Quiantitative Measurements of Superficial and Deep Vascular Density Assessed by Optical Coherence Tomography Angiography. In Healthy Hispanic Population

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ABSTRACT

Purpose: To quantify the normal values for vascular density (VD) of the superficial (SCP) and deep capillary plexus (DCP) in healthy subjects using optical coherence tomography angiography(OCTA).

Materials and methods: 188 volunteers were recruited over a 3-month period. Multicentric, descriptive study that included 365 eyes from healthy subjects, 230 from females and 135 from males. Patients were divided in 3 groups depending on the age, 20-39, 40-59 and 60 or more years. All subjects were evaluated with (RT-Vue XR Avanti) OCTA. 3x3 mm2 and 6x6 mm2 HD scans center at the fovea were taken; SCP VD, and DCP VD were quantitatively measured using Integrated automated algorithms.

Results: Ages range 20-86 average 39.7, SD 15.06. At 3x3 mm2 scan SCP VD and DCP VD median (IQ) are 47,20 (45,3-49,0) and 52,9 (50,8-54,7) respectively. At 6x6 mm SCP VD and DCP VD are 50,8 (48,6-52,7) and 53,5 (49,4-57,3) respectively. There is a significant inversely proportional correlation with age in all plexuses. Correlation was observed between the gender and the vascular density in the foveal 3x3 mm2 SCP VD (P: 0,00) and in all 3x3 mm2 DCP VD (p: 0.00).

Conclusions: This is a multicentric study in which we obtained a significant sample using OCT angiography with an integrated automated algorithm for analysis of patients with high variability of origin. We obtain data of VD on healthy subjects, that can be used as normative database for VD on the Latino population.

Keywords: Optical coherence tomography angiography, vascular density, latino, superficial capillary plexus, deep capillary plexus.

INTRODUCTION

The retina and other end organs (brain and kidney) share similar anatomical and physiological properties, the retinal vessels offer a unique and easily accessible window to study the health and disease of the human microcirculation[1]. The retina is among the most metabolically active tissues of the human body and possesses. an intrinsic autoregulatory mechanism that modifies blood flow in response to different physiologic conditions in order to maintain homeostasis[2]. The macula is recognized as the exquisitely specialized retinal region, with high-resolution visual acuity and oxygen uptake in the macula even higher than in the remaining retina[3]. There are four different retinal capillary plexuses, and only two of them are considered in the macula area: one superficial (inner) and one deep (outer), including the intermediate. The vessels in the nerve fiber layer and the ganglion cell layer form the inner (or superficial) capillary plexus (SCP), while the inner plexiform layer and the outer plexiform layer receive blood from the deep capillary plexus (DCP) located in the junction between them. The radial peripapillary capillary plexus is located in the nerve fiber layer in a small rim surrounding the optic nerve head[4].

The recently introduced technology, Optical coherence tomography angiography (OCTA)[5], is a noninvasive modality for vascular mapping, imaging the capillary

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network and the foveal avascular zone (FAZ) with high resolution[6], without dye injection[7]. It has the advantage of providing high speed, 3 - dimensional imaging of the retinal and choroidal vasculature in vivo[8,9]. Also, OCT-A can use the splits spectrum amplitude decorrelation angiography (SAADA) algorithm to detect erythrocyte movement[10]. This novel technology allowed us to study the normal retinal vasculature in vivo with better depth resolution than previously possible[8].

OCTA has previously been used to describe the retinal vasculature in both normal eyes[4] and various retinal vascular pathologies[11] as diabetic retinopathy[12] vein occlusion[13,14], telangiectasia[15,16] age related macular degeneration[17,18] among others.

The AngioVue (Optovue, Inc., Fremont, CA, USA) is one of the currently commercially available OCT-A machines that allows a four-section division of the retina–choroid complex: superficial capillary plexus (SCP), Deep capillary plexus (DCP), outer retinal layers, and choriocapillaris[8]. A new software update has been recently released. The AngioVue system allows quantification of the vascular density (VD) around the macula[2]. Perfusion maps are generated from the raw data by using the SSADA algorithm. With custom software, the superficial and deep perfusion maps generated by the AngioVue software were superimposed to create a single full microvasculature layer[19]. The skeleton data were used to calculate FAZ area, perimeter, foveal density and A circularity Index (AI) (defined as the ratio of the perimeter of the FAZ and the perimeter of a circle with equal area), as well as vessel density (VD) for each of the regions of interest (ROIs)[20].

Vascular density was defined as the total vessel length divided by the ROI area, the percentage of the simple area occupied by vessel lumens following binary reconstruction of images. The percentage of vessels was defined in the sectors (superior, temporal, inferior, and nasal) as well as the whole image, foveal, perifoveal and parafoveal. The inner and outer rings with a diameter of 1 and 2.5 mm around the fovea were respectively considered for evaluation. To calculate vessel density, the AngioVue Analytics software extracts a binary image of the blood vessels from the grayscale OCTA image, and then calculates the percentage of pixels occupied by blood vessels in the defined region[4,6,12].

Also, this study is important because in Latin America there is a wide variation of what is considered Hispanic subjects. It will give an insight of the possible variations of VD on healthy Hispanic subjects.

This study will allow to collect this data in 6 different groups of Hispanic population, VD values for age and gender will be provide as well as comparison between different subpopulations.

To our knowledge this is the first multicenter descriptive study that obtain data of VD on healthy subjects using OCT angiography with a commercial software and Integrated automated algorithms for analysis. And can be used as normative database for VD on the Latino population. Due to the fact that variations on these values had been reported in several ocular pathologies, establish a normative database for the clinical practice is paramount.

MATERIALS AND METHODS

The study was approved by the Ethics Committee at CREIMED (comité de estudios medicos) institution and was conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants. Volunteers from six Latin American countries were recruited to participate in this study. Demographic data are shown in Table 1

The main objective of this study is to establish a normative database for vascular density (VD) of the superficial (SCP) and deep capillary plexus (DCP) in healthy subjects in 5 Latin American Countries using optical coherence tomography angiography (OCTA).

Table 1: *Distribution of sample by country.*

Country	N Male (%)	N Female (%)	Total N(%)
Argentina	26 (38.8%)	41 (61.2%)	67 (18,4)
Bolivia	8 (14.8%)	46 (85.2%)	54 (14,8)
Chile	19 (25.7%)	55 (74.3%)	74 (20,3)
Mexico	18 (56.3%)	14 43.8%)	78 (21,4)
Colombia	38 (48.7%)	40 (51.3%)	32 (8,8)
Peru	26 (43.3%)	34 (56.7%)	60(16,4)
Total	135 (37%)	230 (63%)	365 (100)

Study Design

This was a multicentric, descriptive study that included 365 eyes from healthy Hispanic subjects. Protocol was in accordance to all the local IRB regulation and was evaluated, accepted and approved by institutional review board (CREI IRB).

Because there are currently no available reports on Hispanic population, sample design was based on the mean and standard deviation of superficial vascular density percentages previously reported by Coscas et al.[4]. Parameters included in the sample calculation were at a confidence level of 95%, precision level of 0.5%, and design effect of 2%, which resulted in a sample size of 157 patients. Volunteer recruiting was not randomized, meaning that the number of eyes scanned per center did not represent the population of the city or country, given the costs of obtaining OCTA images for a sample of that size.

Healthy patients were invited to participated in this study, and were recruited at the ophthalmology services of Mexico (Anzures Ophthalmologic clinic.), Peru (Ophthalmology Service of the San Borja Clinic), Argentina (CEO-NITIDO), Brazil (Neovista Eye Institute), Chile (Rios y Cia.) and Colombia CLOFAN-INIO). All patients signed an informed consent form.

Demographic data, including ophthalmic and systemic histories, were recorded for each patient. A complete ophthalmologic examination was performance to check the inclusion criteria.

This study included healthy Hispanic patients between 20 to 86 years, with a best corrected visual acuity score better than 40 letters ETDRS (equivalent to approximately 0.3 logMAR or 20/20 Snellen chart), with not any refractive error greater than +/- 3.0 D.

Patients diagnosed with any of the following ocular diseases: Age-related macular degeneration (AMD), diabetic retinopathy, glaucoma (average RNFL thickness out of normal limits), myopic degeneration, central serous chorioretinopathy, uveitis, idiopathic macular hole, cataract, intraocular surgery in the past 6 months or laser eye surgery in the last 3 months, and other ocular diseases including severely dry eye that, in the opinion of the investigator, could prevent obtaining reliable OCTA images, were excluded. The presence of pregnancy or any systemic abnormality such as diabetes mellitus, hypertension, treatment with chloroquine, use of sildenafil, smokers, carotid disease and/or cardiovascular disease that could affect the results of OCTA were also excluded. Images with scan quality index lower than 6/10 were not included.

Angiographic imaging and image processing

To obtain OCTA images we used the RTVue-XR Avanti system (Optovue, Inc., Fremont, CA, USA) with split-spectrum amplitude-decorrelation angiography (SSADA) software 7.1. This instrument has an A-scan rate of 70,000 scans per second and uses a light source centred at 840 nm and a bandwidth of 45 nm. Two consecutive B-scans (M-B frames), each containing 304 A-scans, they were captured at each sampling location and SSADA were used to extract OCTA information. We obtained 3x3 mm^2 and HD6x6 mm^2 Angioscans cantered on the fovea. Foveal avascular zone area (FAZ) (mm^2) was evaluated by OCT angiograms that were segmented automatically using the built-in software. Dilation drops were used when they will be needed to obtain a good quality image (scan quality index better than 6/10) and lubricant drops were used in all the cases. OCTA were taken for both eyes.

The vascular density were measured at the superficial (Superficial (ILM~IPL-10) corresponds to SVD) and Deep plexus (Deep (IPL-10 ~ OPL+10) corresponds to DVD). The vascular density (VD) analysis computes the % of area occupied by OCTA detected vasculature. Reported in the ETDRS sectors (superior, temporal, inferior, and nasal) based on the Early Treatment Diabetic Retinopathy Study (ETDRS) grid as well as the whole image vascular density and the foveal, parafoveal and perifoveal vascular density. The automatic Angionalityc software were used. ONH scan and analysis were performed to corroborate inclusion/exclusion criteria. Optic Nerve (ONH) scan were obtain and Retinal Nerve Fiber Layer (RNFL) analysis to ensure subject has not an undetected glaucoma or other optic nerve pathology.

Statistical analysis

Qualitative variables were described in proportions and quantitative variables were analyzed by their mean (X) and standard deviation (SD). Potential differences between age, gender and nationality were evaluated and analyzed of variance (ANOVA). For analysis purposes the subjects were divided in three groups by age: 20-39, 40-59 and older than 60 years. Depending on the distribution, comparisons of means or medians of independent variables will be performed using student's t-test or Mann-Whitney test related to three strata. The paired t-test will be used to compare paired data. A p value < 0.05 will be considered statistically significant. A binary logistic regression model will be built to find association between FAZ areas, independent variables and confounding factors as age, gender and BMI. All statistical analyses will be perform with SPSS version 21.0 (IBM Corp, Armonk, NY, USA).

RESULTS

A total of 365 eyes from healthy Hispanic subjects recruited in 6 centers (230 female eyes, 63%) were included in this study (see table 1 distribution of sample by country) of which 212 eyes were in group 1 (20–39 years old), 106 in group 2 (40–59 years old), and 47 in group 3 (60 years and older) (see table 2 distribution of sample by age and table 3 Age groups according to each country). All study measurements provided high-quality scans.

The mean age of the study subjects was 39.7 years (SD 15.0610 years; range, 20–86 years).

Vascular density values were not normal in the Kolmogrorov Smimov normality test (p:0,200), therefore, non-parametric tests were performed.

At 3x3 mm^2 SCP VD and DCP VD median (IQ) is 47,20 (45,3-49,0) and 52,9 (50,8-54,7) respectively. At 6x6 mm SCP VD and DCP VD is 50,8 (48,6-52,7) and 53,5 (49,4-57,3) respectively.

In the bivariate analysis when using the Mann Whitney U test no correlation was observed between the gender and the vascular density in the whole 3x3 mm^2 SCP VD (P: 0,650), whole 3x3 mm^2 DCP VD (P: 0,52), whole 6x6mm^2 SCP VD (P: 0,268), whole 6x6mm^2 DCP VD (P: 0,463). However, in the Mann Whitney U test, showed that there are differences between gender and foveal density in some of the areas studied. Foveal whole SCP VD 3x3mm^2 only (p: 0.00). And in all 3x3 mm^2 DCP VD with a statistical significance of p: 0.00.

Table 2: *Distribution of sample by age.*

Age	N (%)
20-39 years	212 (58,1)
40-59 years	106 (29)
60 years or more	47 (12,9)
Total	365 (100)

In the bivariate analysis there is a significant inversely proportional correlation with age in all plexuses. (Figure 1a, 1b, 1c 1d)

Also shown tables 4 and 5 that show Normative Data of Vascular Density in 3x3 Superficial and Deep Capillary Plexus; and Normative Data of Vascular Density in 6x6 Superficial and Deep Capillary Plexus respectively.

DISCUSSION

Recent advancements in OCTA technology have enabled more precise descriptions and analyses of the retinal microvasculature. Fluorescein angiography, one of the most commonly used methods, evaluates with precision SCV, however DCV is poorly visualized with this test, for which a complete evaluation of the retinal circular system cannot be obtained, as is now the case with the OCTA. Also OCTA provides depth-resolved imaging and segmentation of the microvascular layers of the macula, allowing separate evaluation and quantification of the SCP versus the DCP[21].

Knowing the normal values of vascular density in our population is of the utmost importance because it is affected in mainly vascular macular pathologies such as DM, retinal vein occlusion or arterial obstructions[12-14].

This is a multicentric study in which we obtained a sample of patients with high degree of variability of origin, all of them Hispanic, and provided for the first time measures of VD on healthy subjects. Being multicentric ensures that there are no biases caused by specific regional characteristics such as height above sea level or genetic characteristics that occur in different regions. Unlike other studies that have been done with previous software, our study is done with software 7.0 which has DualTrac motion correction for OCTA imaging that is equipped to reduce artefacts caused by motion; giving a greater precision of the means.

Table 3: *Age groups according to each country.*

Country	20-39 years N(%)	40 - 59 years N(%)	≥ 60 years N(%)	Total
Argentina	33 (49,3%)	21 (31,3%)	13 (19,4%)	67 (100,0)
Bolivia	42 (77,8%)	10 (18,5%)	2 (3,7%)	54 (100,0)
Chile	43 (58,1%)	23 (31,1%)	8 (10,8%)	74 (100,0)
Colombia	42 (53,8%)	24 (30,8%)	12 (15,4%)	78 (100,0)
Mexico	12 (37,5%)	16 (50,0%)	4 (12,5%)	32 (100,0)
Peru	40 (66,7%)	12 (20,0%)	8 (13,3%)	60 (100,0)
Total	212 (58,1%)	106 (29,0%)	47 (12,9%)	365 (100,0)

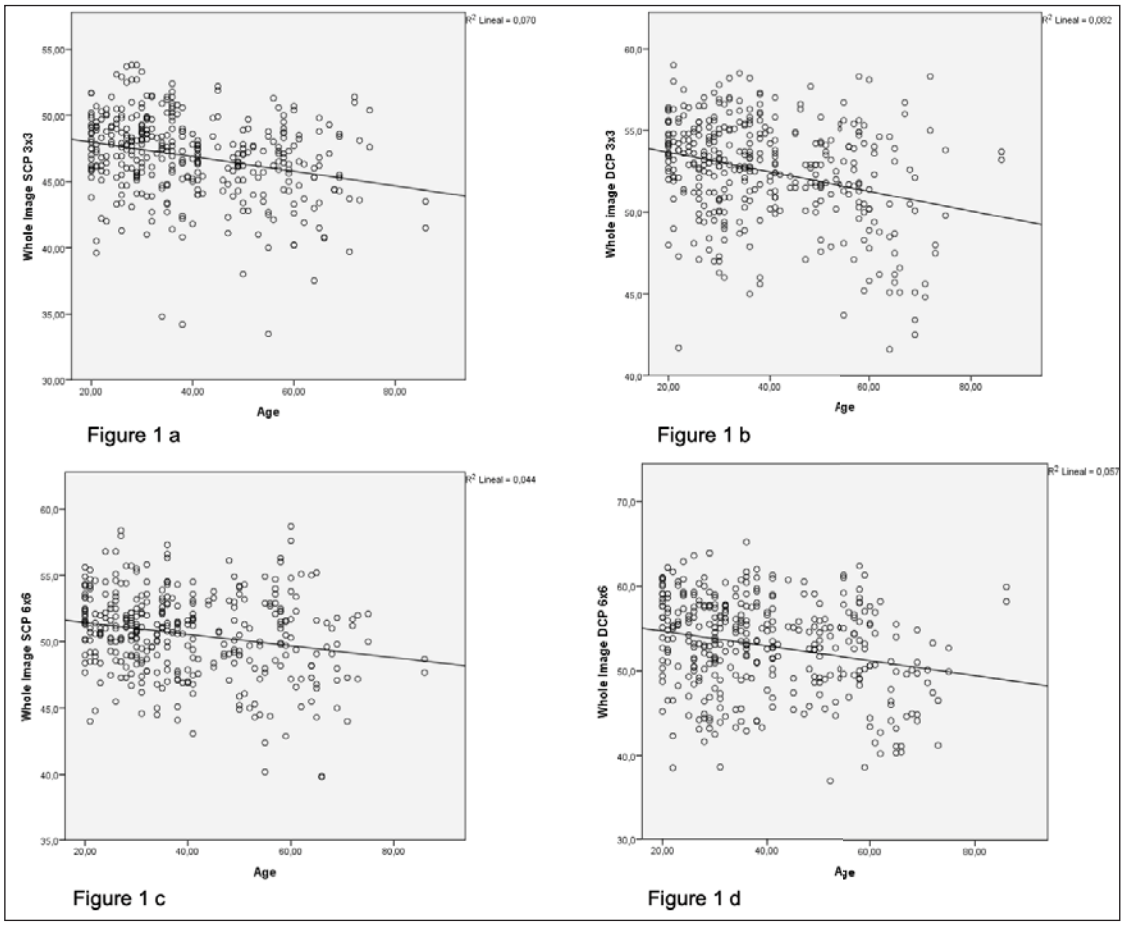

Figure 1: *Relationship of age with 3x3 and 6x6 SCP and DCP. Figure 1a. Relationship of age with 3x3 superficial vascular density. Figure 1b. Relationship of age with 3x3 deep vascular density. Figure 1c. Relationship of age with 6x6 superficial vascular density. Figure 1 d. Relationship of age with 6x6 deep vascular density.*

Table 4: *Normative Data of Vascular Density in 3x3 Superficial and Deep Capillary Plexus; Percentage of Vessels Was Defined in Sectors Based on the ETDRS Chart (Superior, Temporal, Inferior, and Nasal) Where the Fovea Center Was Automatically Determined from the Structure OCT Data, and the Inner and Outer Diameters of the Parafoveal Region Were 1 and 2.5 mm.*

3x3 SCP VD	**20-39 years median (IQR)**	**40-59 years median (IQR)**	**≥ 60 years median (IQR)**
Whole	48,00 (45,9-49,7)	46,50 (45,00-47,80)	45,30 (43,35-48,30)
Fovea	16,70 (12,60-21,70)	15,55 (11,60-20,05)	15,50 (9,85-20,80)
Parafovea	51,20 (48,70-52,80)	49,75 (47,57-50,82)	48,50 (46,25-51,25)
Temporal	49,70 (47,20-51,30)	48,10 (46,20-49,35)	47,3 (44,25-49,85)
Superior	52,20 (49,40-54,70)	51,20 (48,90-52,72)	51,00 (48,50-53,60)
Nasal	50,20 (48,10-52,00)	48,35 (46,9 (50,50)	47,70 (45,35-50,60)
Inferior	51,90 (49,40-54,10)	50,95 (48,90-52,40)	50,20 (46,75-51,60)
3x3 DCP VD	**20-39 years median (IQR)**	**40-59 years median (IQR)**	**≥ 60 years median (IQR)**
Whole	53,40 (51,40-55,10)	52,30 (51,10-54,20)	50,10 (46,40-53,65)
Fovea	32,50 (28,20-37,90)	30,70 (25,57-35,22)	30,10 (23,25-37,30)
Parafovea	55,60 (53,50-57,40)	54,60 (53,27-56,05)	51,80 (49,55-55,70)
Temporal	55,60 (53,70-57,40)	54,70 (53,65-55,72)	52,50 (49,50-55,30)
Superior	55,50 (49,50-55,30)	54,70 (53,10-56,42)	53,20 (49,90-56,20)
Nasal	55,80 (53,90-57,50)	55,05 (53,07-56,52)	52,40 (49,80-54,95)
Inferior	55,60 (52,70-57,40)	54,35 (52,57-56,00)	51,60 (48,30-55,20)

Table 5: *Normative Data of Vascular Density in 6x6 Superficial and Deep Capillary Plexus; Percentage of Vessels Was Defined in Sectors Based on the ETDRS Chart (Superior, Temporal, Inferior, and Nasal) Where the Fovea Center Was Automatically Determined from the Structure OCT Data, and the Inner and Outer Diameters of the Parafoveal Region Were 1 and 2.5 mm.*

6x6 SCP VD	20-39 years median (IQR)	40-59 years median (IQR)	≥ 60 years median (IQR)
Whole	51,00 (49,20-52,80)	50,35 (48,17-52,82)	49,40 (47,15-51,90)
Fovea	19,50 (15,00-24,80)	18,20 (13,32-23,15)	19,60 (10,9-22,5)
Parafovea	53,60 (51,30-55,8)	53,25 (50,67-55,70)	51,90 (49,35-53,85)
Temporal (inner)	53,20 (51,20-55,30)	52,85 (50,17-54,90)	50,90 (49,10-52,65)
Superior (inner)	54,60 (52,60-57,10)	54,20 (51,07-56,60)	54,10 (49,60-56,15)
Nasal (inner)	52,80 (50,70-55,10)	52,40 (49,87-54,32)	50,70 (46,55-53,15)
Inferior (inner)	53,70 (50,90-56,30)	53,40 (50,27-55,82)	52,10 (48,80-54,85)
Perifovea	51,80 (49,80-53,80)	50,95 (48,80-53,30)	50,10 (47,45-52,40)
Temporal (outside)	47,60 (45,70-49,50)	47,10 (44,85-49,12)	46,00 (44,00-49,35)
Superior (outside)	52,10 (49,70-53,90)	50,90 (48,40-53,27)	51,30 (47,65-53,50)
Nasal (outside)	55,20 (53,50-57,00)	54,85 (52,47-56,45)	53,60 (50,85-56,30)
Inferior (outside)	52,10 (49,60-54,10)	51,30 (48,07-53,80)	49,40 (47,3-53,50)
6x6 DCP VD	**20-39 years median (IQR)**	**40-59 years median (IQR)**	**≥ 60 years median (IQR)**
Whole	54,70 (50,50-57,70)	53,35 (49,50-56,15)	49,70 (44,10-53,65)
Fovea	36,80 (31,60-42,50)	35,45 (29,37-42,00)	35,10 (28,45-42,00)
Parafovea	57,30 (54,70-60,30)	57,50 (54,75-59,02)	53,60 (49,85-56,90)
Temporal (inner)	58,40 (55,40-60,80)	57,95 (55,67-60,00)	53,70 (51,20-56,45)
Superior (inner)	57,40 (54,20-60,00)	57,15 (54,42-59,22)	52,10 (48,80-57,90)
Nasal (inner)	58,20 (55,70-60,80)	58,05 (55,67-59,70)	53,00 (50,80-57,95)
Inferior (inner)	56,50 (52,90-59,50)	56,25 (52,70-58,80)	51,80 (48,75-56,80)
Perifovea	56,30 (51,70-59,30)	55,25 (51,52-58,25)	50,70 (44,80-55,50)
Temporal (outside)	57,70 (54,30-60,50)	57,25 (54,37-60,10)	52,70 (48,75-57,90)
Superior (outside)	55,90 (50,80-59,00)	54,80 (49,90-58,62)	50,80 (42,75-58,50)
Nasal (outside)	54,60 (50,30-58,50)	54,05 (50,30-57,42)	47,80 (42,75-53,75)
Inferior (outside)	56,30 (51,20-59,80)	55,30 (48,90-58,10)	48,80 (43,25-55,45)

Our study was conducted in 6 different countries and is the only one that has a sample with 365 eyes studied from different geographical regions. The knowledge that we currently have of normal values comes from retrospective design studies, such as the study by Coscas et al.[4]. This was done with 135 eyes and in a single institution.

We found two cross-sectional studies that evaluated vascular density in healthy patients, one by David et al.[21] and another of Hayati Yilmaz et al.[22] both have a smaller sample than our study and also both were performed in a single center.

Most studies are performed in patients with pathology and there are small healthy control groups that are usually of young people under 60 years of age[2,6,23,24]. In this study we had an important sample of patients older than 60 years and up to 86 years, previously checking that the patient was totally healthy, did not have hypertension and without diabetes, which ensures that these normal values are valid.

Knowing the normal values is important in any group age but it is more relieved in elderly patients where retinal pathologies are more frequent. In this study there were 47 patients over 60 years of age, who were found to have no systemic or ocular disease.

We found a correlation between gender and Vascular Density; however, this correlation is not a strong correlation and only occurs in the deep plexus, being higher in men than in women. There are also some contradictory results in previous studies for example, Coscas et al.[4] declared that

the VD of the female volunteers was significantly greater than that of males while Hayati Yilmaz et al.[22] declared not find any relation between gender and VD.

When dividing the population into different age groups, a statistically significant inverse correlation was observed between age and vascular density in all quadrants of ETDRS in the SCP and PCD in 3x3 mm and 6x6 mm except for foveal measurements, because the FAZ area acts as a confusion variable.

However it was evidenced that the normal values of SCP VD and DCP VD of 3x3 mm and 6x6 mm OCTA scan in all areas other than foveae in the different categories (age and sex) presented very precise intervals, This reflects that this measurement in all the other quadrants is homogeneous and can be an effective measure for the early detection of decrease or increase in vascular flow.

Variations in what is considered normal for DV according to each age group could serve as an early indicator of secondary changes to diseases such as AMD or retinal vascular diseases that frequently affect elderly patients.

In our study, the normal values per segment of the ETDRS and the change that it presents according to the age groups are specified in addition to the total value. This is important since the vascular changes do not necessarily affect the entire macular area, but they can be located in small areas. If value of the DV is take as a whole, small sectorial anomalies can be overlooked.

It is suggested to evaluate in other future studies other variables different to age and sex that may affect VD.

CONCLUSIONS

In conclusion, our study has provided, for the first time measures of VD on healthy subjects done on a multicentric setting. And can be used as normative database for VD on the Latino population as a whole, because as normal values are so accurate any decrease or increase in vascular density can indicate pathology.

The results of our study could help differentiate healthy subjects from patients suffering progressive stages of various retinal vascular diseases.

Limitations

One of the main limitations of this study was the size of the sample, so other studies are required assessing normative data in healthy Hispanic participants.

Compliance with Ethical Standards:

This study was funded by INIO (grant 0002). Claudia Acosta declares that she has no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the CES University ethical committee (permit number Act2018proy011) institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards Informed consent was obtained from all individual participants included in the study.

LIST OF ABBREVIATIONS

-Foveal avascular zone (FAZ)

-Vascular density (VD)

-Superficial capillary plexus (SCP)

-Deep capillary plexus (DCP)

-Optical coherence tomography angiography (OCTA)

-Acircularity Index (AI)

-Optic nerve scan (ONH)

-Retinal nerve fiber layer (RNFL)

-Foveal density (FD)

-Splits spectrum amplitude decorrelation angiography (SAADA) algorithm

-Body mass index (BMI)

-Institutional review board (IRB)

-Early Treatment Diabetic Retinopathy (ETDRS)

- Optic Nerve (ONH)

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