UDC 617.735-005:616-008.9:617.736-003.8-053.9-06:616.379-08.64]-073.75
DOI: 10.14739/2310-1210.2025.1.313930

Metabolic disorders and their impact on retinal blood flow in patients with age-related macular degeneration and diabetes mellitus: data from optical coherence tomography angiography

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Keywords: age-related macular degeneration, insulin resistance, diabetes, metabolic disorders, metabolic syndrome, retinal plexuses, blood flow density, optical coherence tomography angiography.

Zaporozhye Medical Journal. 2025;27(1):38-43

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Aim – to examine the impact of metabolic disorders on retinal blood flow in patients with age-related macular degeneration (AMD) and diabetes mellitus using optical coherence tomography angiography (OCT-A).

Materials and methods. The study included 98 eyes (62 patients) with early dry AMD. OCT-A examinations assessed retinal blood flow density in different areas with manual segmentation to define superficial (SCP), intermediate (ICP), and deep (DCP) capillary plexuses. Laboratory tests evaluated glucose and lipid profiles and homocysteine. Morphometric measurements were also conducted: waist circumference (WC) and body mass index (BMI). Patients were grouped based on carbohydrate metabolism impairment: Group 1 (no abnormalities), Group 2 (insulin resistance (IR)), and Group 3 (type 2 diabetes mellitus (DM)).

Results. The study has identified higher glucose levels in the type 2 DM group (10.67 ± 5.11 mmol/L, p = 0.05) and elevated HOMA index in both IR (4.48 ± 2.17, p = 0.03) and diabetes groups (4.89 ± 1.13, p = 0.04). Homocysteine levels were lower in DM patients (6.36 ± 2.57 μMol/L, p = 0.02). No significant differences have been found in lipid profiles or morphometric parameters (p > 0.05). WC and BMI were strongly correlated with reduced blood flow in the SCP middle / far periphery (r = -0.747, p = 0.001). Elevated blood glucose (r = -0.606, p = 0.017) and HOMA index (r = -0.664, p = 0.013) were associated with reduced macular blood flow in the SCP macular region. Triglycerides have shown the most significant negative effect on the blood flow, especially in the SCP macular area (r = -0.883, p = 0.0001). Homocysteine and cholesterol have also been linked to reduced blood flow in the DCP, while high-density lipoprotein has been found to be protective.

Conclusions. The results suggest that glucose metabolism abnormalities, IR, and elevated lipid and homocysteine levels significantly impair retinal blood flow, particularly in the macula and peripheral regions, emphasizing the importance of metabolic control in patients with AMD and DM.

Ключові слова: вікова макулярна дегенерація, інсуліно-резистентність, цукровий діабет, метаболічні порушення, метаболічний синдром, ретинальні сплетення, щільність кровотоку, оптична когерентна томографія ангіографія.

Запорізький медичний журнал. 2025. Т. 27, № 1(148). С. 38-43

Метаболічні порушення та їхній вплив на ретинальний кровообіг у хворих на вікову макулярну дегенерацію та цукровий діабет: дані оптичної когерентної томографічної ангіографії

Н. С. Луценко, Т. С. Кирилова

Мета роботи – дослідити вплив метаболічних порушень на кровотік у сітківці пацієнтів із віковою макулярною дегенерацією (ВМД) та цукровим діабетом за допомогою оптичної когерентної томографічної ангіографії (ОКТ-А).

Матеріали і методи. До дослідження залучили 62 пацієнтів (98 очей) із ранньою сухою ВМД. Під час обстеження за допомогою ОКТ-А оцінювали щільність кровотоку сітківки в різних ділянках із ручною сегментацією, розрізняючи поверхневе (ПСС), проміжне (ПКС) і глибоке (ГКС) капілярні сплетення. Під час лабораторних досліджень визначали профілі глюкози, ліпідів і гомоцистеїну. Здійснили морфометричні вимірювання, зокрема визначили обвід талії (ОТ) та індекс маси тіла (ІМТ). Пацієнтів поділили на групи за порушеннями вуглеводного обміну: 1 група – без розладів; 2 група – хворі з інсулінорезистентністю (ІР); 3 група – пацієнти з цукровим діабетом (ЦД) 2 типу.

Результати. У результаті дослідження встановили вищі рівні глюкози в групі пацієнтів із ЦД 2 типу (10,67 ± 5,11 ммоль/л, p = 0,05) та підвищення індексу HOMA в обох групах хворих з ІР (4,48 ± 2,17, p = 0,03), а також у групах діабету (4,89 ± 1,13, p = 0,04). Рівень гомоцистеїну нижчий у хворих на ЦД (6,36 ± 2,57 мкмоль/л, p = 0,02). Не визначили суттєвих відмінностей за ліпідними профілями та морфометричними параметрами (p > 0,05). ОТ та ІМТ сильно корелюють зі зниженим кровотоком у середній / дальній периферії ПСС (r = -0,747, p = 0,001). Підвищений рівень глюкози (r = -0,606, p = 0,017) та індекс HOMA (r = -0,664, p = 0,013) зменшили кровотік у макулярній ділянці ПСС. Тригліцериди характеризувалися найістотнішим негативним впливом на кровотік, особливо в макулі ПСС (r = -0,883, p = 0,0001). Гомоцистеїн і холестерин асоційовані зі зменшенням кровообігу в ГКС, а ліпопротеїди високої щільності – захисний фактор.

Висновки. Результати дослідження дали підстави зробити висновок, що порушення метаболізму глюкози, ІР та підвищені рівні ліпідів і гомоцистеїну істотно погіршують кровообіг у сітківці, особливо в макулі та периферичних ділянках. Це підтверджує важливість метаболічного контролю в пацієнтів із ВМД і ЦД.

Age-related macular degeneration (AMD) and diabetes mellitus (DM) are among the leading causes of vision loss in the elderly population. According to the World Health Organization, AMD affects nearly 196 million people worldwide, and this number is expected to rise to 288 million by 2040 [1]. Meanwhile, diabetes mellitus (DM), which statistically affects around 9.3 % of the adult population [2], is not only a metabolic disorder but also a significant risk factor for the development of complications, including retinopathy and AMD [3,4].

The pathogenesis of AMD and diabetic retinopathy is associated with significant changes in the retinal state, including oxidative stress, inflammation, endothelial dysfunction, and alterations in retinal blood flow. In recent years, optical coherence tomography angiography (OCT-A) has become an essential tool for studying the state of retinal blood flow and visualizing vascular abnormalities. Studies have demonstrated that OCT-A can detect changes in the retinal capillary network density at early stages of diseases, that can be used for monitoring the progression of AMD and DM [5,6]. In particular, examining retinal microcirculation using this method allows for finding correlations between changes in retinal blood flow and metabolic parameters such as blood glucose and lipid levels [7].

Researchers have shown that metabolic disorders, such as dyslipidemia, play a crucial role in AMD progression. According to data published in "Retina", elevated triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol levels have been correlated to significant changes in retinal structure which could cause visual dysfunction [8]. Metabolic syndrome that includes a combination of hyperglycemia, dyslipidemia, and hypertension, is also associated with an increased risk of developing AMD, emphasizing the pathogenetic link between these conditions [9,10].

Thus, the presence of metabolic disorders can worsen the function and structure of retinal vessels, as demonstrated by some studies. For instance, it has been shown that patients with dyslipidemia and hyperglycemia had significant retinal microvascular density affections [11]. This underlines the need for further studies on the impact of metabolic disorders on the retinal blood flow state and their potential pathogenetic link to AMD.

The results of this study may be an important insight into the mechanisms underlying vision impairment in this patient population and help to develop new approaches for the prevention and treatment of these diseases.

Aim

To examine the impact of metabolic disorders on retinal blood flow in patients with age-related macular degeneration and diabetes mellitus using optical coherence tomography angiography.

Materials and methods

The study was conducted at the Municipal Nonprofit Enterprise Zaporizhzhia Regional Clinical Hospital of Zaporizhzhia Regional Council from 2019 to 2024 and included 98 eyes (62 patients) with signs of early AMD. The mean age of the subjects was 59.0 ± 8.3 years. There was no significant difference between the sexes: the number of women was 52.6 %, men – 47.4 % (p = 0.67). Metabolic disorders and the status of retinal blood flow were assessed prospectively based on the following inclusion criteria: age over 50 years; presence of ophthalmoscopic signs of early dry AMD in the absence of any other visible retinal pathology; ocular media transparency to allow for a qualitative evaluation of retinal microcirculation status. Exclusion criteria were refractive abnormalities outside the range of -3.0 D to +2.0 D and low-quality OCT-A images (scan quality score (SQ) below 7 points) due to media opacity or involuntary eye movements. The scan quality index was automatically calculated by software on a scale of 1 to 10 points, considering signal strength, image resolution, and the presence of motion artifacts.

All the studies were conducted following the principles of the Helsinki Declaration. A positive decision was also received from the local Ethics Committee. All participants in the study voluntarily submitted a written informed consent form.

To evaluate the status of retinal blood flow, all patients underwent OCT-A examinations using the AngioVue OCT-A system (RTVue XR OCT Avanti, Optovue Inc., Fremont, CA, USA) to determine blood flow density in various retinal topographic areas. For this purpose, angiograms were recorded in the Angio Retina scan mode (3 × 3 mm) with sequential manual shifting of the scanning area from the fovea to the periphery in the temporal sector. Thus, three scans were recorded, covering 1–9 mm from the fovea. Subsequently, the obtained scans were subjected to manual segmentation, focusing on three anatomical retinal vascular plexuses: the superficial capillary plexus (SCP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP). Quantitative analysis was performed using external software for medical image analysis and processing – ImageJ (National Institutes of Health). Each image was divided into 9 quadrants measuring 1 × 1 mm for a more accurate assessment. The data from the three central quadrants of each OCT-A scan were examined from the fovea to the periphery. The indicators were combined into groups based on the retinal topographic areas, where 1–3 mm corresponded to the macula, 4–6 mm – to the near periphery, and 7–9 mm – to the middle / far periphery [12].

To assess the presence of carbohydrate and lipid metabolism disorders, laboratory tests were performed for all the patients: fasting glucose level, glycated hemoglobin, calculation of the Homeostatic Model Assessment (HOMA) index, lipid profile determining triglyceride, HDL and low-density (LDL) cholesterol levels, atherogenic coefficient (AC) calculation, as well as physical examinations measuring waist circumference (WC) and body mass index (BMI).

Depending on the identified disturbances of carbohydrate metabolism, all the patients with early dry AMD were divided into three groups: Group 1 (39 eyes, 25 patients) – with no carbohydrate metabolism disturbances; Group 2 (27 eyes, 15 patients) – with concomitant insulin resistance (IR); Group 3 (32 eyes, 22 patients) – with concomitant type 2 DM.

Descriptive statistics were presented as mean ± standard deviation (M ± SD), and statistical significance was assessed using a t-test. A correlation analysis was carried out using the parametric (Pearson) test, where the results were shown in the form of a correlation coefficient r. The

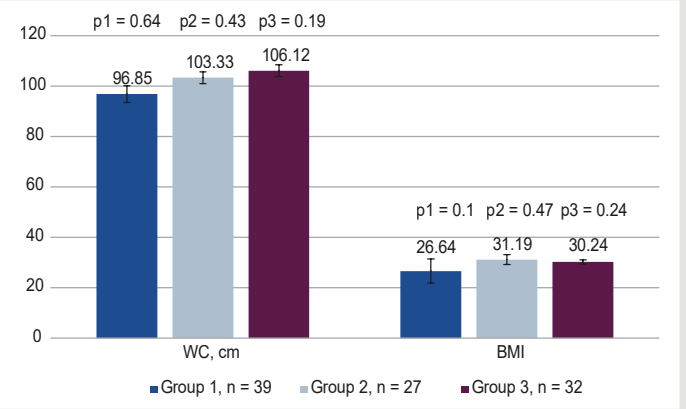

Fig. 1. Comparison of morphometric parameters across three groups.

p1: significant differences between groups 1 and 2; **p2:** significant differences between groups 2 and 3; **p3:** significant differences between groups 1 and 3.

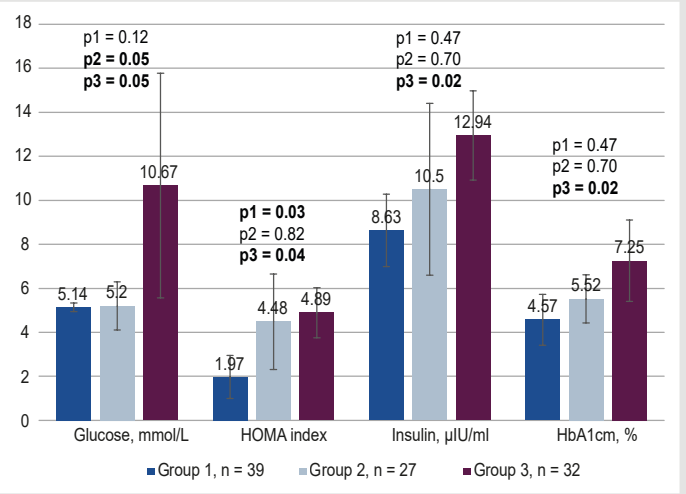

Fig. 2. Comparison of carbohydrate metabolism indicators across three groups.

p1: significant differences between groups 1 and 2; **p2:** significant differences between groups 2 and 3; **p3:** significant differences between groups 1 and 3; bold values indicate statistical significance.

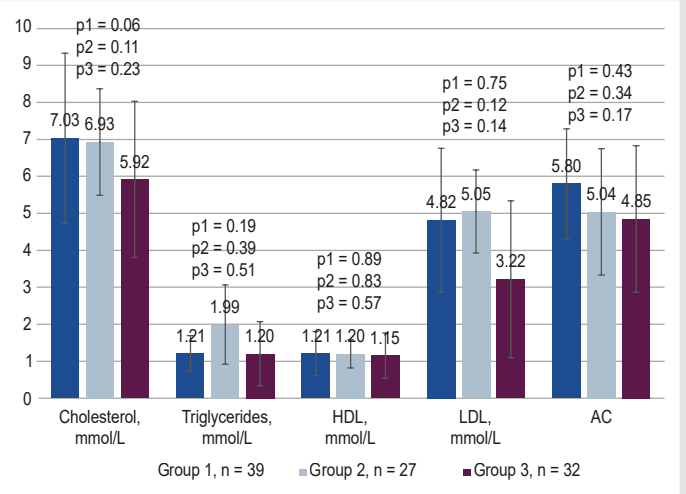

Fig. 3. Comparison of lipid profile across three groups.

p1: significant differences between groups 1 and 2; **p2:** significant differences between groups 2 and 3; **p3:** significant differences between groups 1 and 3.

statistical significance was assessed using the t-test with a level of $p < 0.05$.

Results

The analysis of morphometric parameters, which are important risk factors for metabolic disorders, has not revealed statistically significant differences between the three study groups *(Fig. 1)*.

WC parameters varied across the groups; however, no statistically significant differences have been detected ($p > 0.05$). The highest BMI was observed in IR group (31.19 ± 1.94), but no statistically significant differences have been found between the groups either ($p > 0.05$).

The analysis of carbohydrate metabolism has shown significantly higher glucose levels in patients with concomitant type 2 DM (10.67 ± 5.11 mmol/L) compared to the groups without carbohydrate metabolism disorders or with IR ($p = 0.05$) *(Fig. 2)*.

The HOMA index, used to assess IR, was significantly higher in both IR (4.48 ± 2.17) and DM groups (4.89 ± 1.13) with statistically significant differences between groups 1 and 2 ($p = 0.03$) and groups 1 and 3 ($p = 0.04$).

Insulin levels were also the highest in DM group (12.94 ± 2.03) with statistically significant differences between groups 1 and 3 ($p = 0.02$).

When evaluating homocysteine levels, a significant reduction was observed in patients with DM (6.36 ± 2.57). Statistically significant differences have been detected between groups 2 and 3 ($p = 0.02$) and groups 1 and 3 ($p = 0.04$).

The lipid profile analysis has not demonstrated statistically significant differences in total cholesterol, triglycerides, or HDL and LDL among the groups ($p > 0.05$) *(Fig. 3)*.

Table 1 presents the correlation analysis of retinal blood flow and metabolic disorders for the whole sample rather than for each individual group in order to ensure greater statistical power and significance of the results. Analyzing the whole sample has allowed to better assess the overall impact of metabolic parameters on retinal blood flow, regardless of the group-specific characteristics, considering that the mechanisms of influence may be common in all patients with AMD.

he analysis of relationships between metabolic disorders and retinal blood flow density has revealed a significant negative impact of various metabolic factors with varying effects depending on the retinal region and layers.

The most significant negative impact of WC and BMI has been observed. Increased WC was closely associated with a reduction in blood flow density in the SCP across all retinal regions with the most marked effect in the middle / far periphery ($r = -0.747$, $p = 0.001$). The trend was the same in the ICP with significant correlations observed in all the regions and the strongest effects in the near periphery ($r = -0.589$, $p = 0.021$) and macular areas ($r = -0.546$, $p = 0.035$). Although BMI has demonstrated a similar pattern, the most notable decrease in blood flow has been detected in the SCP middle/far periphery ($r = -0.625$, $p = 0.007$).

Elevated glucose levels have been shown to significantly affect blood flow density in the macular SCP ($r = -0.606$, $p = 0.017$), while correlations in other regions have not

Table 1. Association between retinal blood flow density and metabolic disorders

Parameter, units of measurement	SCP			ICP			DCP		
	Macula	Near periphery	Middle / far periphery	Macula	Near periphery	Middle / far periphery	Macula	Near periphery	Middle / far periphery
	r (n = 98)								
WC, cm	-0.546*	-0.589*	-0.747*	-0.557*	-0.547*	-0.553*	0.143	-0.101	-0.054
	p = 0.035	p = 0.021	p = 0.001	p = 0.031	p = 0.050	p = 0.032	p = 0.611	p = 0.720	p = 0.846
BMI	-0.363	-0.384	-0.625*	-0.328	-0.236	-0.441	0.253	-0.008	0.149
	p = 0.152	p = 0.128	p = 0.007	p = 0.198	p = 0.361	p = 0.076	p = 0.326	p = 0.974	p = 0.566
Glucose, mmol/L	-0.606*	-0.294	-0.170	-0.167	-0.195	-0.299	0.083	-0.106	-0.335
	p = 0.017	p = 0.287	p = 0.543	p=0.550	p = 0.485	p = 0.279	p = 0.768	p = 0.707	p = 0.221
HOMA index	-0.664*	-0.508	-0.507	0.052	-0.204	-0.498	0.180	-0.197	-0.113
	p = 0.013	p = 0.076	p = 0.077	p = 0.864	p = 0.502	p = 0.083	p = 0.556	p = 0.519	p = 0.712
Insulin, μIU/ml	-0.349	-0.323	-0.457	0.160	0.061	-0.350	0.269	0.023	0.044
	p = 0.242	p = 0.280	p = 0.116	p = 0.601	p = 0.842	p = 0.241	p = 0.373	p = 0.939	p = 0.886
HbA1c, %	-0.690*	-0.454	-0.130	-0.113	-0.297	-0.474	-0.098	-0.409	-0.526
	p = 0.013	p = 0.138	p = 0.687	p = 0.726	p = 0.348	p = 0.119	p = 0.761	p = 0.187	p = 0.079
Homocysteine, μMol/L	0.095	-0.534	-0.711*	-0.307	-0.304	0.007	-0.408	0.073	-0.382
	p = 0.792	p = 0.111	p = 0.021	p = 0.387	p = 0,393	p = 0.983	p = 0.242	p = 0.840	p = 0.275
Cholesterol, mmol/L	-0.664*	-0.1555	0.024	-0.263	-0.242	-0.501*	-0.239	-0.672*	-0.518*
	p = 0.005	p = 0.565	p = 0.930	p = 0.325	p = 0.365	p = 0.048	p = 0.372	p = 0.004	p = 0.041
Triglycerides, mmol/L	-0.883*	-0.559*	-0.295	-0.072	-0.414	-0.658*	-0.022	-0.472	-0.331
	p = 0.000	p = 0.024	p = 0.267	p = 0.790	p = 0.110	p = 0.006	p = 0.934	p = 0.065	p = 0.210
HDL, mmol/L	0.207	-0.255	-0.398	0.115	0.040	0.288	0.240	0.654*	0.580*
	p = 0.442	p = 0.339	p = 0.126	p = 0.669	p = 0.881	p = 0.278	p = 0.369	p = 0.006	p = 0.050
LDL, mmol/L	-0.510*	0.028	0.294	-0.161	-0.137	-0.392	-0.372	-0.765*	-0.518*
	p = 0.043	p = 0.916	p = 0.269	p = 0.549	p = 0.611	p = 0.133	p = 0.156	p = 0.001	p = 0.041
AC	-0.428	0.098	0.209	-0.237	-0.129	-0.409	-0.202	-0.671*	0.539*
	p = 0.097	p = 0.717	p = 0.437	p = 0.377	p = 0.633	p = 0.115	p = 0.452	p = 0.004	p = 0.047

*: statistically significant differences.

been found to be statistically significant. The HOMA index, representing IR, has shown a similar effect on the blood flow in the macular SCP (r = -0.664, p = 0.013) and the near periphery of the ICP (r = -0.508, p = 0.076), emphasizing the role of IR in impairing blood flow, particularly in the central retinal regions.

Lipid profile analysis has revealed the greatest adverse effect of triglycerides on blood flow in the macula (r = -0.883, p = 0.000) and near periphery (r = -0.559, p = 0.024) of the SCP, and the middle / far periphery (r = -0.658, p = 0.006) of the ICP, indicating their significant involvement in retinal microcirculatory dysfunction. Total cholesterol levels have also demonstrated a negative impact on blood flow density with the strongest correlations in the near periphery (r = -0.672, p = 0.004) and the middle/far periphery (r = -0.518, p = 0.041) of the DCP.

In contrast, HDL levels have shown a positive correlation with blood flow in the near periphery of the DCP (r = 0.654, p = 0.006), demonstrating a protective effect. LDL, on the contrary, has negatively impacted blood flow in the same areas with the most significant decrease observed in the near periphery of the DCP (r = -0.765, p = 0.001).

On the other hand, homocysteine levels have negatively affected blood flow predominantly in the peripheral regions with a correlation of r = -0.7113 (p = 0.021) observed in the middle / far periphery of the SCP.

The study has demonstrated the most negative impact of metabolic disorders, particularly high WC, BMI, and elevated triglycerides, on blood flow density in the SCP and ICP, especially in the peripheral retinal regions. Moreover, IR (HOMA index) and glucose have primarily affected the macular blood flow; total cholesterol and LDL have significantly negatively affected the DCP, particularly in the peripheral zones. On the contrary, HDL has been shown to be protective with regard to blood flow, particularly in the DCP.

Discussion

The results of our study have demonstrated no significant differences in morphometric parameters between the groups, although the trend toward an increase in these parameters in patients with concomitant carbohydrate metabolism disorders has been shown. It is worth noting that previous studies have also found ambiguous associations between excess body weight and both AMD and DM. In these groups, the association between obesity and retinal manifestations of these diseases has been observed, but no significant correlations with the stages of AMD or diabetic retinopathy have been noted [13,14,15]. We also have revealed strong negative correlations between WC and BMI and blood flow density, especially in the peripheral retina. All these are in good agreement with findings of other studies indicating a link between obesity and reduced retinal perfusion [16,17].

Carbohydrate metabolism parameters were predictably significantly higher in patients with type 2 DM compared to those in other groups, and the HOMA index assessing IR was markedly elevated in both IR and DM groups. It is noteworthy that glucose levels and HOMA index also substantially impacted central retinal blood flow density. Literature data suggest that prolonged hyperglycemia and IR may be associated with an increased risk of developing

AMD [4,18,19], underlining the importance of early glucose control to prevent retinal damage.

No significant differences in lipid metabolism parameters between the groups have been revealed, although lower cholesterol levels have been observed in the group with concomitant DM. This may be due to the use of lipid-lowering therapy in this group of patients. Importantly, triglyceride levels appeared to be the strongest factor influencing blood flow density in the central retina, confirming the findings of earlier studies [20]. In our study, we specifically focused on the significant negative correlations between triglyceride levels and blood flow density at distances of 1–6 mm.

The significant reduction in homocysteine levels in the group with concomitant DM is consistent with previously demonstrated research findings, which also have shown a decrease in this marker in DM patients [21]. In contrast to other parameters, homocysteine levels have been found to be significant only for microcirculation in the peripheral retina. This conclusion is consistent with results from earlier studies indicating an association between elevated homocysteine levels and reduced blood flow and may serve as a marker for vascular disease risk [22]. However, these studies have not shown any regional differences in its impact on microcirculation.

Overall, the findings of our study emphasize the importance of monitoring metabolic factors to maintain retinal health, as well as underline the need for further research aimed at examining the mechanisms through which metabolic disorders affect the retinal microcirculation. These data may have significant implications for developing new treatment and prevention strategies in the context of metabolic syndrome and DM.

Conclusions

1. The analysis of morphometric and metabolic parameters has revealed significant differences in glucose, HOMA index, insulin, and homocysteine levels between study groups, while no statistically significant differences have been found in WC, BMI, or lipid profiles.

2. The correlation analysis has shown significantly affected blood flow density in the SCP macular region ($r = -0.606$, $p = 0.017$) in type 2 DM patients with elevated glucose levels (10.67 ± 5.11 mmol/L). The HOMA index assessing IR also has shown significant correlations with the macular blood flow ($r = -0.664$, $p = 0.013$).

3. Triglyceride levels have demonstrated the most significant negative impact on the blood flow density, particularly in the SCP macular region ($r = -0.883$, $p = 0.000$) and the near periphery ($r = -0.559$, $p = 0.024$). Total cholesterol levels have also negatively affected the blood flow density, especially in the DCP peripheral region ($r = -0.672$, $p = 0.004$).

4. The correlation analysis has revealed negative impacts of homocysteine levels on the blood flow density in peripheral regions with a correlation of $r = -0.711$ ($p = 0.021$) in the SCP middle / far periphery.

Perspectives of subsequent scientific research. These findings emphasize the importance of metabolic factor monitoring for preserving retinal health and suggest the need for further studies on underlying mechanisms linking metabolic disorders to retinal microcirculation.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 24.10.2024
Після доопрацювання / Revised: 05.11.2024
Схвалено до друку / Accepted: 28.11.2024

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