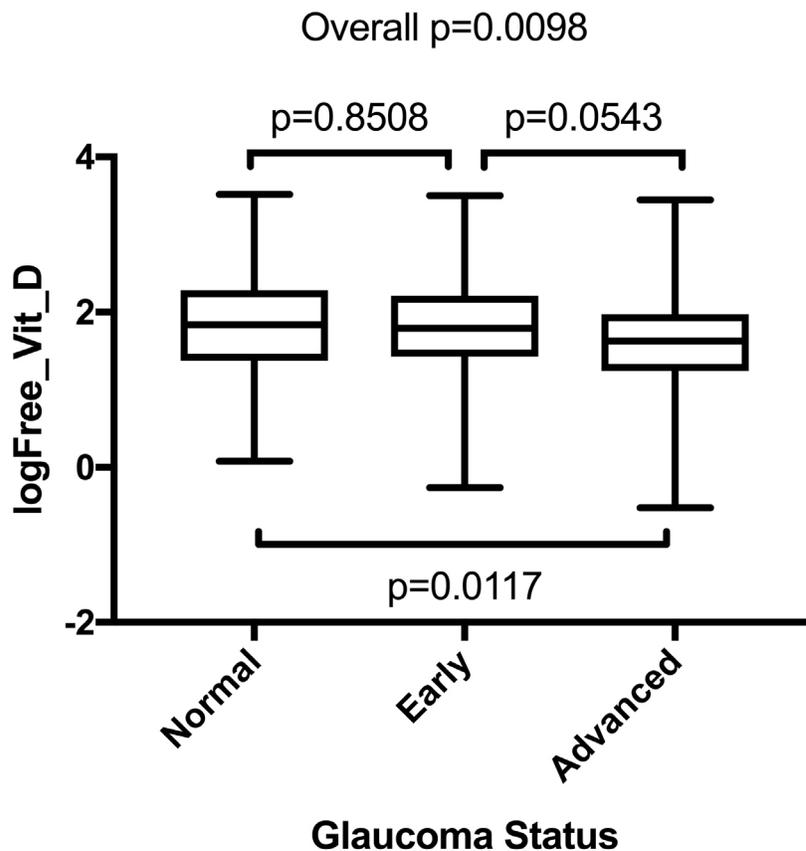


Figure 2. Analysis of variance (ANOVA) analysis of serum free vitamin D levels in the three study groups. The y-axis gives the mean log free vitamin D levels in each of the three study groups. The p value on the right of the figure was obtained from the ANOVA test when comparing the three groups of subjects. On the top of the figure are p values for each pairwise comparison.

factors influencing inflammation contribute to the severity of neurodegeneration [19]. Studies on vitamin D have suggested that it has a key role in regulating the physiological processes involved in the inflammation and degeneration of neuronal tissue [20]. Therefore, it is likely that low levels of vitamin D may not result in development of glaucoma; however, the insufficiency of vitamin D may affect the severity of glaucoma in patients as a result of increased inflammation and neurodegeneration [21]. The design of the current study does not provide information on the rate of glaucoma progression, and therefore, the effect of vitamin D status on the rate of progression is unknown. Gaining an in-depth understanding of the molecular mechanisms underlying glaucoma and the influence of vitamin D on disease pathology may provide insight into the pathophysiology of glaucoma and the effect of vitamin D insufficiency. Furthermore, as serum vitamin D is a modifiable factor, the findings of this study could be helpful in managing the severity of glaucoma by targeting vitamin D.

APPENDIX 1. A SCATTER PLOT SHOWING THE RELATIONSHIP BETWEEN DIFFERENT OCULAR AND CLINICAL TRAITS.

To access the data, click or select the words “[Appendix 1.](#)”

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