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The Effect of Ginkgo Biloba Extract on Macular Thickness in Non-Proliferative Diabetic Retinopathy Patients After Intravitreal Anti-VEGF Injections

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1. INTRODUCTION

Diabetic Retinopathy (DR) is the most serious ophthalmic complication in patients with diabetes mellitus (DM) and is the leading cause of vision loss among working-age adults.[1] According to the International Diabetes Federation (IDF), approximately 1 in 3 individuals with DM develops DR, and 10% of DM patients experience progressive vision loss.[2] In Indonesia, 1 in 4 adults with DM has vision-threatening DR, and 1 in 12 individuals with DR suffers from bilateral blindness. A study by Mahardika et al. reported that the prevalence of DR among patients with type 2 DM in Yogyakarta increased from 1.58% in 2011 to 2.86% in 2012, reflecting a growing burden of this disease.[3,4]

The intravitreal anti-VEGF are one of the standard treatments for DR. However, the treatment modalities carry potential side effects, including macular edema and further deterioration of vision.[5,6] Despite being highly effective, the intravitreal anti-VEGF is invasive and pose risks such as endophthalmitis, intraocular inflammation, retinal detachment, elevated intraocular pressure, and ocular hemorrhage. Furthermore, anti-VEGF agents can enter systemic circulation, potentially leading to hypertension, proteinuria, and increased cardiovascular risks due to VEGF inhibition.[7,8,9]

Among patients with non-proliferative diabetic retinopathy (NPDR) recieving intravitreal anti-VEGF therapy, particularly ranibizumab, progression to proliferative diabetic retinopathy (PDR) can still occur, though at a relatively low rate within 1-3 years.[10] The underlying mechanism of DR progression is closely linked to chronic inflammation and oxidative stress, with pro-inflammatory cytokines, particularly Interleukin-8 (IL-8), playing a key role.[11,12] Elevated IL-8 levels indicate an upregulated inflammatory response to oxidative stress, ultimately causing cellular structural and functional damage. In previous studies, genetic alterations in antioxidant defense mechanisms have been found to be linked to DR progression. These changes highlight oxidative stress as a central pathophysiological mechanism in disease progression.[13,14] Based on this fact, antioxidant supplementation as an adjuvant therapy may play a crucial role in mitigating oxidative stress and slowing the progression of DR.

Several nutraceuticals, phytochemicals, vitamins, and minerals with antioxidant and/or anti-inflammatory properties have been explored for their role in DR management. Among these, Ginkgo biloba (scientifically Ginkgo biloba L., pharmacologically Ginkgo folium) has gained attention for its potential therapeutic effects. Ginkgo biloba extract (EGB) is a cost-effective and therapeutically promising agent for managing uncontrolled DM. EGB improves blood hemorheology by enhancing erythrocyte deformability and blood viscosity, as well as reducing fibrinogen levels, which are crucial for blood coagulation. These changes lead to better blood perfusion, as evidenced by increased retinal capillary blood flow in DR patients.[15]

Regarding its specific effects on DR, EGB has been primarily studied in animal models, where it has been shown to disrupt VEGF regulation in diabetic conditions and alter the retinal ultrastructure in DR.[16] Additionally, some evidence suggests that oral EGB consumption for six months can significantly improve color vision acuity in patients with early-stage DR. EGB has also been reported to enhance retinal microcirculation, increasing microvascular blood flow, speed, and volume in healthy individuals.[17]

Macular thickness is consider as a crucial parameter among DR patients. This parameter reflects the presence and severity of diabetic macular edema (DME), which is one of major cause of vision loss in DR. Increased macular thickness due to fluid accumulation in DME contributes to progressive visual impairment in DR patients. However, no published research has investigated the effects of EGB as an adjuvant therapy in DR cases, particularly its impact on macular thickness. Therefore, in this present study, we aimed to investigate the potential effects of EGB on macular thickness in NPDR patients receiving anti-VEGF therapy.

2. METHODS

This study is a randomized controlled trial with a double-blind design. Subjects are divided into two groups: the treatment group, which receives intravitreal anti-VEGF with Ginkgo biloba extract, and the control group, which receives intravitreal anti-VEGF with a placebo. The inclusion criteria for this study are as follows: patients with DM who meet at least one of the 4:2:1 criteria based on fundoscopic examination, which include severe intraretinal hemorrhage and microaneurysms in all four quadrants, venous beading in two or more quadrants, and moderate intraretinal microvascular abnormality in one or more quadrants. Additionally, patients must have been diagnosed with DM by an internal medicine specialist and show macular edema as detected by optical coherence tomography (OCT). The exclusion criteria are as follows: pregnant DM patients, patients with comorbid conditions, and patients with a history of ocular trauma or increased intraocular pressure. Dropout criteria include patients who pass away due to other illnesses, patients who fail to attend scheduled follow-ups, patients who voluntarily withdraw from the study, patients requiring additional interventions, and those experiencing complications related to the intravitreal anti-VEGF injection.

Subjects included in this study are cases of severe non-proliferative diabetic retinopathy (NPDR) presenting at our institution. The process begins with a visual acuity assessment, followed by intraocular pressure (IOP) measurement using non-contact tonometry. If IOP is within normal limits, an anterior segment examination is conducted. If the anterior segment is also normal, posterior segment evaluation is performed using fundoscopy. If signs of severe non-proliferative diabetic retinopathy, such as severe intraretinal hemorrhage and microaneurysms in all four quadrants, venous beading in two or more quadrants, and moderate IRMA in one or more quadrants, are observed, OCT is conducted to assess macular thickness. Following this, the intravitreal anti-VEGF injection procedure is carried out. Follow-up is conducted every two weeks. The adjuvant treatment involves administering 80 mg EGB capsules starting from the first visit until week 16. After that, the patients continue their routine follow-up visits, with assessments of macular thickness and any other clinical observations related to the disease progression and treatment effects. Macular thickness is measured at baseline, at week 4, 8, 12, and 16 after the intervention.

3. RESULTS

A total of 40 patients participated in this study, with 20 patients in the intervention group and 20 in the control group. Patient characteristics are presented in Table 1.

Table 1. The characteristics of the study subjects.

Characteristics	Intervention (n = 20)	Control (n = 20)
Gender		
• Male	6 (30)	5 (25)
• Female	14 (70)	15 (75)
Age (years)	58.2 ± 7.79	58.1 ± 7.51
• Mean ± SD	57 (42 – 71)	58.5 (40 – 70)
• Median (min – max)		
DM duration		
• <5 years	13 (65)	16 (80)
• >5 years	7 (35)	4 (20)

Change in macular thickness before and after intervention are presented in Table 2. The analysis revealed no significant difference in macular thickness between the intervention and control groups at all time points (p>0.05).

Table 2. Macular thickness before and after the intervention

Macular thickness	Intervention	Control	p*
Pre-intervention			0.148
• Mean ± SD	323.45 ± 70.46	283.6 ± 17.95	
• Median (min – max)	290 (241 – 458)	278 (258 – 326)	
Week 4			0.552
• Mean ± SD	304.75 ± 67.71	272.2 ± 17.97	
• Median (min – max)	273 (231 – 430)	267 (250 – 314)	
Week 8			0.303
• Mean ± SD	273 ± 68.33	253.45 ± 18.4	
• Median (min – max)	235 (205 – 397)	249 (225 – 297)	
Week 12			0.144
• Mean ± SD	242.45 ± 65.09	236.4 ± 17.9	
• Median (min – max)	205 (182 – 375)	234.5 (207 – 278)	
Week 16			0.088
• Mean ± SD	199.2 ± 56.45	209.65 ± 17.77	
• Median (min – max)	164 (150 – 326)	207.5 (185 – 249)	

**Mann Whitney*

Table 3 presented the difference in macular thickness before and after the intervention at week 2, week 4, week 6, week 8, week 10, week 12, week 14, and week 16 in the intervention group. Macular thickness in subjects in the intervention group showed a progressively decreasing trend. Before the intervention, the median macular thickness was 290 µm, and it gradually decreased to a median of 164 µm by week 16 after the intervention. The Friedman test indicated a significant difference in macular thickness over time in the intervention group (p<0.001).

Table 3. The difference in macular thickness in the intervention group

Weeks	Macular Thickness (µm)	p
Pre-intervention	290 (241 – 458)	<0.001*
Week 4	273 (231 – 430)	
Week 8	235 (205 – 397)	
Week 12	205 (182 – 375)	
Week 16	164 (150 – 326)	

**Friedman*

Table 4 presented the post hoc analysis for the difference in macular thickness before and after the intervention at week 2, week 4, week 6, week 8, week 10, week 12, week 14, and week 16 in the intervention group.

Table 4. Post hoc analysis for the difference in macular thickness in the intervention group

Weeks	**p***			
	Week 4	**Week 8**	**Week 12**	**Week 16**
Pre-intervention	0.455	<0.001	<0.001	<0.001
Week 4		0.455	<0.001	<0.001
Week 8			<0.001	<0.001
Week 12				0.455

**Dunn's*

Table 5 presented the difference in macular thickness before and after the intervention at week 2, week 4, week 6, week 8, week 10, week 12, week 14, and week 16 in the control group. Macular thickness in the control group showed a progressively decreasing trend. Before the intervention, the average macular thickness was 283.6 µm, and it progressively decreased, reaching an average of 209.65 µm at the 16th week post-intervention. The Friedman test indicated that there was a significant difference in macular thickness within the control group across the observation period (p<0.001).

Table 5. The difference in macular thickness in the control group

Weeks	Macular Thickness (µm)	p*
Pre-intervention	283.6 ± 17.95	<0.001
Week 4	267 (250 – 314)	
Week 8	253.45 ± 18.4	
Week 12	236.4 ± 17.9	
Week 16	209.65 ± 17.7	

**Friedman*

Table 6 presented the post hoc analysis for the difference in macular thickness before and after the intervention at week 2, week 4, week 6, week 8, week 10, week 12, week 14, and week 16 in the control group.

Table 6. Post hoc analysis for the difference in macular thickness in the control group

Weeks	**p***			
	Week 4	**Week 8**	**Week 12**	**Week 16**
Pre-intervention	0.455	<0.001	<0.001	<0.001
Week 4		0.455	<0.001	<0.001
Week 8			<0.001	<0.001
Week 12				0.455

**Dunn's*

Table 7 showed the delta values (change in macular thickness before and after the intervention) for each study group. In the intervention group, the average delta macular thickness was 124.25 µm (SD = 24.4 µm), while in the control group, the average was 73.95 µm (SD = 6.67 µm). The Mann-Whitney test concluded that there was a significant difference in the delta macular thickness between the intervention and control groups (p < 0.001).

Table 7. Delta difference before and after intervention at week 16 between the intervention and control groups

Macular thickness	Intervention	Control	p*
Mean ± SD	124.25 ± 24.4	73.95 ± 6.67	<0.001
Median (min – max)	121 (78 – 186)	75.5 (63 – 84)	

4. DISCUSSION

Based on the participants in this study, both groups were predominantly by female, with 14 women in the intervention group and 15 women in the control group. The average age in the intervention group was 58.2 years, and in the control group, it was 58.1 years. In the intervention group, 13 participants (65%) had been living with diabetes for more than 5 years, while in the control group, 16 participants (80%) had diabetes for over 5 years. This is different from the study by Wen et al., which divided subjects into intervention and placebo groups of 44 people each. The average age in the intervention group was 60.9 years, and in the placebo group, it was 61.4 years. The average duration of diabetes in the intervention group was 10.5 years, while in the placebo group, it was 11.5 years.[18] This contrasts with the study by Rodriguez et al., which divided participants into intervention and placebo groups of 32 people each. The average age in the intervention group was 56 years, while in the placebo group, it was 56.1 years.[19]

Macular thickness measurements were taken before the intervention and at the 4th, 8th, 12th, and 16th weeks after the intervention. No significant difference in macular thickness was found between the intervention and control groups at all time points ($p>0.05$). In the intervention group, macular thickness showed a decreasing trend. Before the intervention, the median macular thickness was 290 µm, progressively decreasing to a median value of 164 µm at the 16-week follow-up. Using the Friedman test, a significant difference in macular thickness over time was observed in the intervention group ($p<0.001$). Post-hoc testing showed no significant difference between the pre-intervention thickness and the 4th-week follow-up ($p=0.455$). However, there was a significant difference in macular thickness between the pre-intervention and the 8th, 12th, and 16th-week follow-up ($p<0.001$). No significant difference in macular thickness was observed between the 4th and 8th weeks ($p=0.455$), but significant differences were found between the 4th and 12th weeks and between the 4th and 16th weeks ($p<0.001$). Similarly, no significant difference was observed between the 8th and 12th weeks ($p=0.455$), but a significant difference was found between the 8th and 16th weeks ($p<0.001$). There was no significant difference between the 12th and 16th-week observations ($p=0.445$). These findings are consistent with the study by Rodriguez et al., which showed clinical improvement in macular thickness in the left eye of the intervention group (Ginkgo biloba) after 12 months of follow-up ($p=0.016$).[19]

In the control group, macular thickness also showed a decreasing trend. The average pre-intervention macular thickness was 283.6 µm, and it progressively decreased to 209.65 µm by the 16th-week follow-up. A significant difference in macular thickness over time was found in the control group ($p<0.001$). Post-hoc testing showed no significant difference between pre-intervention and the 4th-week follow-up ($p=0.455$). However, there was a significant difference in macular thickness between pre-intervention and the 8th, 12th, and 16th-week follow-up ($p<0.001$). No significant difference was observed between the 4th and 8th weeks ($p=0.455$), but significant differences were found between the 4th and 12th weeks and between the 4th and 16th weeks ($p<0.001$). No significant difference was observed between the 8th and 12th weeks ($p=0.455$), but a significant difference was found between the 8th and 16th weeks ($p<0.001$). There was no significant difference between the 12th and 16th-week observations ($p=0.445$).

In the intervention group, the mean delta of macular thickness was 124.25 µm (SD = 24.4 µm), while in the control group, it was 73.95 µm (SD = 6.67 µm). Using the Mann-Whitney test, a significant difference in delta macular thickness was found between the intervention and control groups ($p<0.001$).

These findings are also consistent with the study by Rodriguez et al., which investigated Alzer supplementation (with Ginkgo biloba as the active ingredient). Alzer, in this study, is a potent antioxidant that works on vascular factors and oxidative damage, both of which are involved in the pathogenesis of diabetic macular edema. Clinical improvement in macular thickness was observed after the study period in patients treated with Alzer, in conjunction with nutritional supplements.[19]

5. CONCLUSION

The findings in the present study suggest the potential effect of EGB as an effective adjunctive therapy in reducing macular thickness in NPDR patients undergoing anti-VEGF treatment.

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