Aqueous Humor Levels of Vascular Endothelial Growth Factor in Patients With Dry Age-Related Macular Degeneration and Subretinal Drusenoid Deposits

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Purpose. We sought to investigate aqueous humor levels of growth factors and cytokines related to human angiogenesis in patients with dry age-related macular degeneration (AMD).

Methods. This prospective study classified patients with dry AMD into two groups of patients—those with soft drusen and those with both soft drusen and subretinal drusenoid deposits (SDDs). Aqueous humor samples were collected from each group and from a control group to analyze intraocular cytokine concentrations and examine their associations with AMD characteristics.

Results. A total of 48 participants, 16 per group, were enrolled in the study. The vascular endothelial growth factor (VEGF)-A level was highest in the soft drusen with SDD group (229.21 ± 88.26 pg/mL) compared to the soft drusen group (167.54 ± 92.71 pg/mL) and the control group (140.73 ± 84.91 pg/mL) ($P = 0.021$). There were no significant differences in the concentrations of angiopoietin-2, placental growth factor, interleukin-1α, interleukin-1β, interleukin-6, interleukin-10, or tumor necrosis factor-α among the groups (all $P > 0.05$). In the soft drusen with SDD group, a higher cube root of drusen volume ($\beta = 0.533$, $P = 0.033$) was significantly associated with an elevated VEGF-A level.

Conclusions. In eyes with dry AMD, those with both soft drusen and SDDs exhibited higher intraocular VEGF-A levels than those with only soft drusen, and these levels correlated with the cube root of drusen volume.

Keywords: age-related macular degeneration, vascular endothelial growth factor, drusen, subretinal drusenoid deposit

Age-related macular degeneration (AMD) is a degenerative retinal disease and a leading cause of legal blindness among the elderly.[1] Dry AMD is typically characterized by drusen-associated findings, which often do not impair visual function.[2] However, when AMD progresses to the late stages—specifically, exudative AMD or geographic atrophy (GA)—significant visual impairment can develop.[2,3]

Exudative AMD involves the deterioration of retinal tissue and visual function due to fluid leakage and hemorrhage originating from newly formed blood vessels in the macular region, a process known as macular neovascularization (MNV).[4] Although the precise pathophysiology of exudative AMD is not fully understood, it is hypothesized that cytokines and growth factors related to angiogenesis, expressed under hypoxic conditions associated with AMD, may contribute to the onset of MNV.[3,4] Among these, vascular endothelial growth factor (VEGF) is a cytokine closely associated with the formation of new blood vessels.[5]

Unlike in the past, when drusen were not classified in detail, recent advancements in retinal imaging have enabled a more precise categorization of drusen types in dry AMD.[6,7] Among these, subretinal drusenoid deposits (SDDs) are characterized by clinical features distinct from those of conventional soft drusen.[6–8] Although the pathogenesis of SDDs remains incompletely understood, choroidal hypoxia has been proposed as a contributing factor to the observed alterations in these eyes. This condition is considered distinct within the spectrum of AMD due to its strong association with type 3 MNV, which has been reported to exhibit higher VEGF levels compared to other types of MNV.[6–9] These findings suggest that, even within dry AMD, the expression of angiogenesis-related cytokines or growth factors may vary depending on the phenotype. Therefore, in the present study, we analyzed aqueous humor samples from patients with dry AMD to evaluate whether the levels of angiogenesis-related factors differ according to presence of the SDDs, with a control group also included for further comparison.

Methods

This prospective study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Korea University

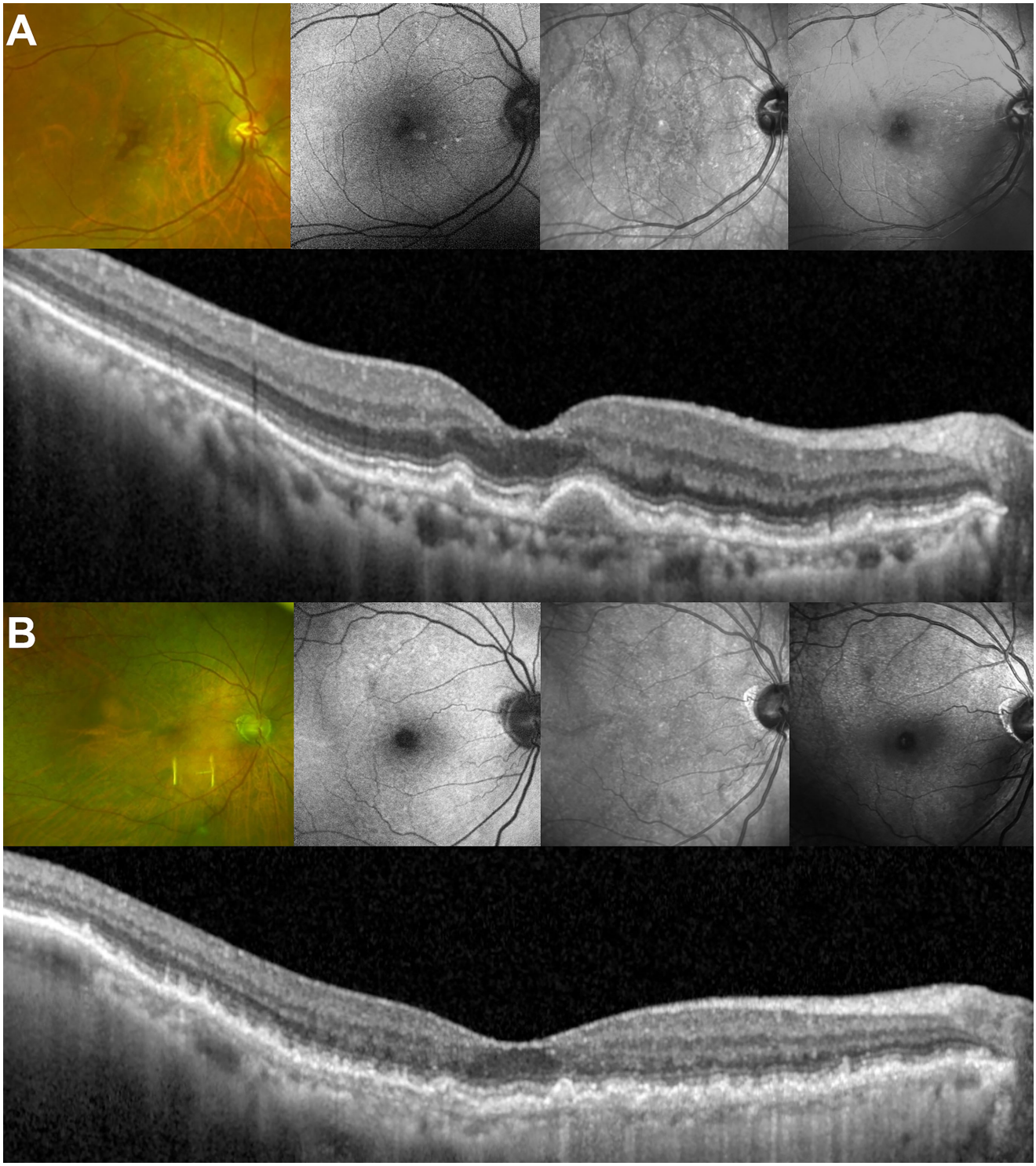

Figure 1. (**A**, **B**) Representative color fundus photography, short-wavelength fundus autofluorescence, near-infrared photography, blue reflectance photography, and optical coherence tomography images of the eye of a 78-year-old female patient with soft drusen (**A**) and the eye of an 85-year-old female patient with soft drusen and subretinal drusenoid deposits (**B**).

Medical Center. From April 2019 to January 2023, patients with early or intermediate AMD who were scheduled for cataract surgery were enrolled in the present study after receiving an explanation and providing informed consent.

All patients underwent a comprehensive ophthalmologic examination prior to surgery, and AMD was diagnosed based on fundus examination, fundus photography using an Optos retinal imaging device (Optos, Dunfermline, UK), short-wavelength fundus autofluorescence, near-infrared photography, blue reflectance photography, and optical coherence tomography (OCT) images acquired using the SPECTRALIS HRA system (Heidelberg Engineering, Heidelberg,

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Germany).[2] The OCT volume scan covered an at least 6 × 6-mm area with a 120-µm interscan distance. Axial length was measured with the IOLMaster 500 Version 7.3.0.0048 (Carl Zeiss Meditec AG, Jena, Germany).

We defined early or intermediate AMD as the presence of one or more medium-sized or larger drusen in the macula observed during fundus examination, and these lesions were confirmed to exist within a 6 × 6-mm area according to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid centered on the fovea in OCT imaging.[2] Soft drusen are defined as yellowish, round or oval deposits larger than 63 µm in size, located in the macula, with weakly defined boundaries, typically clustering in the posterior pole.[6,10,11] These lesions exhibit homogeneous subretinal pigment epithelium (RPE) accumulation on OCT. The presence of SDDs was confirmed primarily by fundus examination and OCT, with reference to short-wavelength fundus autofluorescence, near-infrared photography, and blue reflectance photography.[12] SDDs are reticular lesions observed on fundus examination and images and are defined as hyper-reflective triangular lesions found on top of the RPE in OCT imaging, with the requirement that at least five such lesions are in the affected area for diagnosis (Fig. 1).[8,12,13] One of the retinal specialists involved in the present work (KTN, MC, or K-EC) identified the presence of soft drusen and SDDs in dry AMD patients seeking cataract surgery during their outpatient clinic visits and selected candidates accordingly. A senior grader (CY) reviewed the images again, and only cases with matching results were included in this study. Eyes with SDDs but without soft drusen were excluded from the study.

Subfoveal choroidal thickness was measured from the OCT image using a horizontal line scan and the enhanced-depth imaging option as the distance from Bruch's membrane to the choroidoscleral junction at the fovea center. Drusen volume (mm^3) was obtained using the thickness map available in the built-in OCT software.[14] Volume was calculated by segmenting the outer borders of the RPE and Bruch's membrane and then determining the average volume within the areas of the ETDRS grid based on the thickness between these segmentation lines. For further analysis, the cube root of drusen volume (mm) was calculated from the drusen volume.

Before surgery, patients in whom the presence of drusen was not clearly confirmed or was difficult to categorize were excluded from the study, along with patients with late AMD, including exudative AMD or GA; high myopia (axial length ≥ 26.0 mm); retinal vascular diseases such as diabetic retinopathy or retinal vascular occlusion; or a history of vitreoretinal surgery, retinal laser treatment, or intraocular anti-VEGF injections. Patients diagnosed with glaucoma using intraocular pressure–lowering eye drops or with a history of glaucoma surgery; those with cardiac conditions such as angina, myocardial infarction, or heart failure; those with a history of stroke; and those with anemia (hemoglobin level ≤ 13 g/dL) were also excluded. The control group consisted of patients ≥ 50 years of age undergoing cataract surgery who did not meet the exclusion criteria and who had no concomitant retinal diseases.

Following a standard cataract surgery protocol, topical anesthesia was administered using a proparacaine HCl ophthalmic solution (Paracaine; Hanmi Pharmaceutical, Seoul, Korea), and the pupil was dilated with 0.5% tropicamide/phenylephrine HCl (Tropherine; Hanmi Pharmaceutical). Skin, eyelid margins, and eyelashes were disinfected with povidone–iodine, and the conjunctiva was disinfected with 5% povidone–iodine drops. Before the incision, 0.05 to 0.1 mL of aqueous humor was collected from the anterior chamber using a 27-gauge needle attached to a tuberculin syringe via limbal paracentesis. The aqueous humor was immediately stored in a −80°C freezer until analysis.

Aqueous concentrations of cytokines, including VEGF-A, angiopoietin-2, placental growth factor (PLGF), interleukin (IL)-1α, IL-1β, IL-6, IL-10, and tumor necrosis factor α (TNF-α), were analyzed using Luminex 200 technology (Luminex Corporation, Austin, TX, USA) with the MILLIPLEX analyte cytokine/chemokine/angiogenesis/growth factor panel (MilliporeSigma, Burlington, MA, USA). Samples (each 25 µL) were analyzed according to the manufacturer's protocol. Detection limits for this assay were 13.7, 13.7, 1.4, 4.8, 1.6, 0.64, 2.6, and 6.4 pg/mL, respectively. The standard curve was fitted using a cubic spline model due to its flexibility in capturing nonlinear relationships in the standard curve data. Values below the detection limit were included in the results as estimated values derived using the cubic spline model to interpolate the standard curve data.

The sample size for each group was determined in collaboration with a statistician, referencing a prior study that compared intraocular cytokine levels among different types of MNV in cases of exudative AMD.[15] Calculations were conducted with a significance level of 5% and a statistical power of 80%. Only one eye per patient was included in the study. If both eyes were eligible, aqueous humor was collected from the first eye undergoing surgery. The normality of continuous variables was assessed using the Shapiro–Wilk test. For parametric analysis, the analysis of variance test with Duncan's test as a post hoc analysis was used, and the Kruskal–Wallis test was employed for non-parametric analysis. Factors affecting outcome variables were analyzed using linear regression. All statistical analyses were performed using the SPSS Statistics 20.0 for Windows (IBM Corporation, Chicago, IL, USA), with $P < 0.05$ considered to indicate statistical significance.

Results

A total of 48 patients was included in the study, with aqueous humor samples collected from 16 patients in each group. The mean age was 77.31 ± 5.28 years in the soft drusen group, 80.63 ± 5.00 years in the soft drusen with SDDs group, and 75.75 ± 7.43 years in the control group ($P = 0.074$) (Table 1). There were no significant differences between the groups with respect to sex, history of hypertension, or diabetes ($P = 0.191$, $P = 0.710$, and $P = 0.368$, respectively). The mean drusen volume and drusen cube root volume were similar between the soft drusen group (0.13 ± 0.16 mm^3 and 0.44 ± 0.18 mm, respectively) and the soft drusen with SDDs group (0.12 ± 0.08 mm^3 and 0.46 ± 0.12 mm) ($P = 0.769$ and $P = 0.740$, respectively). Conversely, the subfoveal choroidal thickness differed significantly between the groups, as follows: 190.19 ± 61.15 µm in the soft drusen group, 139.69 ± 32.63 µm in the soft drusen with SDDs group, and 229.38 ± 75.68 µm in the control group ($P < 0.001$). No significant differences in axial length were observed among the groups ($P = 0.729$).

In the analysis of cytokine concentrations in the aqueous humor, VEGF-A levels were higher in the soft drusen with SDDs group (229.21 ± 88.26 pg/mL) compared to those in the soft drusen (167.54 ± 92.71 pg/mL) and control (140.73

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Table 1. Baseline Characteristics of Dry AMD Patients and Controls

	Group			
	Soft Drusen (n = 16)	**Soft Drusen With SDDs (n = 16)**	**Control (n = 16)**	***P***
Age (y), mean ± SD	77.31 ± 5.28	80.63 ± 5.00	75.75 ± 7.43	0.074*
Sex (male:female), n	9:7	4:12	6:10	0.191†
History of hypertension, n (%)	8 (50.0)	8 (50.0)	10 (62.5)	0.710†
History of diabetes, n (%)	4 (25.0)	3 (18.8)	6 (37.5)	0.368†
Drusen volume (mm^3), mean ± SD	0.13 ± 0.16	0.12 ± 0.08	N/A	0.769*
Drusen cube root volume (mm), mean ± SD	0.44 ± 0.18	0.46 ± 0.12	N/A	0.740*
Subfoveal choroidal thickness (µm), mean ± SD	190.19 ± 61.15[a]	139.69 ± 32.63[b]	229.38 ± 75.68[a]	<0.001*
Axial length (mm), mean ± SD	23.49 ± 0.94	23.55 ± 0.74	23.75 ± 1.19	0.729*

The superscripts a and b indicate no significant differences from other values with the same superscripts according to post hoc analysis with the Duncan's test at $P < 0.05$.

* Independent t-test or analysis of variance.

† χ^2 test or Fisher's exact test.

± 84.91 pg/mL) groups ($P = 0.021$) (Fig. 2, Supplementary Table S1). However, levels of angiopoietin-2 and PLGF were not significantly different among the three groups ($P = 0.347$ and $P = 0.409$, respectively). Levels of IL-1α, IL-1β, IL-6, IL-10, and TNF-α also did not significantly differ among the groups ($P = 0.261$, $P = 0.292$, $P = 0.237$, $P = 0.638$, and $P = 0.281$, respectively). In the soft drusen and control groups, no factors were associated with VEGF-A levels, whereas the cube root of drusen volume was associated with VEGF-A level in the soft drusen with SDDs group ($\beta = 0.533$, $P = 0.033$) (Table 2).

Discussion

AMD is a multifactorial disease arising from various factors, and it is hypothesized that both vascular and immune/inflammatory conditions contribute to its pathogenesis.[16] AMD can present with different clinical features depending on its progression, stage, and subtype.[2–6,11] Studies analyzing the aqueous humor of AMD patients have primarily compared wet AMD patients with control participants.[17] Although results vary across studies, many have reported that intraocular VEGF levels are higher in AMD patients compared to controls.[17] Additionally, concentrations of inflammatory cytokines such as IL-1α, IL-1β, IL-6, IL-10, and TNF-α have been reported to show no significant differences, similar to our findings.[17] This result is attributed to the low grade of the inflammatory process, whereas VEGF elevation is associated with MNV in wet AMD.[17] However, early or intermediate AMD represents an initial or mid-stage in the overall progression of AMD.[2,5] There are very few studies that have reported on cytokines and growth factors in the aqueous humor of these eyes. One study measured VEGF levels in patients with intermediate AMD and reported no significant difference compared to those in the control group; however, this study only analyzed seven patients and did not classify dry AMD into subtypes.[18] Compared to previous studies, our research has the advantage of including a relatively larger number of cases and distinguishing between dry AMD subtypes.

The current study found that, among the factors known to be associated with the pathogenesis of AMD—such as angiopoietin-2, PLGF, ILs, and TNF-α—the differences were not significant. The pathogenesis and progression of AMD may involve multiple pathways, with angiogenesis and inflammation being just two of them.[16] As a result, the expression of proteins involved in these processes may not be uniform. In the context of angiogenesis, VEGF-A levels increase early in response to hypoxia, initiating angiogenesis, whereas those of angiopoietin-2 increase later in the process.[19] Therefore, even when the VEGF-A level was elevated, there may have been no significant difference in angiopoietin levels. Furthermore, because AMD is characterized by low-level chronic inflammation, inflammatory factors may not be highly expressed in the early or intermediate stages of the disease.[16]

The pathogenesis of AMD remains incompletely understood, but several hypotheses have been proposed.[3,5] The accumulation of drusen increases the distance between the outer retina, which depends on choriocapillaries for oxygen supply, nutrient delivery, and metabolic waste exchange. This can impair the supply to the outer retina, leading to localized ischemia, an increase in intraocular VEGF concentrations, and potential induction of macular neovascularization.[3,5] In addition to well-established factors such as aging, genetic predisposition, and environmental influences, disruptions in the blood circulation of the outer retinal layers have been suggested to contribute to AMD.[20,21] Previous studies have reported a reduction in choroidal blood flow among patients with AMD, suggesting an association between impaired choroidal circulation and onset or progression of AMD.[20,21] However, these earlier studies classified AMD solely based on the presence of drusen, without considering other accompanying dry AMD phenotypes, such as SDDs. Recent advancements in diagnostic techniques have enabled a more detailed phenotypic classification of dry AMD compared to earlier assessments that relied exclusively on fundoscopy to confirm the presence of drusen.[2] A notable feature observed in dry AMD is the presence of SDDs, which have progression patterns with distinct differences in tendencies toward MNV or GA.[3–6,11] These various studies suggest that eyes previously diagnosed with a single form of macular degeneration may, after detailed examination, exhibit differences in intraocular environments depending on their phenotype. The results of this study support these previous findings.

In this study, the soft drusen with SDDs group showed higher aqueous VEGF levels than the soft drusen and control groups. The cause of the development and progression of SDDs has not yet been clearly elucidated. However, it has been suggested that various factors, such as genes associated with AMD, reduced blood flow in the choroid and choriocapillaris, RPE degeneration, lipid metabolism abnormalities, and chronic inflammation, may be involved.[3,5,7,8,13,22]

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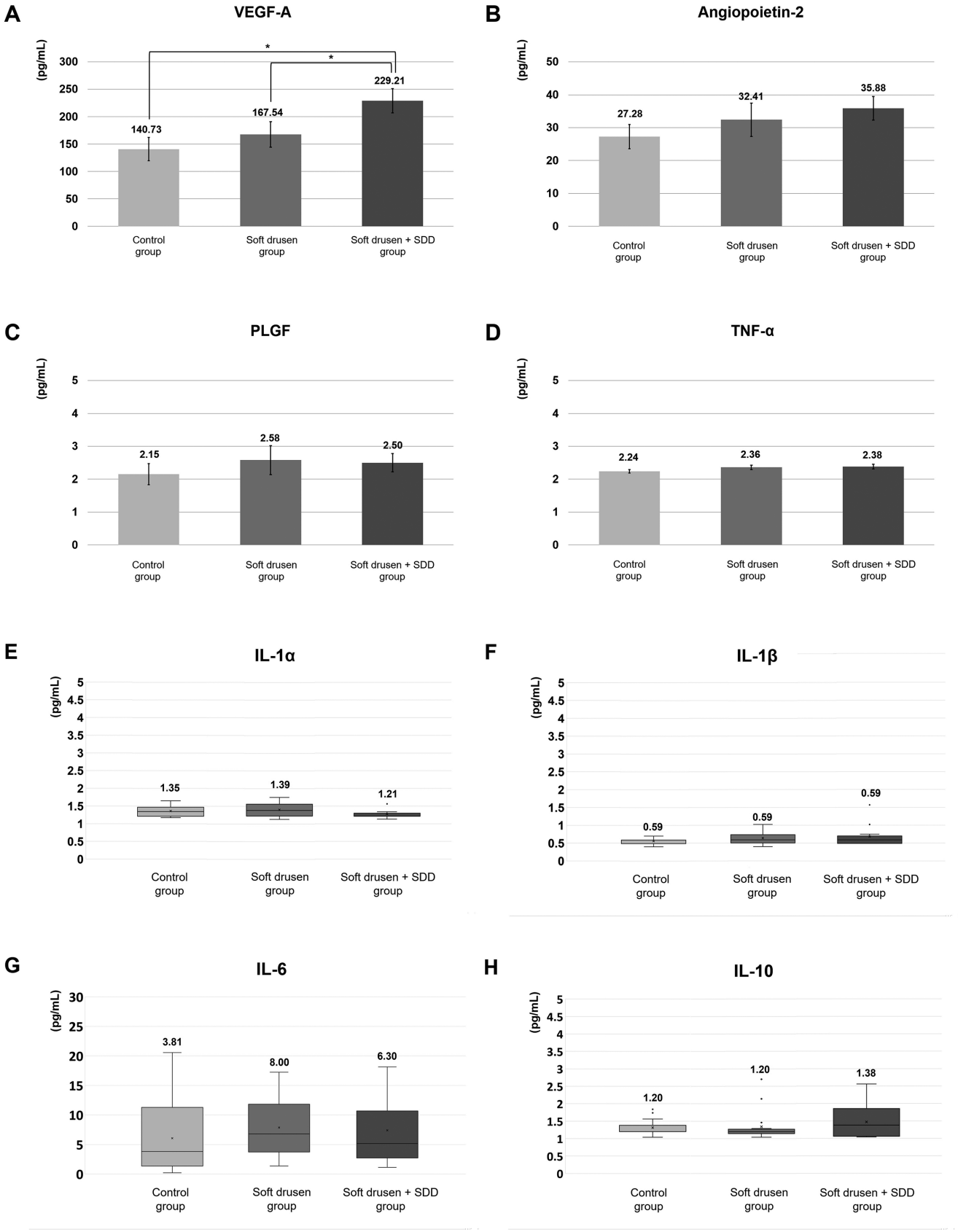

Figure 2. Comparison of cytokine levels among the control group, soft drusen group, and soft drusen with subretinal drusenoid deposits group: (**A**) VEGF-A, (**B**) angiopoietin-2, (**C**) PLGF, (**D**) IL-1α, (**E**) IL-1β, (**F**) IL-6, (**G**) IL-10, and (**H**) TNF-α. *Statistical significance was determined by post hoc analysis using the Duncan test.

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Table 2. Factors Associated With Increased Intraocular VEGF-A Levels in the Study Groups

	Group					
	Soft Drusen		Soft Drusen With SDDs		Control	
	β	P^*	β	P^*	β	P^*
Age (y)	0.315	0.234	−0.010	0.970	0.384	0.142
Sex (female)	−0.088	0.747	0.211	0.433	−0.335	0.204
History of hypertension	0.364	0.165	−0.019	0.943	−0.323	0.223
History of diabetes	−0.205	0.446	0.138	0.610	0.134	0.620
Subfoveal choroidal thickness (μm)	−0.020	0.943	−0.389	0.137	0.146	0.589
Axial length (mm)	−0.143	0.598	−0.042	0.877	−0.086	0.753
Drusen volume (mm^3)	0.442	0.086	0.438	0.089	N/A	N/A
Cube root of drusen volume (mm)	0.373	0.155	0.533	0.033	N/A	N/A

* Linear regression analysis.

Among the various hypotheses, previous studies have shown that eyes with SDDs exhibit impaired blood flow in both the choroid and choriocapillaris.[7,8,11,22–24] This has led to the hypothesis that diffuse choroidal hypoxia is related to the pathogenesis and associated features in eyes with SDDs.[11,22,23,25–27] These previous research findings suggest that AMD eyes with SDDs exist in a more hypoxic environment than AMD eyes with only soft drusen, consistent with our findings of higher intraocular VEGF levels in dry AMD eyes with SDDs. Additionally, some studies have reported that, in such eyes, the accumulation of SDDs is associated with a decline in RPE function, which can increase the burden related to the processing of metabolic substances in aged RPE, resulting in surrounding changes and, consequently, an increase in VEGF.[13,28] This RPE degeneration can also occur in eyes with only soft drusen without SDDs. However, although soft drusen are typically localized to the center of the macula, SDDs are more widely distributed; therefore, the affected area of the RPE and outer retina may be larger. These differences may help explain the variations in VEGF levels.

The pathogenesis of type 3 MNV in neovascular AMD is not yet fully understood, but it is more frequent in eyes with soft drusen and SDDs.[8,9,13,29,30] Based on relevant observations, such as a thinner choroidal thickness compared to other MNV types, it has been hypothesized that eyes with type 3 MNV may exist in a relatively more hypoxic environment.[9,29–32] This hypothesis is supported by a study that measured higher VEGF-A levels in the aqueous humor in eyes with type 3 MNV compared to eyes with type 1 or type 2 MNV.[15] The authors of that study hypothesized that eyes with type 3 MNV are likely to experience more severe choroidal ischemia, leading to increased VEGF levels as a compensatory response to hypoxic conditions.[15] In the present study, VEGF levels in the aqueous humor were elevated in the soft drusen with SDDs group; considering that type 3 MNV tends to occur more frequently in such eyes, this study provides evidence suggesting that VEGF levels may begin to rise before the development of type 3 MNV in predisposed eyes. Furthermore, within the soft drusen with SDDs group, a cube root of greater drusen volume was associated with higher intraocular VEGF levels. A higher drusen load can disrupt the smooth interaction between these two compartments, leading to localized ischemia. Eyes with AMD and SDDs, characterized by greater drusen extent, may experience a more highly hypoxic environment due to diffuse choroidal insufficiency and additional localized factors. Additionally, it is well documented that eyes with AMD with SDDs are more prone to type 3 MNV due to their thinner choroids and greater extent of drusen.[9,29] Taken together, these findings suggest that AMD eyes with SDDs, particularly those with reduced choroidal thickness and greater drusen volume, are more likely to be situated in a hypoxic environment. This condition may lead to elevated intraocular VEGF levels, potentially contributing to the development of type 3 MNV.

This study has several limitations. First, although the number of cases for this prospective study was estimated by a statistician, the number of cases included in this study is small. A future study with a larger sample size and follow-up data could improve the generalizability of the current findings. Second, in this study, when both eyes were eligible, aqueous humor was collected from the first eye undergoing surgery. The choice of which eye to operate on was influenced by the clinical process at the hospital or the patient's preference, which may have introduced selection bias. Third, in a cross-sectional design like the one used in this study, intraocular growth factors or cytokines that change depending on the progression of the disease may not be fully reflected. Thus, longitudinal studies tracking patients over time would be helpful in understanding the characteristics of AMD.

In conclusion, VEGF levels in the aqueous humor of eyes with dry AMD vary depending on the presence of SDDs. Notably, the higher VEGF-A levels measured in eyes with both soft drusen and SDDs compared to eyes with only soft drusen suggest that these eyes exist in a more hypoxic state.

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