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Serum pro-brain natriuretic peptide correlates with optical coherence tomography indices in diabetic retinopathy

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Purpose: Serum pro-brain natriuretic peptide (BNP) is a 108-amino-acid prohormone that inhibits vascular endothelial growth factor (VEGF) secretion, protecting pericytes from cell death and decreasing retinal vascularization. The purpose of this study was to investigate the correlation of serum pro-BNP with optical coherence tomography (OCT) indices in diabetic retinopathy.

Methods: This cross-sectional study investigated 96 consecutive subjects aged between 40 and 65 years: controls n = 24, no diabetic retinopathy (NoDR) n = 24, non-proliferative diabetic retinopathy (NPDR) n = 24, and proliferative diabetic retinopathy (PDR) n = 24. Same-day analysis of blood samples for serum pro-BNP levels was performed and spectral-domain OCT (SD-OCT) was used to measure the following OCT indices: OCT angiography (OCTA) superficial vessel density (SVD), deep vessel density (DVD), and foveal avascular zone (FAZ); OCT retinal nerve fiber layer (RNFL); and OCT ganglion cell analysis (GCA).

Results: The mean serum pro-BNP levels for the control, NoDR, NPDR, and PDR groups were 14.07 ± 11.51, 27.35 ± 11.81, 280.44 ± 106.13, and 122.33 ± 43.66 pg/ml, respectively. The mean values of the various OCT parameters correlated with serum pro-BNP were OCTA SVD (r = 0.360), OCTA DVD (r = 0.408), OCTA FAZ (r = 0.475), OCT RNFL (r = 0.215) and OCT GCA (r = 0.285; p<0.001).

Conclusions: The serum pro-BNP levels were higher in the NPDR group than in the NoDR group and much lower in the PDR group than in the NPDR group, reflecting a lowering of the protective barrier. These results correlated with the changes in various OCT indices.

A sight-threatening microvascular consequence of diabetes mellitus (DM) is diabetic retinopathy (DR) [1]. A strong correlation exists between the duration of diabetes and the prevalence of DR, with the incidence rising from 28.8% in individuals with diabetes for less than 5 years to 77.8% in those with diabetes for over 15 years [2].

Optical coherence tomography (OCT) is used to perform an optical biopsy of the retina [3] for the assessment of retinal diseases, while OCT angiography (OCTA) distinguishes the fine microvascular features of the retinal vasculature in the superficial and deep retinal plexus without the need for fluorescein dye [4,5].

Pre-pro-brain natriuretic peptide (BNP), a 134-amino-acid precursor secreted by cardiac myocytes in response to volume overload, is cleaved into a signal peptide (26 amino acids) and a 108-amino-acid prohormone pro-BNP [6]. Following its release into the bloodstream, pro-BNP is broken down into the physiologically active hormone BNP (77–108 amino acids) and the inactive metabolite N-terminal fragment of the pro-brain natriuretic peptide (NT pro-BNP; 1–66 amino acids) by the proteases furin and corin [7-9]. Because pro-BNP is filtered by the kidneys, unlike BNP, which is digested in the systemic circulation, plasma pro-BNP concentrations are higher than BNP concentrations. With a normal glomerular filtration rate, pro-BNP has a longer half-life and a more stable in vitro chemical structure than BNP [10], leading to slower oscillations and higher circulating levels [11]. Therefore, after blood collection, serum levels of pro-BNP remain steady, but those of BNP fluctuate. Thus, pro-BNP levels in plasma may serve as a reliable indicator of disease. In participants free of clinical cardiovascular disease, higher levels of NT pro-BNP are associated with retinal microvascular damage, suggesting a potential role for NT pro-BNP as a marker for small vessel disease [12].

The understanding, monitoring, and management of DR could be facilitated by investigating the correlation between serum pro-BNP levels and various OCT indices in DR. Hence, a tertiary care center-based study was undertaken for the first time.

Table 1. Association of the age, hemoglobin, plasma glucose and brain natriuretic peptide levels with stages of diabetic retinopathy.

Study variables		Mean ± SD	Range	P value
Age*	Control	54.5±6.1	46–67	0.051
(years)	No DR	55.0±5.4	45–63	
	NPDR	53.8±6.6	44–68	
	PDR	55.1±5.4	45–63	
HbA1c* (%)	Control	4.8±0.5	4.0–5.9	<0.001
	No DR	7. 8±0.4	7.0–8.4	
	NPDR	8.5±1.5	5.6–11.0	
	PDR	9.1±1.1	7.2–11.0	
Fasting plasma glucose* (mg/dl)	Control	91.2±21.0	66–133	<0.001
	No DR	112.8±14.8	91–140	
	NPDR	126.9±37.8	68–200	
	PDR	148.8±43.8	81–248	
2-h plasma glucose* (mg/dl; PPBS)	Control	124.9±19.5	99–167	<0.001
	No DR	166.8±20.4	141–208	
	NPDR	203.1±52.5	112–293	
	PDR	211.8±63.9	143–362	
Serum Pro BNP* (pg/ml)	Control	14.1±11.5	2.6–53.30	<0.001
	No DR	27.4±11.8	13–56.68	
	NPDR	280.4±106.1	125–450.80	
	PDR	122.3±43.6	69.31–197.95	

*ANOVA DR-Diabetic retinopathy, NPDR-Non-proliferative diabetic retinopathy, PDR-Proliferative diabetic retinopathy, BNP-Brain natriuretic peptide

METHODS

A total of 72 consecutive patients with type 2 DM and

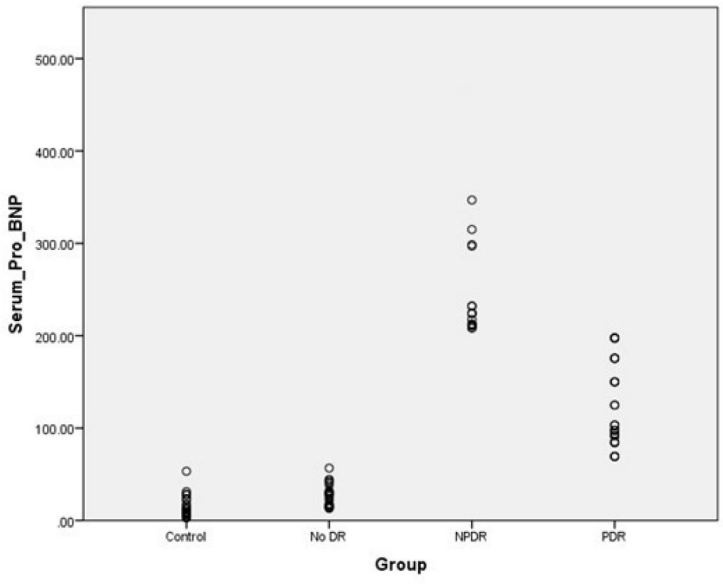

Figure 1. Serum pro-brain natriuretic peptide levels (pg/ml) in various diabetic retinopathy stages. NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy, BNP - brain natriuretic peptide.

Table 2. An association of various optical coherence tomography indices with different stages of diabetic retinopathy.

OCT indices		Mean	Range	P value
OCT Angio (FAZ) *	Control	0.25±0.04	0.189–0.320	<0.001
(%)	No DR	0.27±0.04	0.212–0.376	
	NPDR	0.39±0.06	0.299–0.550	
	PDR	0.53±0.04	0.479–0.601	
OCT Angio (Superficial vessel density) *	Control	48.73±8.55	27.46–61.36	<0.001
(%)	No DR	41.30±6.03	29.45–51.56	
	NPDR	34.62±5.96	22.56–44.57	
	PDR	26.27±6.37	17.45–48.35	
OCT Angio (Deep Vessel Density) *	Control	57.92±3.98	48–64	<0.001
(%)	No DR	55.08±3.29	50–62	
	NPDR	51.60±2.84	45–58	
	PDR	48.72±1.79	46–52	
OCT-RNFL*	Control	93.44±4.66	82–100	<0.001
(μ)	No DR	88.40±3.85	80–95	
	NPDR	87.76±3.76	81–95	
	PDR	86.56±4.43	80–96	
OCT-GCA*	Control	82.08±3.78	76–88	<0.001
(μ)	No DR	79.96±4.65	72–86	
	NPDR	77.52±3.56	71–84	
	PDR	76.40±4.01	70–82	

*ANOVA OCT-Optical coherence tomography, OCTA- OCT-angiography, FAZ-Foveal avascular zone, RNFL-Retinal nerve fiber layer, GCA-Ganglion cell analysis, DR-Diabetic retinopathy, NPDR-Non-proliferative diabetic retinopathy, PDR-Proliferative diabetic retinopathy

24 healthy controls between the ages of 40 and 65 years presenting to this tertiary care center were included. The patients were categorized into three groups based on the Early Treatment Diabetic Retinopathy Study (ETDRS) classification: no diabetic retinopathy (NoDR, n = 24), non-proliferative diabetic retinopathy (NPDR, n = 24), and proliferative diabetic retinopathy (PDR, n = 24) [13].

Approval from the institutional ethics committee was granted. The study was registered with the Trial Registry of India (ECR/262/Inst/UP/2013/RR-19) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after an explanation of the nature of the study.

The inclusion criteria were eyes with natural crystalline lenses and eyes with nuclear sclerosis up to grade 2 (LOCS III) [14]. In patients with bilateral involvement, the eye with more severe disease was included, and patients with OCT scans of signal strength exceeding 5 were included. Individuals who had previously undergone laser treatment, ocular surgery, or intravitreal injections were excluded. Furthermore, people with systemic disorders that could influence the retinal vasculature, such as chronic kidney disease, pulmonary diseases (e.g., pulmonary embolism and pulmonary hypertension), chronic obstructive pulmonary disease, essential hypertension, or cardiovascular diseases (e.g., heart failure with reduced or preserved ejection fraction, right ventricular failure, valvular heart disease, coronary artery disease, and myocardial diseases, such as left ventricular hypertrophy and myocarditis, and arrythmias) were also excluded.

The comprehensive ophthalmological workup included best corrected visual acuity assessment (logMAR BCVA), slit lamp biomicroscopy, and fundus evaluation with a +90D lens and indirect ophthalmoscopy. The diagnostic workup included OCTA superficial vessel density (SVD), deep vessel density (DVD), and foveal avascular zone (FAZ), and the OCT retinal nerve fiber layer (RNFL), and OCT ganglion cell analysis (GCA) were performed using SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditech, Inc., Dublin, CA).

The biochemical workup included collection of whole blood samples of 6–7 ml using a metal-free plastic syringe

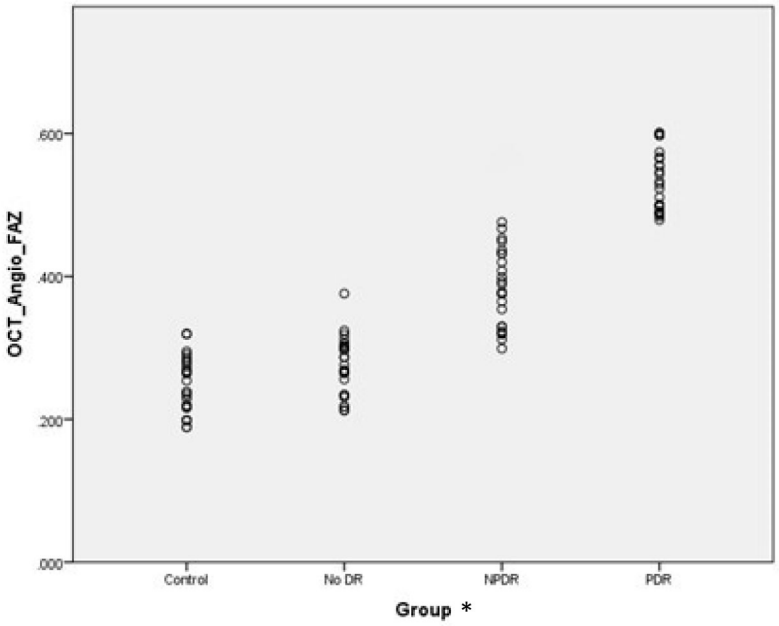

Figure 2. Foveal avascular zone values (%) on optical coherence tomography angiography in different diabetic retinopathy stages. *Control versus NPDR and PDR: significant differences, with the control having lower FAZ values. NoDR versus NPDR and PDR: significant differences, with NoDR having lower FAZ values. NPDR versus PDR: significant difference, with NPDR having lower FAZ values. OCTA - optical coherence tomography angiography, FAZ - foveal avascular zone, NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy.

and a 24-gauge stainless steel needle for aseptic venipuncture and same-day analysis of blood samples. On an autoanalyzer, the conventional technique was used (automatic biochemical analyzer) for measuring fasting blood glucose (FBS) and postprandial blood glucose (PPBS). For the glycosylated hemoglobin (HbA1c) level measurement, standard methods (mass spectroscopy and chromatographic techniques) were used. Serum pro-BNP levels were estimated on a Roche Elecsys cobas e 411 (Roche Diagnostics Limited, Basel, Switzerland) based on the test principle of electrochemiluminescence. The total duration of the assay was 18 min.

Statistical analysis: The data were analyzed using SPSS version 23 for Windows. The mean and standard deviation (±

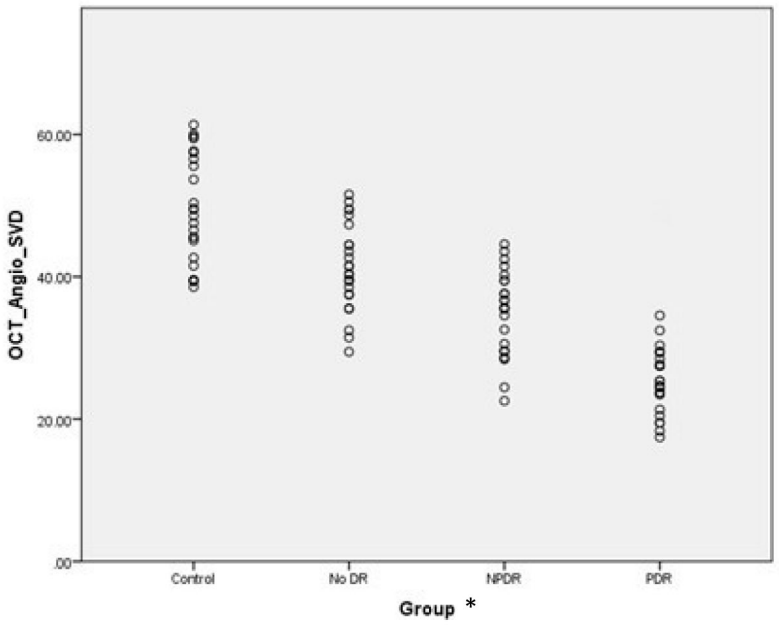

Figure 3. Superficial vessel density values (%) on optical coherence tomography angiography in different diabetic retinopathy stages. *Control versus NoDR, NPDR, and PDR: significant differences, with the control having higher vessel density. NoDR versus NPDR and PDR: significant differences, with NoDR having higher vessel density. NPDR versus PDR: significant difference, with NPDR having higher vessel density. OCTA - optical coherence tomography angiography, SVD - superficial vessel density, NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy.

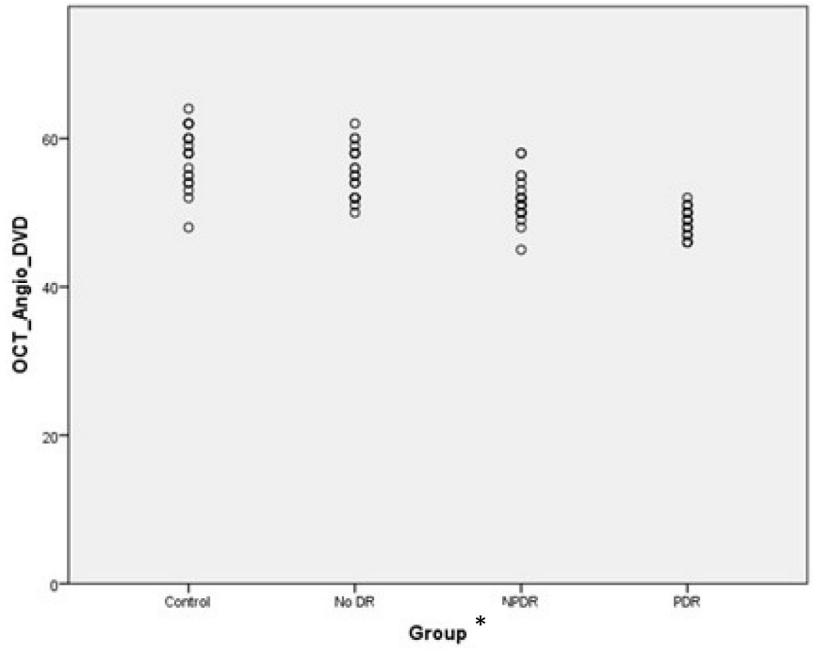

Figure 4. Deep vessel density values (%) on optical coherence tomography angiography in different diabetic retinopathy stages. *Control versus NoDR, NPDR, and PDR: significant differences, with the control having higher vessel density. NoDR versus NPDR and PDR: significant differences, with NoDR having higher vessel density. NPDR versus PDR: significant difference, with NPDR having higher vessel density. OCTA - optical coherence tomography angiography, DVD - deep vessel density, NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy.

SD) were used to describe the quantitative data with normal distributions. A one-way ANOVA was used to evaluate the differences between the groups (ANOVA). Dunnett's T3 test was used to compare the means of the study groups with the control group and with each other. The discrete (categorical) groups were compared with a chi-square ($\chi 2$) test; $p<0.05$ was considered statistically significant. A Pearson correlation analysis was used to examine the linear relationships.

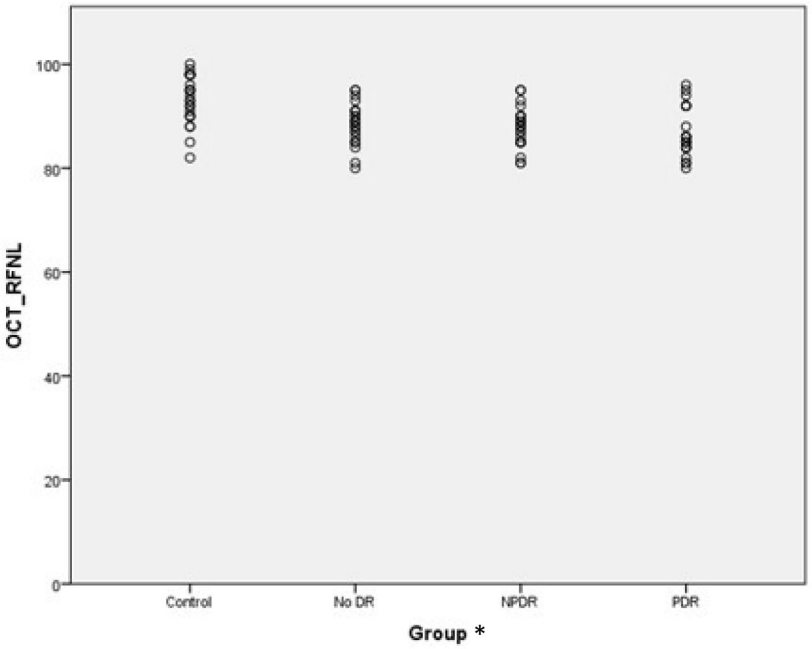

Figure 5. Retinal nerve fiber layer thickness values (μ) on optical coherence tomography in different diabetic retinopathy stages. *Control versus NoDR, NPDR, and PDR: significant differences, with the control having higher RNFL thickness. NoDR versus NPDR and PDR: no significant differences. NPDR versus PDR: no significant differences. OCT - optical coherence tomography, RNFL - retinal nerve fiber layer, NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy.

Table 3. Correlation of OCT parameters with serum pro-BNP levels.

Serum pro-BNP levels		OCTA FAZ	OCT SVD	OCTA DVD	OCT RNFL	OCT GCA
Serum Pro BNP	r value	0.475**	−0.360**	−0.408**	−0.215*	−0.285**
	P value	<0.001	<0.001	<0.001	0.032	0.004

OCT-Optical coherence tomography, OCTA- OCT-angiography, FAZ-Foveal avascular zone, RNFL-Retinal nerve fiber layer, GCA-Ganglion cell analysis, SVD- Superficial vessel density, DVD- Deep Vessel Density, BNP-Brain natriuretic peptide. **Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).

RESULTS

Table 1 shows the association of various demographic, clinical, and biochemical variables with the severity of DR. Of the 96 study subjects, 54 were male and 42 were female. No significant differences were observed in age and sex between the cases and controls (p>0.05). Various DR stages showed a statistically significant association with FBS, PPBS, HbA1c, and serum pro-BNP (p<0.001).

Figure 1 depicts the distribution of serum pro-BNP according to DR severity. Table 2 shows statistically significant correlations between different OCT indices and DR severity. The mean SVD and DVD were observed to decrease along with the RNFL and ganglion cell thinning. The mean FAZ increased with DR severity (p<0.001).

The values of various OCT indices associated with different DR stages are presented in Figure 2, Figure 3, Figure 4, Figure 5 and Figure 6. The bivariate analysis showed that serum pro-BNP had a negative correlation with the OCT indices, whereas OCTA FAZ had a positive correlation (p<0.01; Table 3). Table 4 presents a comparison of the means for all variables across the study groups with the control group as well as the comparisons between the study groups. Similarly, Table 5 shows the comparison between the means of all the values of the various OCT indices in the study groups and the control group, as well as with each other.

DISCUSSION

Our study's purpose was to gain an understanding of the relationship between OCT parameters, serum pro-BNP, and the presence of DR. New insights into the processes underlying natriuretic peptide (NP) have contributed to the acknowledgment of these peptide hormones as a significant system governing cardiovascular function, as well as the regulation of water and electrolyte balance. These substances dilate the blood arteries and intensify natriuresis and diuresis. In clinical practice, BNP, a neurohormone, is widely employed as a diagnostic and predictive biomarker for heart failure [15]. It is becoming evident that BNP can mediate peripheral vasodilation and affect fibrosis, inflammation, and oxidative

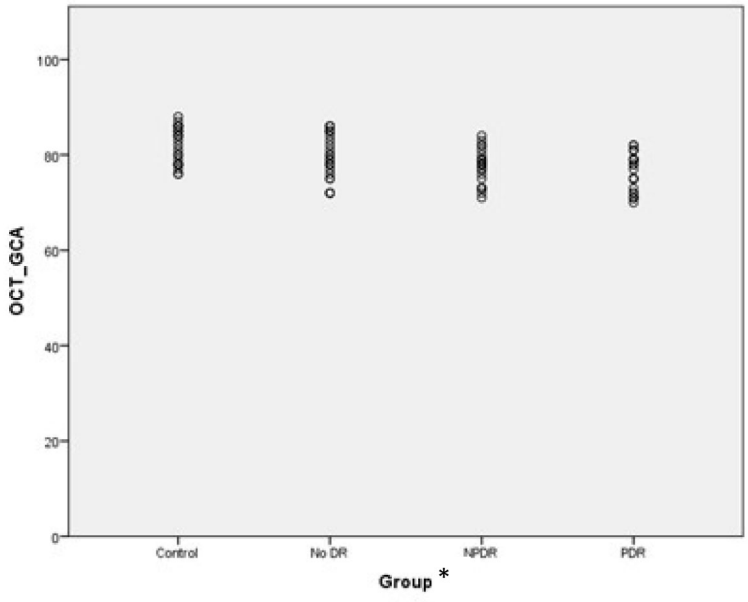

Figure 6. Ganglion cell layer analysis on optical coherence tomography (μ) in different diabetic retinopathy stages. *Control versus NPDR and PDR: significant differences, with the control having higher GCA thickness. NoDR versus PDR: significant difference, with NoDR having higher GCA thickness. NPDR versus PDR: no significant differences. OCT - optical coherence tomography, GCA - ganglion cell analysis, NoDR - no diabetic retinopathy, NPDR - non-proliferative diabetic retinopathy, PDR - proliferative diabetic retinopathy.

Table 4. Multiple Comparisons of the means for all variables across the study groups with the control group, as well as comparisons between the study groups themselves. (Dunnett T3).

Dependent variable	(I) group	(J) group	Mean difference (I-J)	Std. error	95% Confidence interval		Sig. (p-value)
					Lower bound	Upper bound	
Age	Control	No DR	-0.080	1.533	-4.28	4.12	1.000
		NPDR	1.280	1.726	-3.45	6.01	0.973
		PDR	0.560	1.641	-3.93	5.05	1.000
	No DR	Control	0.080	1.533	-4.12	4.28	1.000
		NPDR	1.360	1.716	-3.35	6.07	0.963
		PDR	0.640	1.630	-3.83	5.11	0.999
	NPDR	Control	-1.280	1.726	-6.01	3.45	0.973
		No DR	-1.360	1.716	-6.07	3.35	0.963
		PDR	-0.720	1.813	-5.69	4.25	0.999
	PDR	Control	-0.560	1.641	-5.05	3.93	1.000
		No DR	-0.640	1.630	-5.11	3.83	0.999
		NPDR	0.720	1.813	-4.25	5.69	0.999
HBA1c	Control	No DR	-2.9640*	0.1367	-3.339	-2.589	0.000*
		NPDR	-3.7000*	0.3199	-4.598	-2.802	0.000*
		PDR	-4.2880*	0.2417	-4.960	-3.616	0.000*
	No DR	Control	2.9640*	0.1367	2.589	3.339	0.000*
		NPDR	-0.7360	0.3156	-1.625	0.153	0.146
		PDR	-1.3240*	0.2360	-1.983	-0.665	0.000*
	NPDR	Control	3.7000*	0.3199	2.802	4.598	0.000
		No DR	0.7360	0.3156	-.153	1.625	0.146
		PDR	-0.5880	0.3733	-1.614	0.438	0.529
	PDR	Control	4.2880*	0.2417	3.616	4.960	0.000*
		No DR	1.3240*	0.2360	0.665	1.983	0.000*
		NPDR	0.5880	0.3733	-0.438	1.614	0.529
Fasting plasma Glucose	Control	No DR	-21.560*	5.221	-35.93	-7.19	0.001*
		NPDR	-35.630*	8.697	-59.69	-11.57	0.001*
		PDR	-57.560*	9.754	-84.67	-30.45	0.000*
	No DR	Control	21.560*	5.221	7.19	35.93	0.001*
		NPDR	-14.070	8.119	-36.79	8.65	0.426
		PDR	-36.000*	9.242	-61.96	-10.04	0.003*
	NPDR	Control	35.630*	8.697	11.57	59.69	0.001*
		No DR	14.070	8.119	-8.65	36.79	0.426
		PDR	-21.930	11.567	-53.63	9.77	0.319
	PDR	Control	57.560*	9.754	30.45	84.67	0.000*
		No DR	36.000*	9.242	10.04	61.96	0.003*
		NPDR	21.930	11.567	-9.77	53.63	0.319

Dependent variable	(I) group	(J) group	Mean difference (I-J)	Std. error	95% Confidence interval		Sig. (p-value)
					Lower bound	Upper bound	
Plasma glucose 2hr	Control	No DR	-41.88000*	5.64245	-57.3298	-26.4302	0.000*
		NPDR	-78.13880*	11.20032	-109.5208	-46.7568	0.000*
		PDR	-86.84000*	13.36195	-124.4522	-49.2278	0.000*
	No DR	Control	41.88000*	5.64245	26.4302	57.3298	0.000*
		NPDR	-36.25880*	11.26297	-67.7792	-4.7384	0.018*
		PDR	-44.96000*	13.41450	-82.6843	-7.2357	0.013*
	NPDR	Control	78.13880*	11.20032	46.7568	109.5208	0.000*
		No DR	36.25880*	11.26297	4.7384	67.7792	0.018*
		PDR	-8.70120	16.53962	-54.0540	36.6516	0.995
	PDR	Control	86.84000*	13.36195	49.2278	124.4522	0.000*
		No DR	44.96000*	13.41450	7.2357	82.6843	0.013*
		NPDR	8.70120	16.53962	-36.6516	54.0540	0.995
Serum Pro BNP	Control	No DR	-13.28000*	3.29837	-22.3110	-4.2490	0.001*
		NPDR	-266.36440*	21.35094	-327.1155	-205.6133	0.000*
		PDR	-108.25400*	9.03026	-133.7441	-82.7639	0.000*
	No DR	Control	13.28000*	3.29837	4.2490	22.3110	0.001*
		NPDR	-253.08440*	21.35768	-313.8487	-192.3201	0.000*
		PDR	-94.97400*	9.04618	-120.4972	-69.4508	0.000*
	NPDR	Control	266.36440*	21.35094	205.6133	327.1155	0.000*
		No DR	253.08440*	21.35768	192.3201	313.8487	0.000*
		PDR	158.11040*	22.95249	93.9787	222.2421	0.000*
	PDR	Control	108.25400*	9.03026	82.7639	133.7441	0.000*
		No DR	94.97400*	9.04618	69.4508	120.4972	0.000*
		NPDR	-158.11040*	22.95249	-222.2421	-93.9787	0.000*

*The mean difference is significant at the 0.05 level.

Table 5. Multiple comparisons between means of all the values of various OCT indices in study groups with the control group, as well as with each other.

Dependent variable	(I) group	(J) group	Mean Difference (I-J)	Std. error	95% Confidence interval		Sig. (p-value)
					Lower Bound	Upper Bound	
OCT Angio FAZ (%)	Control	No DR	-0.025400	0.011412	-0.05665	0.00585	0.167
		NPDR	-0.142160*	0.014687	-0.18266	-0.10166	0.000*
		PDR	-0.283240*	0.011446	-0.31458	-0.25190	0.000*
	No DR	Control	0.025400	0.011412	-0.00585	0.05665	0.167
		NPDR	-0.116760*	0.014851	-0.15767	-0.07585	0.000*
		PDR	-0.257840*	0.011656	-0.28975	-0.22593	0.000*
	NPDR	Control	0.142160*	0.014687	0.10166	0.18266	0.000*
		No DR	0.116760*	0.014851	0.07585	0.15767	0.000*
		PDR	-0.141080*	0.014877	-0.18205	-0.10011	0.000*
	PDR	Control	0.283240*	0.011446	0.25190	0.31458	0.000*
		No DR	0.257840*	0.011656	0.22593	0.28975	0.000*
		NPDR	0.141080*	0.014877	0.10011	0.18205	0.000*
OCT Angio (Superficial Vessel Density) (%)	Control	No DR	7.43560*	2.09241	1.6807	13.1905	0.006*
		NPDR	14.11240*	2.08438	8.3780	19.8468	0.000*
		PDR	22.46200*	2.13242	16.6044	28.3196	0.000*
	No DR	Control	-7.43560*	2.09241	-13.1905	-1.6807	0.006*
		NPDR	6.67680*	1.69526	2.0353	11.3183	0.002*
		PDR	15.02640*	1.75399	10.2235	19.8293	0.000*
	NPDR	Control	-14.11240*	2.08438	-19.8468	-8.3780	0.000*
		No DR	-6.67680*	1.69526	-11.3183	-2.0353	0.002*
		PDR	8.34960*	1.74440	3.5727	13.1265	0.000*
	PDR	Control	-22.46200*	2.13242	-28.3196	-16.6044	0.000*
		No DR	-15.02640*	1.75399	-19.8293	-10.2235	0.000*
		NPDR	-8.34960*	1.74440	-13.1265	-3.5727	0.000*
OCT Angio (Deep Vessel Density) (%)	Control	No DR	2.840*	1.033	0.01	5.67	0.049*
		NPDR	6.320*	0.978	3.63	9.01	0.000*
		PDR	9.200*	0.873	6.77	11.63	0.000*
	No DR	Control	-2.840*	1.033	-5.67	-0.01	0.049*
		NPDR	3.480*	0.870	1.10	5.86	0.001*
		PDR	6.360*	0.749	4.28	8.44	0.000*
	NPDR	Control	-6.320*	0.978	-9.01	-3.63	0.000*
		No DR	-3.480*	0.870	-5.86	-1.10	0.001*
		PDR	2.880*	0.672	1.03	4.73	0.001*
	PDR	Control	-9.200*	0.873	-11.63	-6.77	0.000*
		No DR	-6.360*	0.749	-8.44	-4.28	0.000*
		NPDR	-2.880*	0.672	-4.73	-1.03	0.001*

Dependent variable	(I) group	(J) group	Mean Difference (I-J)	Std. error	95% Confidence interval		Sig. (p-value)
					Lower Bound	Upper Bound	
OCT-RNFL (μ)	Control	No DR	5.040*	1.208	1.73	8.35	0.001*
		NPDR	5.680*	1.196	2.40	8.96	0.000*
		PDR	6.880*	1.286	3.36	10.40	0.000*
	No DR	Control	-5.040*	1.208	-8.35	-1.73	0.001*
		NPDR	0.640	1.076	-2.31	3.59	0.991
		PDR	1.840	1.175	-1.38	5.06	0.535
	NPDR	Control	-5.680*	1.196	-8.96	-2.40	0.000*
		No DR	-0.640	1.076	-3.59	2.31	0.991
		PDR	1.200	1.162	-1.99	4.39	0.881
	PDR	Control	-6.880*	1.286	-10.40	-3.36	0.000*
		No DR	-1.840	1.175	-5.06	1.38	0.535
		NPDR	-1.200	1.162	-4.39	1.99	0.881
OCT-GCA (μ)	Control	No DR	2.120	1.199	-1.17	5.41	0.397
		NPDR	4.560*	1.039	1.71	7.41	0.000*
		PDR	5.680*	1.103	2.66	8.70	0.000*
	No DR	Control	-2.120	1.199	-5.41	1.17	0.397
		NPDR	2.440	1.171	-0.78	5.66	0.225
		PDR	3.560*	1.228	0.19	6.93	0.033*
	NPDR	Control	-4.560*	1.039	-7.41	-1.71	0.000*
		No DR	-2.440	1.171	-5.66	0.78	0.225
		PDR	1.120	1.073	-1.82	4.06	0.875
	PDR	Control	-5.680*	1.103	-8.70	-2.66	0.000*
		No DR	-3.560*	1.228	-6.93	-0.19	0.033*
		NPDR	-1.120	1.073	-4.06	1.82	0.875

*The mean difference is significant at the 0.05 level.

stress [16]. Changes in circulating BNP levels have also been reported to contribute to diabetic microangiopathies, including diabetic nephropathy and DR [17]. Our recent study highlighted serum pro-BNP as a novel molecular biomarker for PDR [18].

The retinal microvasculature is critical for the visual function of the neural retina. In the retinal microvasculature, pericytes and endothelial cells are the two key cellular elements. Pericyte–endothelial interactions are crucial for the integrity and functionality of the retinal neurovascular unit, including vascular cells, retinal neurons, and glial cells. The equilibrium of the microvasculature requires pericyte–endothelial interactions, which are disturbed in DR. Oxidative stress and inflammation in DR can disturb the critical communication between pericytes and endothelial cells, thereby resulting in the breakdown of the blood–retinal barrier [19]. Pro-BNP and concurrent microvascular issues have been found to be significantly associated with DR [20]. Higher levels of pro-BNP have been linked to retinal microvascular damage in individuals without clinical cardiovascular illness, indicating a possible role for pro-BNP as a marker for small vessel disease [21]. The inner and outer plexiform layers of the rat retina have been found to contain atrial natriuretic peptide [22]. Additionally, transforming growth factor-β1 (TGF-β1)-induced pericyte loss has been found to be inhibited by NP signaling [23]. Improving endogenous NP/NPR-A/cGMP signaling could lead to new treatment options for retinopathies associated with neovascularization by identifying a new target for medication.

In this study, mean serum pro-BNP levels were higher in the NPDR group than in the No-DR group. The levels in the PDR group were much lower than in the NPDR group. This can be explained by the fact that BNP inhibits VEGF secretion via TGF-β1 and cyclic guanosine monophosphate signaling in pericytes and astrocytes, thereby protecting pericytes from death and decreasing retinal vascularization. VEGF suppresses NP secretion from endothelial cells, while NP reduces VEGF production [23,24]. When the proliferative DR stage occurs, BNP levels decrease, which lowers the defense mechanisms and disturbs this equilibrium [18].

Hee et al. [25] reported that OCT may be used to both objectively and subjectively track retinal thickness over time due to its high repeatability. Our study found that all OCT variables, representing neovascularization, played a significant role in the transition from the NoDR to NPDR to PDR stages. Circulating levels of pro-BNP were significantly increased in patients with DR. Retinal vascularity was reduced when blood serum pro-BNP levels were increased, as shown by a decrease in the SVD and DVD values and an increase in the FAZ mean values on OCTA. An increase in serum pro-BNP was also associated with damage to the cell body (reflected in the ganglion cell layer) and axons (reflected by the RNFL), as seen from the decreasing mean OCT RNFL and OCT GCA values.

The present study has a few limitations. It was a cross-sectional study with a small sample size. Another limitation is the lack of measurement of pro-BNP levels in the vitreous in our study groups. To the best of our knowledge, no such studies have been reported in the available literature. Investigating serum pro-BNP levels in the vitreous is a potential area for exploration in our future interventional studies, particularly for the PDR group. Since this was an observational study, no interventions were performed in the study groups. However, for the first time, this study highlighted the extent of the association of serum pro-BNP with various OCT parameters in DR to facilitate the earlier detection and management of retinal changes. It can be concluded that serum pro-BNP levels increase with increasing severity of DR and correlate well with various OCT indices.

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