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ORIGINAL RESEARCH

Activated Growth Factor From Platelets as Treatment for Diabetic Retinopathy Through Antioxidant-Oxidative Stress Pathway

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Background: Reactive oxygen species (ROS) is known to play a significant role in the activation of chronic inflammatory processes in diabetic retinopathy. This study was aimed to evaluate activated growth factor (AGF) from platelet for diabetic retinopathy treatment, utilizing an in vivo investigation to regulate the antioxidant-oxidative stress pathway.

Methods: The activated growth factor was initially derived by extracting intravenous blood from the rats. Advanced glycation end products (AGEs), p38 mitogen activated protein kinase (p38 MAPK), nuclear factor-κβ (NF-κβ), reactive oxygen species (ROS), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), superoxide dismutase (SOD) and vascular endothelial growth factor (VEGF) was assessed using enzyme linked immunoassay (ELISA). In vivo, diabetic retinopathy rat models were induced by streptozotocin injection and were evaluated by retinal funduscopy.

Results: The mean diameter of the retinal artery was significantly reduced when activated growth factor with transforming growth factor-β concentration of 10 ng/mL or 100 ng/mL was administered ($p<0.05$). The retinal tissue of diabetic rats showed a decline in antioxidant activity due to oxidative stress. AGF containing TGF-β (10 ng/mL and 100 ng/mL) significantly increased SOD activity ($p<0.05$). AGF administration effectively decreased proinflammatory cytokines like TNF-α and IL-1β.

Conclusion: The study shows that AGF, with TGF-β concentrations of 10 ng/mL and 100 ng/mL, can reduce AGEs, p38MAPK, Nf-κβ, ROS, TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF in diabetic retinopathy rats' retinal tissue, while increasing antioxidant SOD concentration, suggesting AGF may help treat diabetic retinopathy by reducing inflammation and oxidative stress.

Keywords: cytokines, inflammation, reactive oxygen species, transforming growth factor

Introduction

Diabetic retinopathy is a microvascular condition caused by diabetes mellitus, which can lead to blindness.[1] The buildup of advanced glycation end products (AGEs) in the retina weakens retinal capillaries, causing blood leakage. This interaction between AGES and receptor for AGEs (RAGEs) triggers the release of reactive oxygen species (ROS), which triggers the activation of the inflammatory response cascade in the retina.[1,2] This leads to the release of pro-inflammatory cytokines like TNF-α and IL-1β. The accumulation of these cytokines triggers microglia cells to produce glutamate, matrix metalloproteinases, nitric oxide synthases, TNF-α, and IL-1β. This leads to ongoing inflammation in the retinal tissue, causing retinal edema and impaired visual function.[2,3]

Platelets are hematological elements that contribute to the process of tissue regeneration.[4] The platelets' capacity to mend tissue injury is attributed to the presence of growth factors within them.[5] Transforming growth factor-β (TGF-β), a potent growth factor, is predominantly present in platelets.[6] Activated growth factor from platelets is a more

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sophisticated method of platelet-rich plasma (PRP). PRP specifically involves the isolation of platelets from the blood, which are then directly given to the tissue.[7] In contrast, activated platelet growth factor requires a separate technique to activate the growth factor from the platelets.

TGF-β is a growth factor that functions as an anti-inflammatory cytokine and stimulates the activation of antioxidants. Antioxidants are substances and proteins that have the ability to counteract the effects of oxidants, such as reactive oxygen species (ROS).[8] It is believed that TGF-β has the capacity to activate antioxidant activity, which may decrease the activity of reactive oxygen species (ROS).[9] ROS is known to play a significant role in the activation of chronic inflammatory processes.[10] It is hypothesized that suppressing chronic inflammatory processes may reduce the progression of retinal tissue damage in diabetic retinopathy. The study aims to evaluate activated growth factor from platelet for diabetic retinopathy treatment, utilizing an in vivo investigation to regulate the antioxidant-oxidative stress pathway.

Materials and Methods

Ethical Approval

All rat experiments in this study were approved by Animal Care and Ethics Committee at Faculty of Medicine, Universitas Sriwijaya, Indonesia (Reference number: 257/2023) and the animals were treated in accordance with the National Institute of Health and Nutrition Guidelines for the care and use of laboratory.

Reagents

AGEs (catalogue no: abx150316, Abbexa, Cambridge, UK), p38 mitogen activated protein kinase (p38 MAPK) (catalogue no: KHO0061, ThermoFisher Scientific, Singapore, Singapore), nuclear factor-κβ (NF-κβ) (catalogue no: 85–86,081-11, ThermoFisher Scientific, Singapore, Singapore), ROS (catalogue no: 88–5930-74, ThermoFisher Scientific, Singapore, Singapore), TNF-α (catalogue no: E-EL-R2856, Elabscience, Texas, US), IL-1β (catalogue no: 900-K91K, ThermoFisher Scientific, Singapore, Singapore), VCAM-1 (catalogue no: E-EL-R1061, Elabscience, Texas, US), ICAM-1(catalogue no: E-EL-H6114, Elabscience, Texas, US), and VEGF ELISA kit (catalogue no: ERVEGFA, ThermoFisher Scientific, Singapore, Singapore)) were utilized in this research. Streptozotocin (STZ) was obtained from Sigma Aldrich (Singapore) and prepared in 10 mm sodium citrate buffer with a pH of 4.5.

Diabetic Retinopathy Model

Thirty two Wistar rats (*Rattus norvegicus*) were purchased from Eureka Research Laboratory (Indonesia). They were housed in a controlled environment with a 12:12-hour light-dark cycle, provided with standard rodent diet and water, and acclimatized for at least three days before experiment. All animals randomly divided into four groups, with eight animals in each group; (1) control group; (2) group with diabetic retinopathy (DR); (3) DR group with activated growth factor (AGF) containing TGF-β concentration of 10 ng/mL; (4) DR group with AGF containing TGF-β concentration of 100 ng/mL. Rats in groups 2, 3, and 4 underwent intravenous injection of streptozotocin (STZ) (Sigma-Aldrich, Singapore) at a dosage of 60 mg/kg BW to induce diabetes. On the other hand, rats in group 1 were only administered intravenous injections of sodium citrate buffer, matching the drugs volume of the treatment group. Blood glucose levels were measured three days after induction using a glucose meter (Roche Diagnostics, Tokyo, Japan) by extracting blood from the tail vein. Serum glucose levels were tested by the colorimetric method with the Pars Azmoon assay kit (Pars Azmoon Co., Tehran, Iran). We conducted the examination in accordance with the manufacturer's instructions. Diabetes mellitus was successfully induced in groups 2, 3, and 4. For the next six weeks, the rats in group 2, 3 and 4 were given 40% dextrose solution. Retinal fundoscopy were conducted after six weeks to assess the macroscopic vascular appearance of the retinal tissue. The diameter of retinal blood vessels in treatment groups were increased, indicating an effective induction of diabetic retinopathy. The duration of experimental procedure was from December 2023- June 2024.

Retinal Fundus Examination

The animals were initially sedated by intraperitoneal injections of a combination containing 100 mg/kg of ketamine and 10 mg/kg of xylazine. Next, the animal's eye attempts to provide tropicamide 1% in order to dilate the pupil. A Nikon

camera (Nikon, Tokyo, Japan) was used with a 90D lens to capture the photograph. It was subsequently mounted on a 16x-enlarged slit lamp and positioned in front of the animal's eyes. The cornea is moisturized using a solution containing 0.7% hydroxypropyl methyl cellulose. Three independent observers randomly picked the retina for evaluation. The mean values were determined from three measurements of the retinal blood vessel diameter.

Production of Activated Growth Factor From Platelets

The activated growth factor was initially derived by extracting intravenous blood from the rats. Exactly 3 mL of blood is extracted from a periorbital vein and then added to a tube containing 1 mL of a solution with a concentration of 0.01% acid citrate dextrose (ACD). Next, the centrifugation procedure was performed at a velocity of 3000 rpm for a duration of 10 minutes. This would allow for the separation of the blood plasma components from the blood cells. Following this, the growth factor of the blood components was activated by incubating them at temperature of 37.5°C for 10 minutes. Additionally, 1% of trypsin was added to the mixture. The activated growth factor component was located in supernatant. Subsequently, the concentration of transforming growth factor (TGF-β) was evaluated using the enzyme-linked immunosorbent assay (ELISA) technique.

Sample Collection

After 21 days of AGF treatment, all rats were fasted and subsequently euthanized with an intraperitoneal injection of 100 mg/kg ketamine and 10 mg/kg xylazine mixture. Blood samples were taken via heart puncture. The blood sample was centrifuged at a speed of 2000g for 10 minutes at 4°C, and then the serum was separated and stored at a temperature of −80°C for biochemical measurements. Next, the rats' eyes were immediately evacuated and dissected the retinal tissue to isolate it from the surrounding tissue. The retinal tissue were homogenized and stored at a temperature of −80°C for molecular examination.

The Enzyme-Linked Immunosorbent Assay (ELISA)

The retinal tissue was homogenized and dissolved using a cold RIPA buffer that containing protease inhibitors cocktail. The homogenate was subjected to centrifugation at a speed of 10,000 g for a duration of 20 minutes at a temperature of 4°C. The levels of AGEs, p38 mitogen activated protein kinase (p38 MAPK), nuclear factor-κβ (NF-κβ), ROS, TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF in the supernatant fraction of retinal tissue homogenates were measured using the rat ELISA kit (CloudClone®, Hangzhou, PRC). An analysis was conducted on the levels of AGEs, SOD, p38 MAPK, NF-κβ, ROS, TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF. The examination was performed according to the instructions provided in the ELISA kit's product manual.

Statistical Analysis

All statistical analysis were performed using SPSS version 26.0 for Windows (IBM, Jakarta, Indonesia). Normality of data performed with the Kolmogorov–Smirnov test (K-S). All groups were expressed as mean ± standard deviation (SD). Differences between several groups were compared using Kruskal Wallis test, followed by a post-hoc Games Howell test. $P < 0.05$ is defined as statistical significance.

Results

The study found that rats with diabetic retinopathy, a condition causing weight loss, showed an increase in body weight after administering AGF-TGF-β doses of 10 ng/mL and 100 ng/mL. The rats in group 3 and group 4 showed an average body weight of 232.34 grams and 241.12 grams respectively (Table 1 and Figure 1). The treatment group and the negative control showed a statistically significant difference in average body weight (Table 1 and Figure 1). The study also found that rats with pre-existing diabetic retinopathy had significantly elevated average serum glucose levels (Figure 1), indicating that diabetic retinopathy can lead to elevated glucose levels in the bloodstream. The rats exposed to AGF-TGF-β concentrations of 10 ng/mL and 100 ng/mL showed a significant disparity in average serum glucose levels (p-value < 0.05).

Table 1 Comparison of Body Weight and Serum Glucose Levels Between Groups

Groups	Mean Body Weight (gram) ± SD	Mean Serum Glucose Level (mg/dL) ± SD	Mean Retinal Artery Diameter (µm)±SD
1 (normal control)	248.43 ± 20.32*	100.23 ± 12.45*	40.33±2.67*
2 (negative control)	176.76 ± 15.23	303.45 ± 21.32	86.67±3.56
3 (AGF-TGF-β 10 ng/mL)	232.34 ± 18.41*	225.21 ± 16.84*	75.17±5.34*
4 (AGF-TGF-β 100 ng/mL)	241.12 ± 19.87*	219.18 ± 15.67*	66.67±4.76*

Notes: *p < 0.05 versus negative control group.
Abbreviations: AGF-TGF-β, Activated growth factor with TGF-β concentration; SD, standard deviation.

The study found that the mean diameter of the retinal artery in the control group was normal, while in the negative control group, it increased significantly, indicating diabetic retinopathy (Table 1 and Figure 1). The mean diameter of the retinal artery was significantly reduced when AGF was administered with a TGF-β concentration of 10 ng/mL or 100 ng/mL. A significant difference was observed in the mean diameter between the treatment group and the negative control, with a p-value of less than 0.05. Figure 2 provides a visualization of the fundus images of each group.

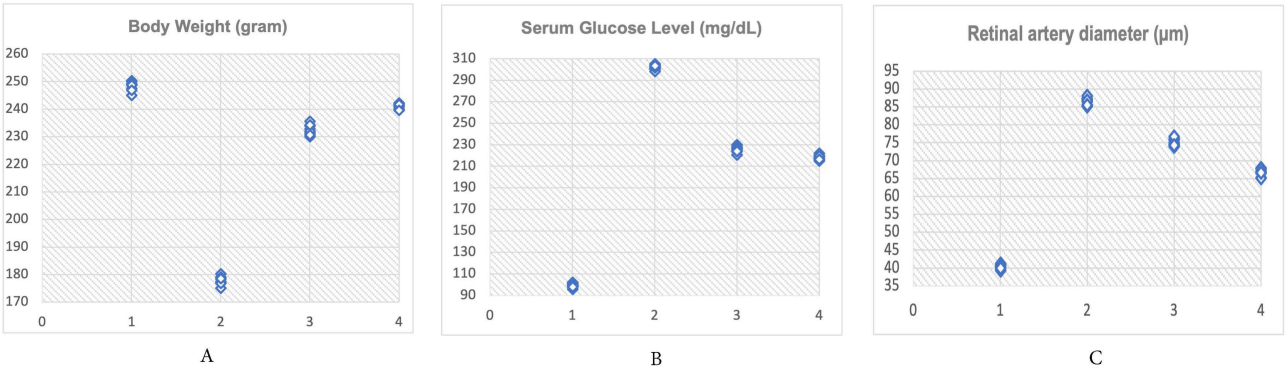

Figure 1 Scatter plot for visualization comparison and distribution data from body weight, serum glucose level and retinal artery diameter. (**A**) Average body weight; (**B**) Average serum glucose level; (**C**) Average retinal artery diameter for each group.
Notes: (1) Group 1, (2) Group 2, (3) Group 3, and (4) Group 4.

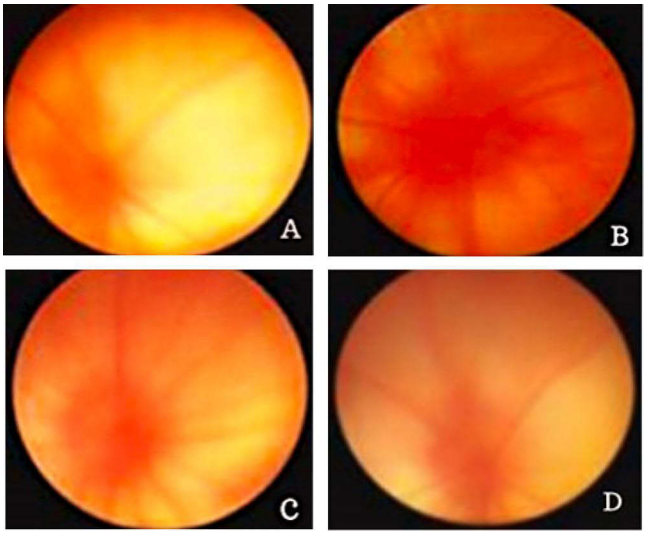

Figure 2 Fundus images. (**A**) Normal control; (**B**) negative control; (**C**) AGF with concentration TGF beta 10 ng/mL; (**D**) AGF with concentration TGF beta 100 ng/mL.

Table 2 Comparison of Mean Concentrations of AGEs, SOD, p38 MAPK, Nf-κβ, and ROS in Retinal Tissue of Rats Between Groups

Groups	AGEs (pg/mL) ± SD	SOD (U/mL) ± SD	p38 MAPK (pg/mL) ± SD	Nf-κβ (pg/mL) ± SD	ROS (U/mL) ± SD
1 (normal control)	12.13 ± 1.14*	189.21 ± 11.18*	22.15 ± 1.32*	18.33 ± 1.75*	10.11 ± 1.08*
2 (negative control)	235.65 ± 14.23	37.77 ± 2.34	278.95 ± 16.45	297.87 ± 17.56	323.98 ± 18.67
3 (AGF-TGF-β 10 ng/mL)	134.41 ± 12.34*	84.21 ± 7.45*	145.47 ± 14.56*	165.33 ± 15.67*	187.87 ± 16.78*
4 (AGF-TGF-β 100 ng/mL)	101.13 ± 10.45*	123.18 ± 11.56*	121.87 ± 12.67*	125.23 ± 13.78*	133.45 ± 14.89*

Notes: *p < 0.05 versus control negative.
Abbreviations: AGEs, advanced glycation end products; AGF-TGF-β, Activated growth factor with TGF-β concentration; Nf-κβ, nuclear factor-κβ; p38 MAPK, p38 mitogen activated protein kinase; ROS, reactive oxygen species; SD, standard deviation; SOD, superoxide dismutase.

Our study found that the normal control group had normal glycation levels in their retinal tissue, while the diabetic retinopathy group had significantly increased AGE concentrations (Table 2 and Figure 3). AGF with TGF-β concentrations of 10 ng/mL and 100 ng/mL significantly reduced AGE concentrations in the retinal tissue of rats with diabetic retinopathy. The statistically significant difference ($p<0.05$) suggests that AGF can effectively lower the buildup of AGEs in retinal tissue. The study found that superoxide dismutase (SOD) activity in the normal control group was within normal range (189.21 ± 11.18 U/mL), while the negative control group had lower levels (37.77 ± 2.34 U/mL) (Figure 3). The retinal tissue of diabetic rats showed a decline in antioxidant activity due to oxidative stress. AGF containing TGF-β (10 ng/mL) and AGF with TGF-β concentration (100 ng/mL) significantly increased SOD activity.

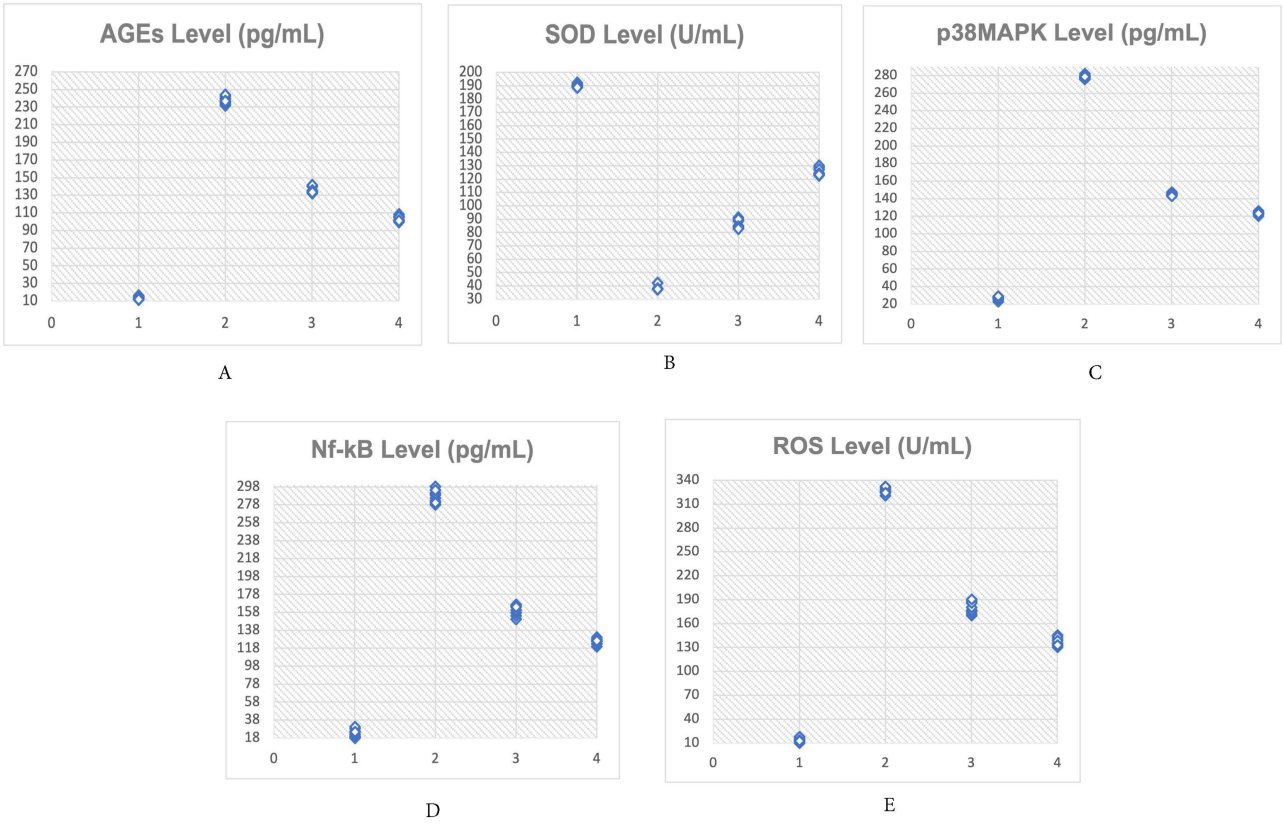

Figure 3 Scatter plot for visualization comparison and distribution data from AGEs, SOD, p38MAPK, Nf-κβ and ROS. (**A**) AGEs level; (**B**) SOD level; (**C**) p38MAPK level; (**D**) Nf-κβ level; (**E**) ROS level for each group.
Notes: (1) Group 1; (2) Group 2; (3) Group 3; (4) Group 4.

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Table 3 Comparison of the Average Concentrations of TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF in the Retinal Tissue of Rats Across Different Groups

Groups	TNF-α (pg/mL) ± SD	IL-1β (pg/mL) ± SD	VCAM-1 (pg/mL) ± SD	ICAM-1 (pg/mL) ± SD	VEGF (pg/mL) ± SD
1 (normal control)	15.21 ± 1.21*	13.29 ± 1.16*	21.23 ± 1.54*	19.87 ± 1.67*	21.18 ± 1.12*
2 (negative control)	323.78 ± 16.23	279.97 ± 15.34	332.78 ± 16.45	328.77 ± 17.56	325.87 ± 18.67
3 (AGF with TGF-β concentration 10 ng/mL)	198.33 ± 14.34*	175.32 ± 13.45*	175.76 ± 14.56*	195.77 ± 15.67*	197.55 ± 16.78*
4 (AGF with TGF-β concentration 100 ng/mL)	154.56 ± 12.45*	122.13 ± 11.56*	123.76 ± 12.67*	142.76 ± 13.78*	137.63 ± 14.89*

Notes: *p < 0.05 versus control negative.
Abbreviations: AGF-TGF-β, activated growth factor with TGF-β concentration; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1β; SD, standard deviation; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

The study examined the effects of AGF on retinal tissue in rats with diabetic retinopathy. The normal control group had a typical p38 MAPK concentration, while the negative control group showed a significant increase in p38MAPK levels due to diabetic retinopathy (278.95 pg/mL) (Figure 3). AGF administration in groups 3 and 4 significantly decreased p38MAPK concentrations, suggesting AGF can reduce oxidative stress by activating p38MAPK less. The study also found that AGF can effectively lower inflammation by stopping Nf-κβ activation in the retinal tissue of diabetic retinopathy rats (Figure 3). The control group showed normal oxidative stress, but the negative control group showed a significant increase in reactive oxygen species (ROS) concentrations (Figure 3). AGF administration in groups 3 and 4 significantly decreased ROS concentrations, suggesting AGF can effectively lower oxidative stress by stopping ROS from activating in the retinal tissue of diabetic retinopathy rats.

The study found that diabetic retinopathy induces significant inflammation in retinal tissue, with TNF-α concentrations increasing dramatically in the negative control group (Table 3 and Figure 4). AGF administration effectively decreased TNF-α concentrations, suggesting that AGF can mitigate inflammation by decreasing TNF-alpha expression. IL-1β concentrations also decreased in the negative control group, suggesting chronic inflammation caused by diabetic retinopathy. AGF administration in groups 3 and 4 resulted in a significant reduction in IL-1β concentrations, suggesting that AGF can reduce IL-1β expression in rats with diabetic retinopathy (Figure 4).

VCAM-1 expression levels were within normal range in the control group, but increased to 332.78 pg/mL in the negative control group (Figure 4). AGF administration in groups 3 and 4 led to a substantial decrease in VCAM-1 concentrations, suggesting that AGF can inhibit endothelial cell and leukocyte activation, leading to a decrease in inflammation in retinal tissue. ICAM-1 concentrations rose to 328.77 pg/mL in the negative control group with diabetic retinopathy, indicating an increase in leukocyte attachment to retinal tissue. AGF administration in groups 3 and 4 resulted in a substantial decrease in ICAM-1 concentrations, suggesting that AGF can inhibit leukocyte cell adhesion, reducing inflammation in retinal tissue (Figure 4).

VEGF expression was within the normal range in the normal control group, but increased to 325.87 pg/mL due to diabetic retinopathy. AGF administration in groups 3 and 4 significantly decreased VEGF concentrations, suggesting that AGF can inhibit aberrant blood vessel growth by decreasing VEGF expression (Figure 4). Overall, AGF effectively and significantly decreased protein expression of TNF-α, IL-1β, VCAM-1, and ICAM-1 in rats with diabetic retinopathy.

Discussion

Diabetic retinopathy is a condition affecting the retina's microvascular system, leading to vision impairment.[2,3] Symptoms include weight loss, high blood sugar levels, and an enlargement of retinal arteries. According to recent literature, there is no definitive treatment for diabetic retinopathy.[11] Activated growth factor (AGF), which contains TGF-β, can counteract inflammation, oxidative stress, and promote fibrosis. Our study showed that administering AGF contained TGF-β can mitigate weight loss, reduce serum glucose levels, and narrow retinal arteries in rats with diabetic retinopathy. TGF-β can increase appetite, stimulate protein synthesis, and enhance fat degradation, thereby reducing

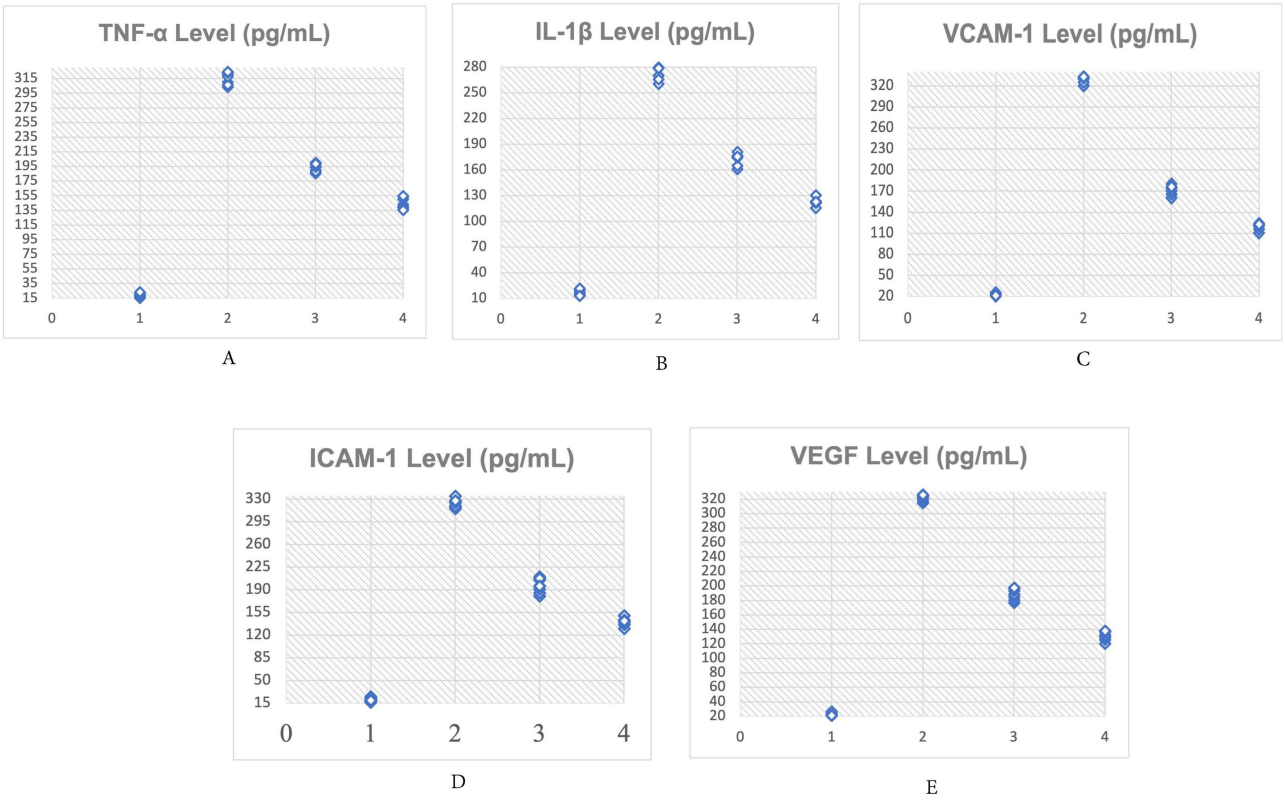

Figure 4 Scatter plot for visualization comparison and distribution data from TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF. (**A**) TNF-α level; (**B**) IL-1β level; (**C**) VCAM-1 level; (**D**) ICAM-1 level and (**E**) VEGF level for each group.
Notes: (1) Group 1; (2) Group 2; (3) Group 3; (4) Group 4.

weight loss.[9,12] It can also augment the body's insulin response, reduce blood glucose levels, and stimulate collagen synthesis, strengthening retinal artery walls.[13] Unregulated hyperglycemia can lead to weight loss, damage to endothelial cells, and inflammation, ultimately resulting in retinal artery enlargement.

Diabetic retinopathy is caused by persistent inflammation and oxidative damage, which can be triggered by hyperglycemia and oxidative stress.[14] Oxidative stress triggers inflammation by activating pathways like NF-κB and p38MAPK, causing the production of proinflammatory cytokines like TNF-α and IL-1β.[14–16] These cytokines can increase blood vessel permeability and facilitate white blood cell adhesion to endothelial cells. Abnormal blood vessel formation, known as aberrant angiogenesis, can cause retina damage and contribute to diabetic retinopathy.

TGF-β, a type of platelet-derived autologous growth factor, has been shown to significantly reduce the development of diabetic retinopathy.[13] It enhances the production of sRAGE, a soluble version of RAGE, which competes with membrane-bound RAGE in binding to AGEs. TGF-β also suppresses glycation enzymes involved in the creation of AGEs, reducing their buildup in retinal tissue.[17] It also inhibits the AGE-RAGE pathway, which induces inflammation and oxidative damage. TGF-β also enhances enzymes that break down AGEs, facilitating their removal from retinal tissue. It also inhibits the activation of p38MAPK and Nf-β pathways, which are involved in inflammation. TGF-β also enhances the efficacy of antioxidants, neutralizing reactive oxygen species (ROS) and mitigating oxidative stress.[12] This combination of factors effectively slows down the progression of diabetic retinopathy.

TGF-β has anti-inflammatory and anti-angiogenic properties that contribute to diabetic retinopathy.[18] It inhibits the NF-kβ and p38MAPK signaling pathways, which produce cytokines like TNF-α and IL-1β, reducing inflammation and oxidative stress. TGF-β also suppresses the expression of VCAM-1 and ICAM-1 in retinal vascular endothelial cells, reducing leukocyte infiltration and inflammation.[19] Additionally, TGF-β inhibits the expression of VEGF, a vascular growth factor that stimulates aberrant angiogenesis, preventing blood leakage and retinal edema.[20] This slows the progression of diabetic retinopathy.

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Conclusion

Our study shows that AGF, with TGF-β concentrations of 10 ng/mL and 100 ng/mL, can reduce AGEs, p38MAPK, Nf-κβ, ROS, TNF-α, IL-1β, VCAM-1, ICAM-1, and VEGF in diabetic retinopathy rats' retinal tissue, while increasing antioxidant SOD concentration, suggesting AGF may help treat diabetic retinopathy by reducing inflammation and oxidative stress. The limitation of this study is that we have not evaluated the side effects of AGF for diabetic retinopathy. Future studies should evaluate the toxicity and safety of AGF as a future therapy for diabetic retinopathy.

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Disclosure

The authors report no conflicts of interest in this work.

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