Assessment of morphological and functional alterations in patients with early stage of non-proliferative diabetic retinopathy by optical coherence tomography angiography and microperimetry

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Research article

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Abstract

Background To analyze the optical coherence tomography angiography(OCTA) and microperimetry features in diabetic patients without diabetic retinopathy(NDR group) and patients with early stage of non-proliferative diabetic retinopathy(NPDR group). Methods This was a cross-sectional study including 24 eyes of the NDR group, 24 eyes of the NPDR group, and 24 eyes of healthy volunteers(control group). OCTA was used to measure foveal avascular zone(FAZ), vessel flow density of superficial capillary plexus(SCP) and deep capillary plexus(DCP) in the macular area(3×3mm). The latest version of microperimeter, MP-3, was used to quantitate retinal light sensitivity and fixation stability in the central 10° of the macular region. Results The NPDR group had a larger FAZ area, reduced vessel flow densities of both SCP and DCP, deceased retinal sensitivity and less stable fixation compared with the control group. Statistical differences were only found in the FAZ area, vessel flow density of DCP and retinal sensitivity between the NDR and the NDPR group. Conclusions The FAZ enlargement, vessel flow density decrease and retinal sensitivity reduction may be morphological and functional indicators of progression of diabetic retinopathy. Microvascular alterations in deep capillary plexus may precede superficial capillary alterations in diabetic retinopathy.

Background

Diabetic retinopathy(DR) is the most common microvascular complication of diabetes, and the leading cause of vision loss in working-age adults.[1] Conventional concepts of pathophysiology of diabetic retinopathy is microvascular lesions in the retina, with clinical manifestations including microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, and venous caliber changes.[2] Albeit being regarded mainly as a microvascular disorder, early retinal function deficits accompany the retinal lesions in patients with diabetes.[3] Therefore, it is significant to develop an early assessment method in detecting microvascular and visual function changes in diabetic patients.

Fundus fluorescein angiography(FFA) is the gold standard imaging technique in assessing macular vascular abnormalities. Numerous documents have demonstrated that the foveal avascular area is enlarged in diabetic retinopathy based on FFA results, and appears to be larger as the stage of retinopathy advances. Besides, the vessel flow density is decreased with progression of DR. These changes are most likely related to macular ischemia.[4][5] However, FFA is an invasive examination and may cause various complications as nausea, vomiting, and more severe but less infrequently, anaphylactic reactions. These complications restrict the broad use of FFA. Additionally, imaging angiograms of the deep retinal vasculature or segmentation of different layers are not routinely possible due to dye leakage and poor stereopsis.[6][7][8] Optical coherence tomography angiography is a new, non-invasive imaging approach comparing decorrelation signal between two sequential OCT cross-sectional scans at the same cross-section in order to construct a map of blood flow. The advent of OCTA allows imaging different layers of the retinal vasculature, including the deep layers, and quantitative analysis of the retinal vessels.[8]

In addition to monitoring macular morphological changes in diabetes by OCTA, precise quantification of retinal function at specific loci is needed. In this respect, microperimetry has been developed to determine the retinal sensitivity thresholds in the macular area and correlate them with certain retinal lesions. [9][10][11] Compared with MP-1, the latest version of microperimetry, MP-3, has an automatic eye-tracking system and an improved dynamic range, which allows precise mapping of the central visual field.[12]

In the present study, we aimed to compare retinal vascular flow parameters by OCTA and retinal sensitivity by MP-3 between healthy volunteers, diabetic patients with no symptoms of DR, and NPDR patients. The study results provided new insight into the pathophysiology of diabetic retinopathy.

Methods

For this cross-sectional study, we evaluated 24 eyes of 13 normal healthy individuals (control group), 24 eyes of 12 diabetic patients without diabetic retinopathy (NDR group), 24 eyes of 15 diabetic patients with non-proliferative diabetic retinopathy (NPDR group). Non-proliferative diabetic retinopathy group was classified by the same retina specialist. Changes in NPDR include hemorrhages, microaneurysms, and/or soft exudates, venous beading, or intra retinal microvascular abnormalities. The study was conducted from March 2018 to November 2018. Each patient provided informed consent in accordance with the Declaration of Helsinki, and the study was approved by the local ethics committee.

Blood biochemical tests for glycosylated hemoglobin (HbA1c) and fasting plasma glucose levels were run on all patients. All cases underwent ophthalmological examinations including best corrected visual acuity (BCVA), intraocular pressure, slit-lamp biomicroscopy, indirect fundus ophthalmoscopy, and color fundus photographs.

BCVA was scored based on logarithmic visual acuity chart correctly and converted to the logarithm of the minimum angle of resolution (logMAR).

Exclusion criteria included refusal to give informed consent, other ocular diseases such as to significant media opacities, glaucoma, macular disorders; poor fixation; and any retinal surgery or treatment.

Optical coherence tomography angiography (OCTA)

RS3000 Advance (Nidek Technologies, Padova, Italy), was used to capture the OCTA images. A 3 × 3 mm field of view centered on the fovea was chosen for each patient. In the obtained OCT angiograms, capillary perfusion status of each superficial and deep capillary layer was determined. Macular thickness (MT) was defined as mean full retinal thickness. We defined Foveal Avascular Zone(FAZ) as the inside area of the inner boundary of the central capillary ring. Quantifying FAZ areas were manually outlined by

the same examiner and then the software calculated the outlined areas and converted into square millimeters. (Figure 1)

Microperimetry

The examination should be carried out in the darkroom. The pupil size of all the examiners should be larger than 4 mm in diameter, and the contralateral eye was patched. The MP-3 has an improved dynamic range between 0 and 34dB (the maximum luminance of the MP-3 is 10,000 asb). The specifications used in the study included a fixation target consisting of a red ring, 10°in diameter; 34 stimulation points, 4-2 threshold, duration of stimulus. being 200 ms, Goldmann size III stimulus, white background with intensity at 4 asb. Mean sensitivity(MS) was evaluated within the central 10°and 2°, approximately covering 1 mm and 3mm of the central retina area on OCT mapping and expressed in decibel. The fixation stability was automatically calculated the percentage of fixations within 2° and 4° and the bicurve ellipse area(BCEA). The MP-3 BCEA calculations were taken into 3 standard deviation measures(BCEA68.2 deg^2/ BCEA95.4 deg^2/ BCEA99.6 deg^2) of each recorded eye movement. We used Photoshop (Adobe Systems, San Jose, CA, USA) for processing of the microperimetry images. The central macular area (10°) was divided into five zones, similar to the Fast Macular Thickness OCT program, to record the MS.(Figure 2)

Statistical analysis

Statistical analyses were performed using SPSS for Windows statistical software (ver. 17.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Mean values data did not show a Gaussian distribution, so it was compared by the Kruskal-Wallis test and Mann-Whitney u test. The Bonferroni correction was applied for post hoc analysis. Pearson's coefficient was used to check correlation between retinal morphologic parameter (MT, VFD[%] and FAZ[mm^2]),and functional parameters(MS). $P<0.01$ was interpreted as statistically significant.

Results

The baseline characteristics of participants recruited in the study are summarized in Table 1. There was no statistically significant difference in age and intraocular pressure among the three groups. Kruskal-Wallis test of best-corrected visual acuity showed statistically significant differences between the control group and the diabetic group ($P <0.01$). Furthermore, the BCVA significantly reduced in NPDR group compared with the normal group ($P <0.01$) and the NDR group ($P <0.01$), but there was no significant difference between the control group and NDR group ($P = 0.84$) in BCVA. Kruskal-Wallis test of

mean HbA1c level showed statistically significant differences between the control group and the diabetic group (P <0.01). The mean HbA1c level was significantly lower in control group compared with the NPDR group (P <0.01) and the NDR group (P <0.01) , but there was no significant difference between the NPDR group and NDR group (P = 0.99) in HbA1c level.

Microperimetry examination results for each group are listed in Table 2. When MS in NPDR group was compared with that in control group(superior: 28.82 ± 1.598 dB vs. 25.37 ± 3.537dB, P <0.001; inferior: 28.68± 1.234dB vs. 24.76 ± 4.237dB, P <0.001; temporal: 29.45 ± 1.065 dB vs. 25.07 ± 4.889dB, P <0.001; nasal: 29.18 ± 1.11 dB vs. 24.14 ± 5.828dB, P <0.001; fovea area: 29.16 ± 1.37 dB vs. 24.86 ± 4.233dB, P <0.001) and NDR group(superior: 28.63 ± 1.592dB vs. 25.37 ± 3.537dB, P <0.001; inferior: 28.22 ± 1.366 dB vs. 24.76 ± 4.237 dB, P <0.001; temporal: 29.07 ± 1.315 dB vs. 25.07 ± 4.889dB, P <0.001; nasal: 28.98 ± 1.449 dB vs. 24.14 ± 5.828dB, P <0.001; fovea area: 28.56 ± 1.381dB vs. 24.86 ± 4.233dB, P <0.001), significant reduction was observed in all five quadrants. When MS in NDR group was compared with that in control group in all five quadrants (superior: 28.82 ± 1.598 dB vs. 28.63 ± 1.592dB, p=0.9959; inferior: 28.68 ± 1.234 dB vs. 28.22 ± 1.366dB, p=0.288; temporal: 29.45 ± 1.065 dB vs. 29.07 ± 1.315dB, p=0.2479; nasal: 29.18 ± 1.11 dB vs. 28.98 ± 1.449dB, p=0.963; fovea area: 29.16 ± 1.37 dB vs. 28.56 ± 1.381dB, p=0.1453), no significant difference was found.

Automatically calculation of fixation stability in each group are listed in Table 2. When fixation stability within 2° and 4° in NPDR group was compared with that in control group (2°: 94.43 ±0.9909 vs. 84.72± 2.102, P <0.001; 4°:98.41±0.4661 vs. 95.42 ±0.9286，P <0.001), statistically significant decrease was showed. But, there was no significant difference between the NPDR group and the NDR group (2°: 87.96 ±2.386 vs. 84.72± 2.102, p=0.1801; 4°:95.75±1.11 vs. 95.42±0.9286，p=0.2526) at the level of fixation stability within 2° and 4°. Similarly, no significant difference was observed between the control group and the NDR group (2°: 94.43 ±0.9909 vs. 87.96 ±2.386, p=0.1117; 4°:98.41±0.4661 vs. 95.75±1.11， p=0.1123).

When BCEA(68.2 deg^2, 95.4 deg^2, 99.6 deg^2) in NPDR group was compared with that in the control group (68.2 deg^2: 1.000 ± 0.1172 vs. 2.058 ± 0.2659, <0.001; 95.4 deg^2: 2.692± 0.3103 vs. 5.575 ± 0.7108, p<0.001; 95.4 deg^2: 5.154 ± 0.5898 vs. 10.67 ± 1.363, p<0.001), statistically significant increases were observed. However, there was no significant difference between the NPDR group and the NDR group (68.2 deg^2: 1.792 ± 0.3197vs. 2.058 ± 0.2659, p=0.2654; 95.4 deg^2: 4.825± 0.8554 vs. 5.575 ± 0.7108, p=0.2443; 95.4 deg^2: 9.225 ± 1.637 vs. 10.67 ± 1.363, p=0.2485) at the level of BCEA. Similarly, no significant difference was observed between the control group and the NDR group (68.2 deg^2: 1.000 ± 0.1172 vs. 1.792 ± 0.3197, p=0.0934; 95.4 deg^2: 2.692± 0.3103 vs. 4.825± 0.8554, p=0.0841; 95.4 deg^2: 9.225 ± 1.637 vs. 10.67 ± 1.363, p=0.0786) .

On OCTA examination, mean value of regional MT in each group are listed in Table 3. There was no significant difference in temporal side and superior side among the there groups. The central MT in NPDR group was statistically significant thicker than that in control group(252 ± 27.03 mm vs. 277.2 ± 28.02mm, P <0.01). But no significant difference was observed in other four quadrants between the

NPDR group and the NDR group. In addition, there was no statistically significant difference in all five quadrants MT when we compared the NPDR group with the NDR group and the NDR group with the control group.

Automatically calculation of superficial and deep vessel flow density (VFD) and Foveal Avascular Zone(FAZ) in each group are listed in Table 3. The mean superficial VFD of the NPDR group was statistically significant lower than that of the control group (16.36% ± 3.328% vs. 20.07% ± 2.858%, P <0.01).However, there was no statistically significant difference at the level of superficial VFD when we compared the NPDR group with the NDR group and the NDR group with the control group. The mean deep VFD of the NPDR group was statistically significant lower than that of the control group (31.31% ± 3.442% vs. 33.61% ± 2.531%, P <0.01) and the NDR group (31.31% ± 3.442%vs. 33.38% ± 1.305%, P <0.01). There was no statistically significant difference when we compared the deep VFD between the control group and the NDR group(p=0.7788).

The mean value FAZ at the superficial capillary plexus(SCP) of the NPDR group was statistically significant larger than that of the control group (0.4779 ± 0.2249 vs. 0.33 ± 0.1103, P <0.01) and the NDR group (0.3321± 0.1121 vs. 0.33 ± 0.1103, P <0.01). But no significant statistical difference was observed in the FAZ at the SCP between the control group and the NDR group (p=0.8579). The mean value FAZ at the deep capillary plexus(DCP) of the NPDR group was statistically significant larger than that of the control group (0.6896 ± 0.2 vs. 0.5592 ± 0.1826, P <0.01) and the NDR group (0.6896 ± 0.2 vs. 0.5338 ± 0.1223, P <0.01). But no significant statistical difference was observed in the FAZ at the DCP between the control group and the NDR group (p=0.8621).

There was no significant correlation between the MS and the mean CMT, FAZ or VFD in NDR group and NPDR group (Figure 3).

Discussion

In this study, we combined OCTA and microperimetry in evaluating morphological and functional alterations in patients with and without manifestations of diabetic retinopathy. Compared with the healthy control group, the NPDR group showed significant enlargement of the FAZ and reduction in vessel flow densities of both superficial and deep capillary plexus layer. Besides, microperimetry results indicated that the NPDR group had a lower retinal light sensitivity and a less stable fixation. However, there were no statistical differences between the NDR group and the healthy control group regarding the FAZ, vessel flow densities of the superficial capillary layer and the deep capillary layer, and microperimetry outcomes.

Visual loss caused by diabetic retinopathy can be prevented by early detection and treatment of DR. Microperimetry allows a real-time mapping of light sensitivity of the macula and provides topographic information on visual function beyond visual acuity. Previous studies have reported decrease of light sensitivity in diabetic patients without DR, and in patients with diabetic macular edema.[13][14][15] We

assessed the functional alterations in NDR and NPDR group and noted a significant decrease of light sensitivity in all five quadrants of the macula area in NPDR group, and the NDR group showed a reduced light sensitivity although no significant difference was reached. Furthermore, the NPDR group showed a less stable fixation. Loss of central vision in diabetic patients occurs late with the presence of DME or in the PDR stage, and retinal structural alterations are not paralleled with patient's visual acuity.[9] Using MP-3, we got a more comprehensive understand of the visual function change of diabetic patients. Macular light sensitivity decreases with the progression of DR.

OCTA offers a rapid, non-invasive and high-resolution method to visualize various layers of the retinal vasculature, and can also detect early subtle lesions that are undetectable on funduscopy examination. Our OCTA data demonstrated a markedly enlargement of the FAZ in NPDR cohorts, which is in line with previous reports. [16][17][18]The FAZ is responsible for epicritic vision and central vision and has been reported to be larger in DR using FFA. [19][20] The enlargement of the FAZ is strongly related to capillary occlusion and retinal ischemia, which is one major pathophysiological mechanisms of DR. [16] However, accurate FAZ measurements are usually limited by the quality of FFA images.[21] OCTA believed to be more accurate than FFA to demarcate and measure the FAZ, as it is not obscured by leakages, pooling or staining from fluorescein.[22] On the other hand, data in the literature regarding the FAZ area in diabetic patients without DR are conflicting. Kim et al and some other research groups reported a noted enlargement of the FAZ in NDR group in comparison with the control group.[18][20][23] Whereas Cao et al found no significant difference in FAZ area of superficial capillary layer in diabetic patients without DR comparing with control group, which is consistent with our findings.[24] There may be various possible explanations for this discrepancy. First, the differences may be attributable to the small sample size, and the area of FAZ varies considerably between individuals in the NDR group.[25] Second, data obtained by different OCTA devices may not have good consistency due to various algorithms. Besides, one hypothesis of capillary occlusion in early stage of diabetes is the enhanced expression of ICAM-1 and temporal aggregation of leukocytes in the vessels, and this occlusion is transient and might be reversible. [26] Nonetheless, the enlargement of FAZ is a good indicator of vascular dropout, and is associated with disease progression in diabetic microvascular disease.

We noted an obvious reduction of the vessel density in the deep capillary plexus between the healthy volunteers, NDR, and NPDR group. Similarly, Dimitrova et al reported a decreased vessel densities of deep retina in patients without diabetic retinopathy. [23]This indicates that vascular alterations in deep layers may precede superficial layers in the progression of diabetic retinopathy. One postulation is that diabetic retinal ischemia can be associated with photoreceptor compromise, and ischemia at the deep capillary plexus play an important role in these outer retinal changes.[27]This finding merits further investigation by using OCTA, since conventional FFA provides little information of the deep capillary layer due to light scattering.

To the best of our knowledge, few studies have investigated morphological and functional features of diabetic patients without DR and NPDR patients simultaneously using OCTA and microperimetry. Our

study indicated confirmed that patients with early stage of diabetic retinopathy have larger FAZs, less vessel flow densities and decreased retinal sensitivities. And we discovered that the decrease of vessel density in the deep layer may precede the superficial layer.

We acknowledge some limitations to this study. This was a single-center, cross-sectional trial with a limited number of samples. And due to the algorithms of OCTA, artifacts cannot be avoided. Furthermore, this only measure the central foveal area of 3×3mm, which may be limited in detecting early microvascular changes in outer region.

In summary, the results of this study confirmed the morphological and functional alterations in NPDR, and the functional changes accord with vascular lesions, specifically the enlargement of the FAZ and reduction in vessel density. Vascular alterations in the deep layer may precede the superficial layer. It should be emphasized that OCTA and microperimetry can offer massive date that are not limited to the FAZ metrics, vessel flow density and light sensitivity, and their clinical relevance are not fully investigated. The conjunction of OCTA and microperimetry shows promises in DR patients diagnosis and treatment.

Abbreviations

diabetic retinopathy(DR) ; optical coherence tomography angiography(OCTA); Fundus fluorescein angiography(FFA) ; without diabetic retinopathy (NDR); with non-proliferative diabetic retinopathy (NPDR); best corrected visual acuity (BCVA) ; Macular thickness (MT) ; Mean sensitivity(MS);Foveal Avascular Zone(FAZ) ; bicurve ellipse area(BCEA)

Declarations

Ethics approval: All experiments were approved by the ethics committee of The Nanjing Drum Tower Hospital (No.2018KY150).

Consent for publication: All subjects give their consent for their information to be published.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors have declared no conflicts of interest.

Data availability statement: The table data used to support the findings of this study are included within the article.

Grant support: None

Authors' contributions: Dandan Zhu collected , analyzed the data and wrote the manuscript; Xun Liu designed and supervised the study. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics of participants

Parameters	control(n=24)	NDR(n=24)	NPDR(n=24)	P value
Age	51.46±0.5773	56.08±1.671	56.33±1.773	0.55
BCVA（logMAR）	0.025 ±0.009	0.05833 ±0.03557	0.2725 ± 0.0881	0.001
HbA1c	5.059±0.1051	8.058 ± 0.2837	8.504 ± 0.3440	0.002
IOP	14.26±0.2284	14.79±0.7790	15.48±0.6784	0.42

Table 2 Microperimetry Measurements in each group（3*3mm）

Parameters(mean±SD)	control	NDR	NPDR	P
Mean sensitivity				
quadrantwise				
fovea	29.16±1.37	28.56±1.381	24.86±4.233	<0.001
tempo	29.45±1.065	29.07±1.315	25.07±4.889	<0.001
superior	28.82±1.598	28.63±1.592	25.37±3.537	<0.001
nasal	29.18±1.11	28.98±1.449	24.14±5.828	<0.001
inferior	28.68±1.234	28.22±1.366	24.76±4.237	<0.001
Fixation stability				
2°（%）	94.43 ±0.9909	87.96 ±2.386	84.72± 2.102	<0.001
4°（%）	98.41±0.4661	95.75±1.11	95.42 ±0.9286	<0.001
BCEA68.2 deg2	1.000 ± 0.1172	1.792± 0.3197	2.058 ± 0.2659	0.007
BCEA95.4 deg2	2.692± 0.3103	4.825± 0.8554	5.575 ± 0.7108	0.012
BCEA99.6 deg2	5.154 ± 0.5898	9.225 ± 1.637	10.67 ± 1.363	0.009

Table 3 OCTA Measurements in each group（**3*3mm**）

Parameters(mean±SD)	control	NDR	NPDR	P
MT(mm)				
quadrantwise				
fovea	252±27.03	263.3±13.14	277.2±28.02	0.01
tempo	327.4±16.04	337.1±14.15	335.7±26.35	0.16
superior	337.3±18.68	347.6±14.12	345.3±24.86	0.12
nasal	337.2±19.87	349.6±14.38	348.2±26.92	<0.001
inferior	337.7±17.51	346.6±15.65	343.9±27.98	<0.001
FAZ SCP	0.33 ±0.1103	0.3321±0.1121	0.4779± 0.025	0.01
FAZ DCP	0.5592±0.1826	0.5338±0.1223	0.6896 ±0.2	0.01
VFD SCP	20.07 ±2.858	18.17± 2.755	16.36 ± 3.328	0.03
VFD DCP	33.61± 2.531	33.38± 1.305	31.31 ± 3.442	0.01

Figures

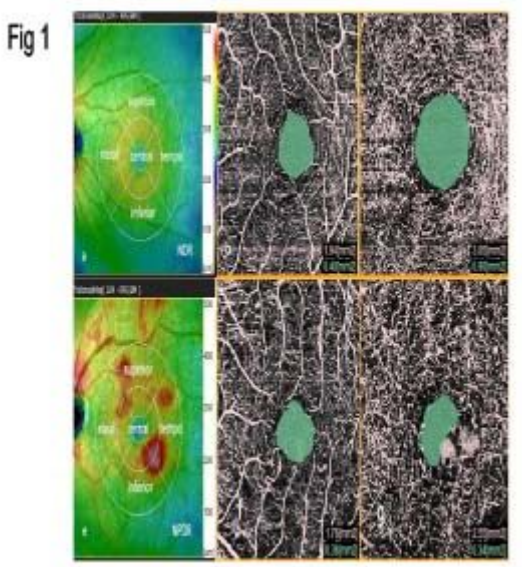

Figure 1

OCTA examination in NDR and NPDR group a: Macular thickness measurement zone division in NDR group; b: NDR superficial retinal blood flow measurement; c: NDR deep retinal blood flow measurement;e: Macular thickness measurement zone division in NPDR group;f: NPDR superficial retinal blood flow measurement; g: NPDR deep retinal blood flow measurement; the green area is foveal avascular zone

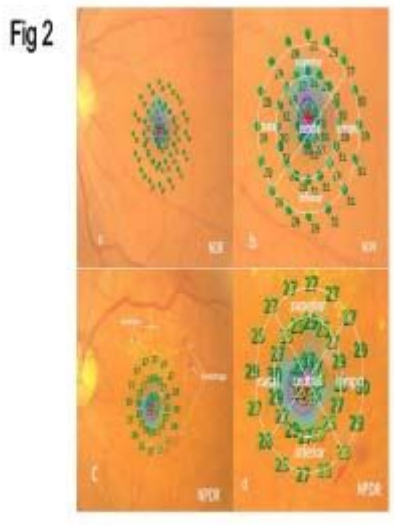

Figure 2

The retinal mean sensitivity measurement a: The retinal mean sensitivity measurement in NDR group; b: Enlarged image of NDR group after photoshoping. The 10 ° area of macular center is divided into superior quadrant, temporal quadrant, inferior quadrant, nasal quadrant and fovea area; c: The retinal mean

sensitivity measurement in NPDR group; The white arrow is retinal hemorrhage and exudation; d: Enlarged image of NPDR group after photoshoping, The 10 ° area of macular center is divided into superior quadrant, temporal quadrant, inferior quadrant, nasal quadrant and fovea area

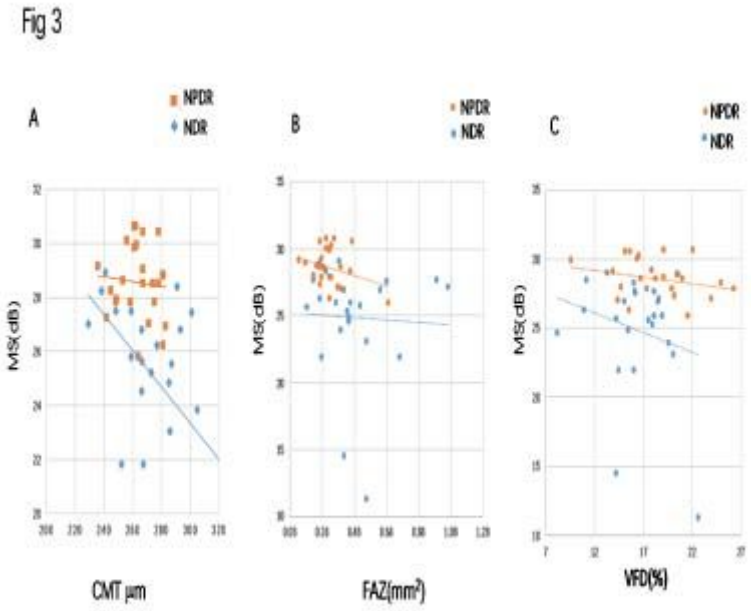

Figure 3

Correalation analysis in NDR group and NPDR group (A) MS and CMT (B)MS and FAZ(C) MS and VFD