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Short Communication

HOMA-IR value in predicting retinal microvascular dysfunction

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Abstract

Obesity and retinal microvasculature dysfunction are linked and impact visual acuity. The aim of this study was to determine the relationship between the HOMA-IR score and the presence of vascular dysfunction (capillary perfusion and flux index) of the optic nerve head (ONH) of the retina in obese patients and to determine its diagnostic performance to predict vascular dysfunction. A case-control study was conducted in 2022 involving individuals from obese and non-obese groups. Insulin resistance was measured using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) score using the levels of insulin and fasting glucose. Optical coherence tomography angiography (OCT-A) was performed to evaluate the flux index and capillary perfusion of ONH. The correlation between HOMA-IR, flux index, and capillary perfusion was assessed using Pearson's correlation, and the diagnostic performance of HOMA-IR, including sensitivity, specificity, and the area under the curve (AUC), was measured. Logistic regression was used to identify the association between the HOMA-IR cutoff score with the presence of retinal microvascular dysfunction. A total of 80 individuals were included from each obese and non-obese group. The HOMA-IR score showed significant negative correlations with the perfusion of the superior (p<0.001), inferior (p<0.001), and outer (p=0.008) regions of the retinal of ONH. For the flux index, the HOMA-IR score had significant negative correlations with the superior (p=0.001), inferior (p<0.001), nasal (p=0.003), and outer (p=0.035) regions of ONH of the retina. The receiver operating characteristic (ROC) curve analysis for the HOMA-IR score at a cutoff value of 5.51 demonstrated an area under the curve (AUC) of 0.819, with a 95% confidence interval (CI) ranging from 0.727 to 0.912, suggesting its effectiveness in detecting vascular dysfunction. Multivariate logistic regression revealed a significant association between the HOMA-IR cutoff score of 5.51 with capillary perfusion of the superior (p=0.005) and nasal region (p=0.043), as well as the flux index of the inferior (p=0.013) and outer (p=0.022) regions of the ONH. These findings suggest that HOMA-IR is a promising biomarker for predicting retinal microvascular dysfunction in obese patients.

Keywords: HOMA-IR, insulin resistance, flux index, capillary perfusion, biomarker

Introduction

The World Health Organization (WHO) estimated that approximately 2.2 billion people worldwide experienced vision impairment in 2023 [1]. In Indonesia, the prevalence of blindness is approximately 2.8%, as reported by the Rapid Assessment of Avoidable Blindness (RAAB) between 2013 and 2017 [2]. Notably, up to 80% of blindness cases are preventable or treatable, with a significant focus on managing conditions like retinal vascular damage [1]. Key risk factors

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contributing to retinal vascular dysfunction include obesity, age, smoking, hypercholesterolemia, and hypertension [3]. It is predicted that approximately 1.12 billion people will be living with obesity globally by 2030 [4]. In Indonesia, the National Basic Health Survey 2018 reported a sharp increase in obesity prevalence, from 14.8% in 2013 to 21.8% in 2018, with East Java province experiencing a similar rise from 8.4% to 22.37% over the same period [5]. Obesity contributes to atherosclerosis by promoting fat and plaque accumulation, leading to thickening of the intima layer in blood vessels, impairing blood flow, and causing vascular dysregulation and this could affect the retinal vascular as well [6].

Obesity is also closely linked to insulin resistance, a pathological condition in which peripheral tissues respond poorly to insulin, disrupting glucose and lipid metabolism [6]. Insulin resistance significantly contributes to arterial stiffness and exacerbates vascular dysfunction [7,8]. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a widely used method for quantifying insulin resistance and can be easily applied in clinical settings [8]. Despite the well-known impact of insulin resistance on metabolic regulation, its relationship with retinal microvascular dysfunction remains underexplored.

Given these obesity-induced vascular changes, early identification of retinal microvascular dysfunction is crucial for preventing long-term complications [6]. Advanced imaging techniques, such as optical coherence tomography angiography (OCT-A), provide non-invasive methods to assess retinal vascular health [9]. Retinal vascular dysregulation, particularly in the optic nerve head (ONH), can be evaluated using OCT-A, which provides quantitative assessments of flux index and capillary perfusion in ONH vessels [9].

To date, no studies have combined OCT-A with HOMA-IR to investigate vascular dysfunction in the ONH. The aim of this study was to evaluate HOMA-IR as a biomarker for detecting retinal microvascular dysfunction, specifically capillary perfusion and flux index across all regions (superior, inferior, temporal, nasal, and outer) of the retina, by comparing non-obese and obese patients.

Methods

Study design and setting

A case-control study was conducted at the Ophthalmology Outpatient Clinic of Dr. Saiful Anwar General Hospital in Malang, Indonesia, in 2022. Patients were selected and underwent comprehensive assessments comprising detailed history-taking (including systemic and metabolic conditions) and physical examinations to measure body height, weight, body mass index (BMI), and blood pressure. Based on BMI, patients were categorized into obese and non-obese groups for further analysis. Laboratory evaluations included fasting blood glucose (FBG), lipid profile parameters and a complete blood count. Individuals diagnosed with metabolic syndrome were excluded to ensure homogeneity of the study samples. Following laboratory assessments, all patients underwent detailed ophthalmic evaluations. These included the best corrected visual acuity (BCVA) measurement, intraocular pressure (IOP) assessment, posterior segment evaluation via direct fundoscopy, and imaging studies using optical coherence tomography (OCT) and OCT-A for structural and vascular analysis of the retina.

Sampling strategy

Based on a previous study and hospital data on obesity prevalence [10], a sample size calculation was performed to estimate the minimum required participants. The minimum sample size calculation determined that 56 patients per group were required to ensure adequate representation and statistically meaningful comparisons. Consecutive sampling was employed in the patient recruitment process.

Patients and criteria

This study included patients aged 25–54 years who provided written informed consent. Eligible patients had no history of metabolic or systemic diseases nor pre-existing significant retinal conditions. Additionally, they were required to meet the following criteria: IOP <21 mmHg, absence of posterior segment abnormalities (including retinal, macular, or ONH abnormalities),

and no refractive media anomalies. BCVA was required to have a LogMAR score of 0.0, confirming the absence of refractive media abnormalities. Laboratory tests were used to confirm the absence of metabolic syndrome, with participants showing the following normal values: fasting blood glucose (FBG) <100 mg/dL, total cholesterol <200 mg/dL, triglycerides <150 mg/dL, high-density lipoprotein (HDL) >50 mg/dL, and low-density lipoprotein (LDL) <100 mg/dL. Patients who did not adhere to the study procedures throughout its duration and those whose OCT-A results showed artifacts that could compromise the integrity of the data were excluded from the study.

Patients were then categorized into two groups based on BMI: the non-obese group (BMI 18.5–22.9 kg/m²) and the obese group (BMI >22.9 kg/m²). In addition, the non-obese group was required to have an absence of metabolic and systemic diseases, as confirmed through both physical and laboratory assessments.

Data collection

The data collection process involved a comprehensive medical history, eye-related complaints, obesity, and systemic conditions such as metabolic diseases. A detailed physical examination followed, including the measurement of blood pressure, body height, body weight, waist circumference, and BMI. Ophthalmological evaluations were performed to assess BCVA, IOP, and both anterior and posterior segments of the eye through direct fundoscopy. Retinal microvasculature analysis was conducted using OCT-A, with a focus on flux index and capillary perfusion across all retinal regions. Blood samples were collected via venipuncture, ensuring patients had fasted for 10–12 hours prior to the procedure. Approximately 10 mL of blood was drawn for laboratory analyses, which included fasting blood glucose, lipid profile, and a complete blood count.

Ophthalmology examination

The ophthalmologic examination was conducted using standardized and validated methods to assess various parameters. Visual acuity was measured with the LVRC ETDRS Sloan Letters LogMAR chart (Good-Lite, Elgin, USA) under controlled lighting conditions, ensuring consistency in measurement. IOP was measured using noncontact tonometry with the Rodenstock device (Rodenstock GmbH, Munich, Germany), adhering to proper calibration protocols to guarantee accurate readings.

Fundoscopic examination of the posterior segment was performed with an indirect Wide Lens Super Field 90D lens (Optos, Dunfermline, UK), enabling thorough visualization of the retinal and optic nerve head structures. The ONH perfusion was assessed by quantifying the flux index and capillary perfusion using the Angioplex OCT-A system (Cirrus HD OCT 5000, Carl Zeiss Meditec AG, Jena, Germany), with a scan area of 4.5 mm × 4.5 mm. The flux index, reflecting the perfusion strength of blood vessels, was calculated based on the intensity of blood flow signals in the superior, nasal, inferior, temporal, and outer regions, utilizing the AngioPlex technique and data from radial peripapillary capillaries (RPC). Capillary perfusion was quantified as a percentage of the total capillary perfusion area in the same regions, also derived from AngioPlex RPC data.

To ensure reliability and minimize artifacts, OCT-A imaging was repeated three times. The retinal nerve fiber layer (RNFL) thickness was evaluated using OCT, with one eye randomly selected from each participant to avoid selection bias and ensure representative analysis.

Biomarker assessment

The primary biomarker parameter assessed in this study was HOMA-IR, which was calculated using insulin and fasting glucose levels. Insulin concentrations were measured using the Human Insulin (INS) enzyme-linked immunosorbent assay (ELISA) kit (Elabscience, Wuhan, China). Fasting glucose levels were also measured in mmol/L units to calculate the HOMA-IR index. The calculation of the HOMA-IR index followed the standard formula: insulin (mU/L) multiplied by fasting glucose (mmol/L) divided by 22.5 [11]. This approach has been widely validated and recognized as a reliable indicator of insulin resistance in clinical and research settings [11].

Statistical analysis

Continuous variables were presented as means ± standard deviations (SD), while categorical variables were reported as frequencies with percentages. Data normality and homogeneity were assessed using the Shapiro-Wilk test. The independent Student t-test or Mann-Whitney test was used to compare the characteristics of demographics, physical examinations, and laboratory results, including HOMA-IR score and ophthalmology parameters (flux index and capillary perfusion) between obese and non-obese groups, as appropriate. The correlation between HOMA-IR, flux index, and capillary perfusion was assessed using Pearson's correlation coefficient. Receiver operating characteristic (ROC) curves were generated to assess the diagnostic performance of the tests, including the determination of cutoff points, sensitivity, specificity, and the area under the curve (AUC). Univariate and multivariate logistic regression was used to identify the association between HOMA-IR scores and retinal microvascular dysfunction (capillary perfusion and flux index). All data were analyzed using SPSS version 26 (IBM, New York, USA), and statistical significance was considered at $p<0.05$.

Results

Characteristics of the patients

A total of 160 patients were included, evenly distributed between non-obese (n=80) and obese (n=80) groups and the summary of their characteristics is presented in **Table 1**. The groups were comparable in age (38.9±8.22 vs 39.6±9.09 years) and sex distribution. Significant differences were observed in BMI (31.48±4.03 vs 21.94±0.77 kg/m^2; $p<0.001$), body weight (80.12±12.515 vs 56.93±6.187 kg; $p<0.001$), and waist circumference (94.98±8.008 vs 77.32±6.569 cm; $p<0.001$). Laboratory findings revealed higher total cholesterol (206.65±36.286 vs 176.67±20.235 mg/dL; $p<0.001$), LDL cholesterol (137.58±39.112 vs 92.3±9.03 mg/dL; $p<0.001$), and HOMA-IR score (9.32±4.75 vs 4.05±2.45; $p<0.001$) in the obese group. No significant differences were found in body height, blood pressure (systolic and diastolic), hemoglobin, fasting blood glucose, HDL cholesterol, or triglyceride levels. The BCVA results showed a LogMAR of 0.0 in both the obese and non-obese groups, which indicated no refractive media abnormalities. On the LogMAR scale, a score of 0.0 corresponds to normal vision (6/6 or 20/20).

Table 1. Characteristics of the individuals within obese and non-obese groups included in the study (n=160)

Characteristics	Groups, mean±SD		*p*-value
	Non-obese (n=80)	Obese (n=80)	
Age (year)	38.9±8.22	39.6±9.09	0.330
Sex, n (%)			0.180
Male	26 (32.5)	32 (40)	
Female	54 (67.5)	48 (60)	
Physical examination			
Body mass index (BMI) (kg/m^2)	21.94±0.77	31.48±4.03	<0.001*
Body height (cm)	161.05±7.179	159.3±7.035	0.243
Body weight (Kg)	56.93±6.187	80.12±12.515	<0.001*
Blood pressure systole (mmHg)	117.88±7.917	120.75±7.97	0.107
Blood pressure diastole (mmHg)	75.5±6.385	77.5±8.086	0.320
Waist circumference (cm)	77.32±6.569	94.98±8.008	<0.001*
Laboratory assessment			
Hemoglobin (Hb)	13.692±1.44	13.812±1.359	0.399
Fasting blood glucose (mg/dL)	91.43±12.399	98.7±28.452	0.291
Total cholesterol (mg/dL)	176.67±20.235	206.65±36.286	<0.001*
High-density lipoprotein (HDL) (mg/dL)	56.1±11.764	53.58±11.679	0.338
Low-density lipoprotein (LDL) (mg/dL)	92.3±9.03	137.58±39.112	<0.001*
Triglyceride (mg/dL)	98.1±34.766	148.3±139.387	0.084
HOMA-IR	4.05±2.45	9.32±4.75	<0.001*
Best-corrected visual acuity (BCVA)	0.0±0.0	0.0±0.0	NA

HOMA-IR: homeostatic model assessment for insulin resistance; NA: not conducted
*Statistically significant at $p<0.01$

Comparison of retinal vascular parameters between obese and non-obese groups

Comparison of ophthalmologic parameters between obese and non-obese groups revealed notable differences in capillary perfusion and flux index across regions (**Table 2**). While RNFL thickness and IOP did not differ significantly between groups, capillary perfusion was significantly reduced in the obese group across the superior (43.7±2.33% vs 45.67±2.72%; $p<0.001$), inferior (45.76±1.87% vs 47.27±1.88%; $p=0.001$), nasal (44.69±3.04% vs 46.2±2.72%; $p=0.021$), temporal (46.98±2.44% vs 48.91±2.22%; $p<0.001$), and outer region (45.64±1.33% vs 46.85±1.34%; $p<0.001$). Similarly, the flux index was lower in the obese group in the superior (0.43±0.02 vs 0.46±0.01; $p<0.001$), inferior (0.44±0.02 vs 0.45±0.01; $p=0.001$), nasal (0.45±0.04 vs 0.48±0.03; $p<0.001$), temporal (0.47±0.02 vs 0.49±0.02; $p=0.001$), and outer regions (0.44±0.04 vs 0.46±0.02; $p<0.001$) (**Table 2**).

Table 2. Comparison of ophthalmology parameters between obese and non-obese groups

Parameters	Groups, mean±SD		*p*-value
	Non-obese (n=80)	Obese (n=80)	
Retinal nerve fiber layer (RNFL) (μm)	103.95±8.60	101.50±9.82	0.102
Intraocular pressure (IOP) (mmHg)	14.09±2.65	14.66±2.50	0.930
Capillary perfusion (%)			
Superior	45.67±2.72	43.7±2.33	<0.001**
Inferior	47.27±1.88	45.76±1.87	0.001**
Nasal	46.2±2.72	44.69±3.04	0.021*
Temporal	48.91±2.22	46.98±2.44	<0.001**
Outer	46.85±1.34	45.64±1.33	<0.001**
Flux index			
Superior	0.46±0.01	0.43±0.02	<0.001**
Inferior	0.45±0.01	0.44±0.02	0.001**
Nasal	0.48±0.03	0.45±0.04	<0.001**
Temporal	0.49±0.02	0.47±0.02	0.001**
Outer	0.46±0.02	0.44±0.04	<0.001**

*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

Correlation between HOMA-IR and retinal vascular parameters

The Pearson correlation coefficients between HOMA-IR score and retinal vascular parameters for each corresponding region are presented in **Table 3**. Significant negative correlations were observed between HOMA-IR score and capillary perfusion in the superior ($p<0.001$), inferior ($p<0.001$), and outer ($p=0.008$) regions. No significant correlation was found in the nasal or temporal regions. For the flux index, significant negative correlations were noted in the superior ($p=0.001$), inferior ($p<0.001$), nasal ($p=0.003$), and outer ($p=0.035$) regions. No significant correlation was found in the temporal region (**Table 3**).

Table 3. Pearson correlation between homeostatic model assessment for insulin (HOMA-IR) and retinal vascular parameters for each corresponding region of the retina

Parameters	HOMA-IR	*r* coefficient	*p*-value
Capillary perfusion	Superior	-0.398	<0.001**
	Inferior	-0.392	<0.001**
	Nasal	-0.195	0.083
	Temporal	-0.208	0.064
	Outer	-0.295	0.008**
Flux index	Superior	-0.354	0.001**
	Inferior	-0.434	<0.001**
	Nasal	-0.325	0.003**
	Temporal	-0.196	0.082
	Outer	-0.236	0.035*

*Statistically significant at $p=0.05$
**Statistically significant at $p=0.01$

The ability of HOMA-IR to distinguish the risk of decreasing retinal microvascular dysfunction

A ROC analysis was performed to assess the prognostic ability of HOMA-IR to distinguish the risk of decreasing retinal microvascular dysfunction in obese patients. This analysis was conducted to establish the cutoff value for HOMA-IR that best predicted the changes in two parameters of retinal microvascular dysfunction (capillary perfusion and flux index). The AUC value was 0.819, indicating a strong diagnostic ability [10], with a cutoff value for HOMA-IR set at 5.51, yielding a sensitivity of 75% and a specificity of 75%. In the non-obese group, a higher proportion of subjects had a HOMA-IR <5.51, whereas in the obese group, a greater proportion of subjects had a HOMA-IR >5.51 (**Figure 1**).

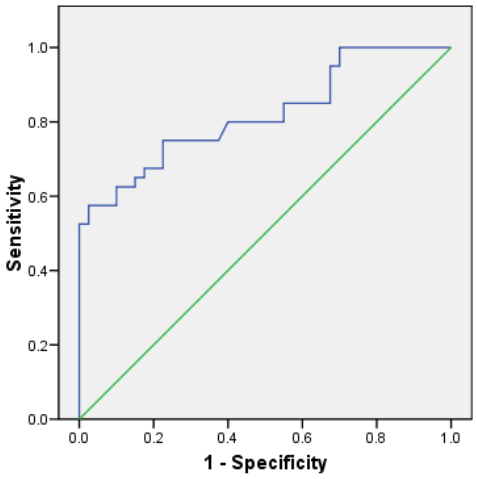

Figure 1. Receiver operating characteristic (ROC) curve of HOMA-IR as a predictor of retinal microvascular dysfunction.

Association between HOMA-IR and retinal vascular parameters

Univariate and multivariate logistic regression analyses were conducted to identify the association between HOMA-IR score cutoff 5.51 and retinal microvascular parameters (flux index and capillary perfusion), and the results are presented in **Table 4**. HOMA-IR score showed a significant association with capillary perfusion in the superior region in both univariate analysis (hazard ratio (HR)=1.247; 95%CI: 1.053–1.475; p=0.010) and multivariate analysis (HR=1.255; 95%CI: 1.072–1.469; p=0.005). The association with nasal capillary perfusion became significant after multivariate adjustment (HR=1.136; 95%CI: 1.004–1.286; p=0.043) (**Table 4**). HOMA-IR score also showed a significant association with the flux index of inferior in multivariate analysis (HR=1.262; 95%CI: 1.051–1.516; p=0.013). Similarly, the HOMA-IR score was significantly associated with the outer flux index after adjustment (HR=1.166; 95%CI: 1.023–1.329; p=0.022) (**Table 4**). These results suggested that a HOMA-IR >5.51 is associated with changes in capillary perfusion, particularly in superior and nasal regions, as well as flux index, particularly in inferior and outer regions.

Table 4. Univariate and multivariate analyses showing the association between the HOMA-IR score with a cutoff value of 5.51 and the presence of retinal microvascular dysfunction

Variable and region	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Capillary perfusion (%)				
Superior	1.247 (1.053–1.475)	0.010*	1.255 (1.072–1.469)	0.005**
Inferior	1.022 (0.824–1.266)	0.845		
Nasal	1.116 (0.973–1.281)	0.117	1.136 (1.004–1.286)	0.043*
Temporal	1.053 (0.904–1.227)	0.508		
Outer	1.079 (0.787–1.480)	0.636		
Flux index				
Superior	0.999 (0.872–1.144)	0.983		
Inferior	1.204 (0.986–1.471)	0.069	1.262 (1.051–1.516)	0.013*
Nasal	1.059 (0.938–1.197)	0.353		

Variable and region	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Temporal	0.999 (0.857–1.164)	0.987		
Outer	1.119 (0.966–1.296)	0.125	1.166 (1.023–1.329)	0.022*

*Statistically significant at p=0.05
*Statistically significant at p=0.01

Discussion

This study aimed to evaluate the HOMA-IR as a potential biomarker for retinal microvascular dysfunction by assessing its influence on capillary perfusion and flux index across all retinal quadrants (superior, inferior, temporal, nasal, and outer regions). The findings demonstrated that HOMA-IR effectively captured microvascular alterations in both non-obese and obese patients, indicating its utility in detecting early microvascular changes associated with metabolic disturbances. These results suggest that HOMA-IR could play a critical role in enhancing diagnostic approaches and guiding therapeutic strategies for obesity-related retinal complications.

The global prevalence of obesity is progressively increasing, and almost all countries face an obesity epidemic. Industrialization and urbanization have contributed to more sedentary lifestyles and diets high in fats [12]. Obesity-induced insulin resistance can lead to various metabolic problems, including diabetes, dyslipidemia, and vascular diseases. Excessive accumulation of free fatty acids (FFA) in insulin-sensitive non-adipose tissue leads to abnormal lipid deposition and lipotoxicity. In addition to chronic inflammation, oxidative stress, and mitochondrial dysfunction, lipotoxicity is a significant contributor to insulin resistance [13]. When adipose tissue grows, mitochondrial transcription decreases, impairing the tissue's ability to use glucose. Simultaneously, increased production of adipokines and decreased adiponectin levels result in systemic chronic inflammation, which can lead to degenerative diseases like heart disease and neurological disease. Adiponectin, however, has protective effects by reducing oxidative stress and lowering the risk of insulin resistance [13].

Insulin resistance develops when normal blood insulin levels are unable to lower glucose in target tissues. This dysfunction involves glucose transporter 4 (GLUT4), which is the main transporter of insulin. High insulin concentrations can reduce GLUT4 expression, causing persistent hyperglycemia and overproduction of insulin by the pancreas. HOMA-IR is a method that uses fasting glucose and plasma insulin to detect insulin resistance [13,14]. A previous study proved that there was an increase of HOMA-IR in Normal Weight Obesity (NWO), a condition where the body has an excess of fat although the BMI is normal [13]. Similarly, another study claimed that body fat had a greater impact on HOMA-IR than BMI [15]. However, according to another study, body fat has a secondary effect on HOMA-IR, while BMI has the most significant impact [14,16]. The correlation between body fat, HOMA-IR, and BMI remains unclear. This may help explain the presence of elevated insulin and HOMA-IR in healthy individuals [17]. The current study showed a significant difference in BMI and HOMA-IR between groups (p<0.001).

OCT-A is a device used to identify blood vessel damage. The condition of blood vessels can be evaluated using parameters such as flux index and capillary perfusion. Flux index provides information about a region's perfusion strength per unit area by measuring the average intensity of blood flow or red blood cells that pass through the area per unit of time, while capillary perfusion refers to the total area per unit of perfused capillaries in an area [18]. In this study, significant differences in capillary perfusion were observed between groups across the superior (p<0.001), inferior (p=0.001), nasal (p=0.021), temporal (p<0.001) and outer (p<0.001) regions. The multivariate analysis identified a significant correlation between HOMA-IR and perfusion in the superior (p=0.005) and nasal (p=0.043) regions, as presented in **Table 4**. Additionally, a significant correlation was observed between HOMA-IR and flux index in the inferior (p=0.013) and outer (p=0.022) regions. According to a previous study involving the eyes of 27 obese patients and 26 healthy individuals, there was no significant difference in the flux index and capillary perfusion between the obese and the control groups [19]. Conversely, another study revealed lower capillary perfusion and flux index in the obese group. They categorized the participants into normal weight (68 eyes), overweight (60 eyes), and obese (56 eyes) groups. The results revealed a significant decrease in the obese and overweight groups compared to the normal weight group

[25]. However, both studies found a significant correlation between BMI with flux index and capillary perfusion [19,20].

In obesity, increased adipose tissue leads to vascular dysfunction. While adiponectin synthesis is decreased, there is an increase in FFA, TNF-α, leptin, resistin, and other inflammatory factors [21]. Adiponectin stimulates endothelium-dependent vasodilation of the retinal arterioles, and adiponectin receptor (AdipoR) is expressed in the endothelial cells of the retinal arterioles [13]. A previous study reported a negative correlation between adiponectin and retinal artery vascular resistance but a positive correlation with retinal blood flow [22]. Vasodilatation and increased vascular resistance would reduce blood flow, leading to a decrease in capillary perfusion and flux index [23].

Further, a recent study conducted in 2024 found that adiponectin was correlated with cup-to-disc ratio, which may be due to the vasodilation of isolated retinal arterioles via the production of nitric oxide (NO), a powerful vasodilator of retinal arterioles, from the vascular endothelium [24]. Adiponectin receptors, found on skeletal muscle (AdipoR1) and liver cells (AdipoR2), are expressed in the vascular endothelial layer of the retinal arterioles [34]. This suggests that adiponectin may increase retinal blood flow by enhancing velocity through vasodilation of resistance vessels. However, evidence on the role of adiponectin and leptin levels as key regulators in metabolic syndrome and normal-tension glaucoma has been lacking. Overall, these results imply that endothelin-1 may counteract adiponectin-regulated retinal circulation. Further investigation is required to explore the association between endothelin-1 and adiponectin in the retinal circulation.

The difference in the nasal flux index may be attributed to variations in the Watershed Zones (WSZ), which are the boundaries between two end arteries in different distribution regions. These areas have relatively low vascularity and are highly susceptible to ischemia, making WSZs play an important role in ischemic optic neuropathy (ION) and glaucomatous optic neuropathy (GON). Conversely, some studies claim that watershed zones are primarily located in temporal regions [25,26,27]. A study explained that the disorder in the nasal region was caused by vascular dysregulation [28]. The outer optic nerve head is the Ganglion Cell Inner Plexiform Layer (GCIPL). Many studies have explained that a decrease in GCIPL thickness can be caused by chronic disorders in the eyes, such as ION [11]. In contrast, capillary perfusion often remains unaffected due to autoregulation mechanisms, which are affected by perfusion pressure, vascular resistance, and blood velocity [29]. Hence, it is still possible for capillary perfusion to remain unaffected even when the flux index is disturbed.

This study shows that higher HOMA-IR is associated with lower flux index and capillary perfusion. Insulin resistance disrupts endothelial signaling, which contributes to inflammation and imbalance of vasodilator and vasoconstrictor mechanisms. Long-term exposure will damage blood vessels throughout the body, which will reduce the flux index and capillary perfusion in the optic nerve head, as evaluated using OCT-A [24]. The methodology employed in this study is novel and addresses the gap in the existing research. This strategy successfully mitigates the issue of collinearity among independent variables, and this approach allows for more accurate identification of biomarkers associated with retinal microvascular dysfunction, which is indicated by disruptions in capillary perfusion and flux index.

This is the first study designed to determine HOMA-IR as a retinal microvasculature dysfunction predictor with comprehensive analysis. However, there are some limitations in this study. The study could not assess the duration of obesity in the respondents. Additionally, OCT-A research on the optic nerve head can only evaluate the condition of superficial blood vessels and cannot identify deeper blood vessels, thereby failing to detect disturbances in deeper vascular structures. Additionally, OCT-A is not capable of measuring blood flow velocity within the vessels.

Conclusion

HOMA-IR could serve as a biomarker for detecting retinal microvascular dysfunction, including alterations in capillary perfusion and flux index, in both non-obese and obese patients. This finding highlights the potential of HOMA-IR in identifying early microvascular changes associated with obesity and could inform future diagnostic and therapeutic strategies.

Ethics approval

The ethical clearance for this study was obtained from the Research Ethics Committee of Dr. Saiful Anwar Hospital (400/127/K.3/102.7/2022).

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Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools and methodologies in the following capacities for manuscript writing support: AI-based language models, Quillbot was employed to Language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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