ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN TUMOR NECROSIS FACTOR-ALPHA (TNF- α) WITH RETINAL NERVE FIBER LAYER (RNFL) THICKNESS IN DIABETIC RETINOPATHY PATIENTS AT PROF. CPL UNIVERSITAS SUMATERA UTARA GENERAL HOSPITAL AND AFFILIATED HOSPITAL

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ABSTRACT

Introduction: *Retinal neurodegeneration may be an early indicator of diabetic retinopathy, the second most common complication after nephropathy. Tumor Necrosis Factor-Alpha (TNF-α) plays a role in the pathogenesis of inflammatory and neovascular eye disorders and is associated with intraocular inflammatory diseases like macular edema and proliferative diabetic retinopathy. This study aims to find the relationship between TNF-α levels and Retinal Nerve Fiber Layer (RNFL) thickness in diabetic retinopathy patients at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital.*

Methods: *This cross-sectional study included 45 patients with type 2 DM and diabetic retinopathy at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital from March to June 2024. RNFL and posterior segment examinations were conducted. TNF-α levels were measured from blood samples.Blood sugar data were taken from medical records..*

Results: *Of the 45 participants, 24 were men (53.3%) and 21 women (46.7%). 32 (71.1%) had DM for >5 years, and 27 (60%) experienced PDR. Highest location for RNFL thickness examination was superior (19, 42.2%). Average TNF-α with thin RNFL was 65.67 ng/L, and with thick RNFL was 64.78 ng/L. Mean TNF-α with thin superior RNFL was 65.74 ng/L, and thick was 63.70 ng/L. Mean TNF-α with thin inferior RNFL was 65.73 ng/L, and thick was 63.9 ng/L. Mean TNF-α with thin temporal RNFL was 68.73 ng/L, and thick was 67.19 ng/L. Mean TNF-α with thick nasal RNFL was 67.06 ng/L.*

Conclusion: *There was no statistically significant relationship between TNF-α and RNFL thickness in diabetic retinopathy patients.*

Keywords: *Diabetes mellitus, diabetic retinopathy, TNF-α, RNFL layer*

INTRODUCTION

Diabetes mellitus is a common medical condition that has increased in prevalence over the past few decades, becoming a major health challenge in the twenty-first century. Complications traditionally associated with diabetes mellitus include macrovascular conditions such as coronary heart disease, stroke, and peripheral artery disease, and microvascular conditions including diabetic nephropathy, retinopathy, and peripheral neuropathy.[1]

Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus and is the leading cause of vision loss in the elderly.[2,3] In Indonesia, diabetic retinopathy is the

second most common complication after nephropathy. The overall prevalence of diabetic retinopathy is 43.1%, with sight-threatening diabetic retinopathy accounting for 26.1%.[4,5] Meanwhile, in Taiwan, the prevalence of diabetic eye disease ranges from 3.75% to 3.95%, and the prevalence of visual impairment and blindness ranges from 0.29% to 0.35% from 2005 to 2014.[2,6] In Korea, the prevalence of diabetic retinopathy increased from 14.3% in 2006 to 15.9% in 2013.[2,7] Both studies revealed that women with type 2 diabetes have a higher prevalence of diabetic retinopathy than men, but men suffer from more severe retinopathy, poor vision, or blindness. The severity of diabetic retinopathy not only impacts quality of life but also predicts all-cause, vascular, and non-cancer mortality.[2]

The early stages of diabetic retinopathy, such as non-proliferative diabetic retinopathy, may not cause severe visual impairment. Diabetic macular edema and proliferative diabetic retinopathy are collectively known as sight-threatening diabetic retinopathy. If untreated, 26.5% of the population with sight-threatening diabetic retinopathy tends to experience severe visual impairment within 1-2 years. According to the National Diabetic Retinopathy Survey, India, from 2015-2019, diabetic retinopathy occurred in 17% of patients over 50 years old. Timely diagnosis and management of diabetic retinopathy can reduce the risk of severe vision loss by up to 90%, as evaluated by the Early Treatment Diabetic Retinopathy Study (ETDRS). There is a very complex relationship between an individual's socioeconomic status and disease. Unawareness and delays by patients lead to further complications, ultimately increasing the cost of diabetic eye care.[8]

Vascular abnormalities and microvasculopathy are widely accepted factors in diabetic retinopathy. Recent research has found that neurodegeneration, which should be considered a very important component in the pathogenesis of diabetic retinopathy, correlates with microvascular dysfunction. This is supported by evidence from animal studies showing that retinal nerve cell degeneration occurs early in the course of diabetes.[9] Increasing evidence indicates that retinal neurodegeneration plays a crucial role in the pathogenesis of diabetic retinopathy. Cross-sectional studies using OCT have reported a decrease in retinal nerve fiber layer (RNFL) thickness in diabetic patients with or without mild diabetic retinopathy compared to normal controls.[10] Research conducted by Lim et al. found greater peripapillary retinal nerve fiber layer (pRNFL) loss in 103 patients with type 2 DM compared to 63 healthy individuals over 3 years, with even more pronounced reductions in patients with mild diabetic retinopathy.11 Another study by Lee et al. also found greater reductions over 3 years in 85 diabetic patients without diabetic retinopathy compared to 55 normal participants.[12]

Several cross-sectional studies have reported a decrease in RNFL thickness in diabetic patients compared to normal controls. Additionally, it has been reported that diabetic patients without signs of diabetic retinopathy have a larger RNFL, indicating that retinal neurodegeneration may be an early indicator of the development of diabetic retinopathy. In diabetic patients, various molecular pathways have been identified that may mediate retinal nerve damage.[10]

Studies have found that a significant number of inflammatory cytokines are involved in the early stages of diabetic retinopathy, and the expression of inflammatory cytokines in the retina of DM patients is significantly increased. Therefore, inflammation likely plays a crucial role in the development of diabetic retinopathy.[13]

Tumor Necrosis Factor-alpha (TNF-α) is a cytokine produced by macrophages and T-cells, with a major regulatory role in the inflammatory response. Dysregulation of TNF-α has been implicated in the pathogenesis of inflammatory, edematous, neovascular, and neurodegenerative conditions. Blocking the action of TNF-α has been used in the treatment of chronic inflammatory conditions.[14] TNF-α has been found to play a role in the pathogenesis of inflammatory and neovascular disorders in the eye. In vivo retinal injury models indicate that TNF-α plays a detrimental role in ischemia-reperfusion injury, and retinal function is partially protected by direct neutralization of this cytokine.[15]

TNF-α inhibitors are widely used in ophthalmology as off-label alternatives to traditional immunosuppressive and immunomodulatory treatments for non-infectious uveitis. Preliminary studies have shown positive effects of intravenously administered TNF-α inhibitors, especially infliximab, in treating refractory diabetic macular edema and neovascular age-related macular degeneration. Currently, many studies are focusing on the relationship between TNF-α and diabetic retinopathy. Research conducted by Roy et al. found that TNF-α is independently associated with the occurrence of proliferative diabetic retinopathy and macular edema.[13,16] Research by Hang et al. reported that TNF-α levels are significantly increased in patients with proliferative diabetic retinopathy compared to those with non-proliferative diabetic retinopathy and those without diabetic retinopathy.[13,17] Meta-analysis results indicate that TNF-α levels in the proliferative diabetic retinopathy group are higher than in the control group. When interpreting these results, the following issues should be considered. First, TNF-α can stimulate the synergistic release and proliferation of IL-6, IL-8, VEGF, and platelet-derived growth factor (PDGF). Second, TNF-α can inhibit the formation and development of retinal vascular endothelial cells, promote endothelial cell apoptosis, destroy

the normal function of the vascular wall, and affect retinal vascular permeability. Third, TNF-α can induce neovascularization in the eye.[13]

TNF-α has been shown to be associated with various intraocular inflammatory diseases, such as macular edema and proliferative diabetic retinopathy, through its actions as a pro-inflammatory cytokine. Research conducted by Yao et al. suggests that TNF-α can be used as a biomarker for diabetic retinopathy and as a potential therapeutic target.13 Based on the above background, researchers are interested in understanding the relationship between TNF-α and RNFL thickness in diabetic retinopathy patients at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital.

METHODS

RESEARCH DESIGN

This study was conducted using an observational analytic research design with data collection carried out cross-sectionally at the Vitreo-Retina Division Eye Clinic of Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital.

DATA COLLECTION

TNF-α was measured from blood samples. The ELISA (Enzyme-Linked Immunosorbent Assay) kit was used to measure TNF-α levels. RNFL was measured using Optical Coherence Tomography (OCT). This device is commonly used to assess RNFL thickness in similar studies. The research sample size was determined using the consecutive sampling method, which includes all patients visiting the eye clinic at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital. The estimated sample size for this study was calculated using the following formula:

$$n = 3 + \left[\frac{(Z\alpha + Z\beta)}{ln\, 0{,}5\left(\frac{1+r}{1-r}\right)} \right]^2$$

Figure 1. Formula to calculate sample size

n = Number of patients

α = Type I error, set at 5%

Zα = Standard value for alpha 5%, which is 1.96

β = Type II error, set at 20%

Zβ = Standard value for beta 20%, which is 0.84

r = Correlation value = 0.612 (Li and Wang, 2020)[70]

$$n = 3 + \left[\frac{1{,}96 + 0{,}84}{\ln 0{,}5\left(\frac{1+0{,}612}{1-0{,}612}\right)} \right]^2$$

$$n = 3 + \left[\frac{2{,}8}{\ln 0{,}5\left(\frac{1{,}612}{0{,}388}\right)} \right]^2$$

$$n = 3 + \left[\frac{2{,}8}{0{,}729} \right]^2$$

$$n = 17{,}7 \sim 18 \text{ sample}$$

Figure 2. Calculation of sample size

The total number of subjects required is 18, and estimating a 10% drop-out rate, the minimum number of subjects needed for this study is 20.

POPULATION AND SAMPLE

The study population consisted of all type-2 DM patients with and without diabetic retinopathy who visited the eye clinic at Prof. CPL Universitas Sumatera Utara General Hospital from March 2024 to June 2024. The research sample included a portion of type-2 DM patients with diabetic retinopathy who visited the eye clinic at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital from March 2024 to June 2024.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for the study included patients diagnosed with type 2 diabetes mellitus, those diagnosed with diabetic retinopathy, patients with clear refractive media, and those willing to participate in the study. Exclusion criteria included patients with anterior segment abnormalities, diabetic retinopathy with increased intraocular pressure, those diagnosed with any type of glaucoma or having a family history of glaucoma, patients with a history of orbital tumors, eye surgery, anti-VEGF injections, or laser therapy on the eyes.

DATA ANALYSIS

Data analysis was conducted analytically and presented in tabulated form, displaying frequency and percentage values for categorical data. Numerical data were presented by showing the mean, median, minimum, and maximum values. To analyze the relationship between TNF-α, the degree of diabetic retinopathy, and the duration of DM with Retinal Nerve Fiber Layer (RNFL) thickness, Pearson correlation test was used if the data were normally distributed. If the data were not normally distributed, the Spearman test was used. Data were considered significant if a P value of <0.05 was obtained.

RESULTS

DEMOGRAPHIC CHARACTERISTICS OF STUDY SUBJECTS

This study included 45 type-2 DM patients with diabetic retinopathy who visited the eye clinic at Prof. CPL Universitas Sumatera Utara General Hospital. All patients involved in the study met the inclusion criteria. Table 1 presents the demographic characteristics of the study subjects.

Table 1. Demographic Characteristics of Study Subjects

Demographic Characteristics	n = 45
Gender, n (%)	
Male	24 (53,3)
Female	21 (46,7)
Duration of disease course, n (%)	
≤ 5 years	13 (28,9)
6 – 10 years	16 (35,6)
> 10 years	16 (35,6)
Degree of Retinopathy, n (%)	
NPDR	18 (40)
PDR	27 (60)
Location, n (%)	
Superior	19 (42,2)
Inferior	17 (37,8)
Temporal	5 (11,1)
Nasal	4 (8,9)
RNFL thickness, n (%)	
Thinning	22 (48,9)
Thickening	23 (51,1)

The number of male patients was 24 (53.3%). Most patients had DM for more than 5 years, totaling 32 patients (71.1%). A total of 27 patients (60%) had a degree of PDR. The most common location for RNFL thickness examination was the superior region in 19 patients (42.2%), followed by the inferior region in 17 patients (37.8%).

Table 2. The Relationship Between Tumor Necrosis Factor-Alpha (TNF-α) Levels and the Degree of Diabetic Retinopathy with Retinal Nerve Fiber Layer (RNFL) Thickness in Diabetic Retinopathy Patients

	RNFL Thickness		p
	Thinning (n=22)	Thickening (n=23)	
TNF-α, ng/L			
Mean (SD)	65,87 (9,45)	64,78 (11,40)	0,729[a]
Median (Min – Max)	67,34 (50,67-87,34)	64,9 (48,07-85,9)	
Degree of Retinopathy			
NPDR	10 (55,6)	8 (44,4)	0,465[b]
PDR	12 (44,4)	15 (55,6)	

[a]*T Independent,* [b]*Chi Square*

Table 2 presents the results of the analysis of the relationship between TNF-α levels and the degree of retinopathy with RNFL thickness in all diabetic retinopathy patients in this study.

The mean TNF-α level in diabetic retinopathy patients with thin RNFL thickness was 65.87 ng/L (SD = 9.45 ng/L). Meanwhile, in diabetic retinopathy patients with thick RNFL thickness, the mean TNF-α level was 64.78 ng/L (SD = 11.4 ng/L). Using the Independent T-test, no significant relationship was found between TNF-α levels and RNFL thickness in diabetic retinopathy patients.

Among the 18 diabetic retinopathy patients with NPDR, 10 patients (55.6%) had thin RNFL thickness. Meanwhile, among the 27 retinopathy patients with PDR, 12 patients (44.4%) had thin RNFL thickness. Using the Chi-Square test, no significant relationship was found between the degree of retinopathy and RNFL thickness in diabetic retinopathy patients.

Table 3. The Relationship Between Tumor Necrosis Factor-Alpha (TNF-α) Levels and the Degree of Diabetic Retinopathy with Retinal Nerve Fiber Layer (RNFL) Thickness in Diabetic Retinopathy Patients

	Superior RNFL thickness		p
	Thinning (n=12)	Thickening (n=7)	
TNF-α, ng/L			
Mean (SD)	65,74 (9,53)	63,70 (11,03)	0,676[a]
Median (Min – Max)	67,99 (50,67-77,54)	59,89 (50,39-81,04)	
Degree of Retinopathy			
NPDR	5 (71,4)	2 (28,6)	0,656[b]
PDR	7 (58,3)	5 (41,7)	

[a]*T Independent,* [b]*Fischer's Exact*

The mean TNF-α level in diabetic retinopathy patients with thin superior RNFL thickness was 65.74 ng/L (SD = 9.53 ng/L). Meanwhile, in diabetic retinopathy patients with thick superior RNFL thickness, the mean TNF-α level was 63.70 ng/L (SD = 11.03 ng/L). Using the independent T-test, no significant relationship was found between TNF-α levels and superior RNFL thickness in diabetic retinopathy patients.

Among the 7 diabetic retinopathy patients with NPDR, 5 patients (71.4%) had thin

superior RNFL thickness. Meanwhile, among the 12 retinopathy patients with PDR, 7 patients (58.3%) had thin superior RNFL thickness. Using Fischer's Exact test, no significant relationship was found between the degree of retinopathy and superior RNFL thickness in diabetic retinopathy patients.

Table 4. The Relationship Between Tumor Necrosis Factor-Alpha (TNF-α) Levels and the Degree of Diabetic Retinopathy with Inferior Retinal Nerve Fiber Layer (RNFL) Thickness in Diabetic Retinopathy Patients

	Inferior RNFL thickness		p
	Thinning (n=9)	Thickening (n=8)	
TNF-α, ng/L			
Mean (SD)	65,73 (10,41)	63,9 (11,23)	0,662[a]
Median (Min – Max)	66,78 (55,65-87,34)	65,67 (48,07-78,99)	
Degree of Retinopathy			
NPDR	4 (66,7)	2 (33,3)	0,620[b]
PDR	5 (45,5)	6 (54,5)	

[a]*T Independent,* [b]*Fischer's Exact*

The mean TNF-α level in diabetic retinopathy patients with thin inferior RNFL thickness was 65.73 ng/L (SD = 10.41 ng/L). Meanwhile, in diabetic retinopathy patients with thick inferior RNFL thickness, the mean TNF-α level was 63.9 ng/L (SD = 11.23 ng/L). Using the Independent T-test, no significant relationship was found (p = 0.662) between TNF-α levels and inferior RNFL thickness in diabetic retinopathy patients.

Among the 6 diabetic retinopathy patients with NPDR, 4 patients (66.7%) had thin inferior RNFL thickness. Meanwhile, among the 11 retinopathy patients with PDR, 5 patients (45.5%) had thin inferior RNFL thickness. Using Fischer's Exact test, no significant relationship was found (p = 0.620) between the degree of retinopathy and inferior RNFL thickness in diabetic retinopathy patients.

Table 5. The Relationship Between Tumor Necrosis Factor-Alpha (TNF-α) Levels and the Degree of Diabetic Retinopathy with Temporal Retinal Nerve Fiber Layer (RNFL) Thickness in Diabetic Retinopathy Patients

	Temporal RNFL thickness		p
	Thinning (n=1)	Thickening (n=4)	
TNF-α, ng/L			
Mean (SD)	68,73	67,19 (16,45)	-
Median (Min – Max)	-	66,24 (50,39-85,9)	
Degree of Retinopathy			
NPDR	1 (100)	0	0,200*
PDR	0	4 (100)	

**Fischer's Exact*

Only one patient had thin temporal RNFL thickness with a TNF-α level of 68.73 ng/L. Meanwhile, four patients had thick temporal RNFL thickness with a mean TNF-α level of 67.19 ng/L (SD = 16.45 ng/L). Analysis could not be performed because only one patient had thin temporal RNFL thickness. For statistical analysis, at least two data points are required to

calculate the mean value.

One diabetic retinopathy patient with thin temporal RNFL thickness had NPDR, while all four diabetic retinopathy patients with thick temporal RNFL thickness had PDR. Using Fischer's Exact test, no significant relationship was found (p = 0.200) between the degree of retinopathy and temporal RNFL thickness in diabetic retinopathy patients.

Table 6. The Relationship Between Tumor Necrosis Factor-Alpha (TNF-α) Levels and the Degree of Diabetic Retinopathy with Nasal Retinal Nerve Fiber Layer (RNFL) Thickness in Diabetic Retinopathy Patients

	Nasal RNFL thickness		p
	Thinning (n=0)	Thickness (n=4)	
TNF-α, ng/L			
Mean (SD)	-	67,06 (11,04)	-
Median (Min – Max)	-	66,3 (57,55-78,05)	
Degree of Retinopathy			
NPDR	0	0	-
PDR	0	4 (100)	

[a]*T Independent,* [b]*Chi Square*

Among the 4 diabetic retinopathy patients with thick temporal RNFL thickness, the mean TNF-α level was 67.06 ng/L (SD = 11.04 ng/L). Based on the degree of retinopathy, all patients had PDR. Statistical analysis could not be performed due to the homogeneity of the data, as all nasal RNFL layers examined showed thick results and were associated with PDR.

DISCUSSION

The results of this study indicate that the demographic characteristics that can be found in the majority of research patients are male, this is not in accordance with several studies such as those conducted by Sentani et al[18] which stated that diabetic retinopathy sufferers are often found in female patients and in a study conducted by Novianti which stated that female patients have a greater risk of developing diabetic retinopathy.[19]

The results of this study showed that many patients had suffered from DM for 5 years, this is in accordance with research conducted by Novianti in her study which stated that patients with diabetic retinopathy on average suffered from diabetes with a time span of 5-10 years.[19] However, the results of this study do not match the research conducted by Primaputri et al, which stated that diabetic retinopathy sufferers are often found in DM sufferers with a duration of <5 years.[20]

The results of this study also showed that the distribution of RNFL thickness was often found in the superior quadrant, this is in accordance with research conducted by Mehboob et al which stated that RNFL thickness was often found in the superior quadrant in patients with a degree of retinopathy PDR.[21] This is in line with research conducted by Dwijayanti which stated

that there was a positive correlation between RNFL thickness in the superior quadrant.[22] The results of this study showed insignificant results, there was insufficient evidence to state that TNF-α levels were related to RNFL thickness in diabetic retinopathy patients in the samples studied. This is likely due to the condition of the patients in this study being patients with chronic diseases who have received treatment, which allows for suppression of the response to inflammatory stimuli, as stated in a study conducted by Swapan K. De et al.[23] This was also proven in a study conducted by Panchenko M.V et al which stated that increased levels of TNF-α can significantly occur in patients who have a strong drive to induce autoimmune retinal diseases such as autoimmune uveoretinitis.[24] This study also found no significant relationship between TNF-α levels and the level of RNFL thickness with the superior and inferior quadrants in patients with diabetic retinopathy, which is in line with a study conducted by Mehboob, which stated that the thickness of retinopathy cannot be linked regardless of the degree of diabetic retinopathy itself. These results indicate that TNF-α levels may not directly affect superior RNFL thickness in patients in this study.[21]

As for the relationship between TNF-α levels and RNFL thickness levels with the temporal and nasal quadrants, analysis could not be performed so that insignificant results were obtained, this was due to the limited research sample and the available research time. This indicates that TNF-α levels may not play a major role in determining RNFL thickness in the patients studied. Clinically, one patient with thin temporal RNFL thickness was also known to suffer from diabetic retinopathy at the Non-Proliferative Diabetic Retinopathy (NPDR) level, while the other four patients with thick temporal RNFL thickness all experienced Proliferative Diabetic Retinopathy (PDR). This suggests a potential relationship between temporal RNFL thickness and the degree of diabetic retinopathy, although it was not statistically significant in this limited sample.

This indicates the need for further research with a larger sample to confirm these results, given the possible influence of individual variation in response to changes in RNFL thickness and diabetic retinopathy. This highlights the importance of considering additional factors that may influence RNFL thickness, such as other assessments of retinal structure or biomolecular factors other than TNF-α, to obtain a more complete picture of the role of RNFL in the pathophysiology of diabetic retinopathy.

CONCLUSION

In this study, the demographic characteristics of diabetic retinopathy patients at Prof. CPL Universitas Sumatera Utara General Hospital and affiliated hospital were predominantly

male. The frequency distribution of diabetic retinopathy patients by degree in this study showed that the degree of PDR was the most frequently encountered. The duration of diabetes in diabetic retinopathy patients in this study was generally more than 5 years.

The average TNF-α levels in diabetic retinopathy patients with thin and thick RNFL did not show a significant difference (65.87 ng/L vs 64.78 ng/L). Independent T-test results indicated no significant relationship between TNF-α levels and RNFL thickness in the temporal, superior, or inferior regions in diabetic retinopathy patients. Additionally, analysis based on the degree of retinopathy (NPDR vs PDR) showed no significant relationship between the degree of retinopathy and thin RNFL thickness in the temporal, superior, and inferior regions.

Chi-Square and Fischer's Exact tests confirmed that there was no significant relationship between the degree of diabetic retinopathy and RNFL thickness in various layers. These findings suggest that RNFL thickness in diabetic retinopathy patients is not directly related to TNF-α levels or the degree of retinopathy. Differences in RNFL thickness between patients with NPDR and PDR may be influenced by other factors that need to be considered in further research, such as genetic factors, blood sugar control, or therapy use.

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