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Original Article

Correlation between serum VEGF and glycosylated hemoglobin levels with the efficacy and prognosis of laser photocoagulation in patients with diabetic retinopathy

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Abstract: Diabetic retinopathy (DR), a complication of diabetes, is becoming the leading cause of blindness in developed countries. This study aims to explore the associations between vascular endothelial growth factor (VEGF) and glycosylated hemoglobin (HbA1c) levels with the efficacy and prognosis of laser photocoagulation in DR patients. Sixty-five type 2 diabetes mellitus (T2DM) patients without retinopathy were selected as the control group and 183 DR patients formed the case group (the non-proliferative DR (NPDR) and proliferative DR (PDR) groups). Patients in the case group were grouped into effective and ineffective groups. Enzyme-linked immunosorbent assay (ELISA) was used for VEGF and micro-column chromatography for HbA1c. The predictive value of VEGF serum and HbA1c levels on the efficacy was evaluated using receiver operating characteristic (ROC) curves. Multi-factor regression analysis was conducted for risk factors that interfere with therapeutic effects of laser photocoagulation. Disease course was positively correlated with VEGF and HbA1c. After treatment, VEGF and HbA1c levels in the PDR group were higher than those in the NPDR group. VEGF and HbA1c levels post-treatment in the effective group were lower than those pre-treatment. VEGF and HbA1c levels in the effective group were also lower than those in the ineffective group. Patients with higher VEGF and HbA1c levels had worse visual acuity restoration and efficacy. Age, disease course, visual acuity, and VEGF level as independent risk factors on affecting therapeutic effects of laser photocoagulation treatment in DR patients. Lower VEGF and HbA1c levels in DR patients had a better efficacy of laser photocoagulation.

Keywords: Diabetic retinopathy, vascular endothelial growth factor, glycosylated hemoglobin, laser photocoagulation, efficacy, prognosis

Introduction

Diabetic retinopathy (DR), a common complication of diabetes, is a microvascular disease accounting for a third of diabetic patients, leading to blindness in working-age populations [1]. This disease is predicted to be an increasing challenge in the following decades, of which morbidity is estimated to increase to 552 million by 2030, almost 1.5 times that of DR patients in 2011 [2]. DR usually occurs in the retinal posterior first, where micro-aneurysms and endothelial proliferation could be limited to retinal circulation in the venous side, with endothelial degeneration in the arterial capillaries occuring later [3]. DR can be classified into proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) [4]. During the past few decades, hyperglycemia refers to the major contributor and upstream inducer in the development of DR [5]. Therefore, blood pressure and serum glucose control are a potential therapuetic method to reduce the incidence of DR induced blindness, while early diagnosis and prompt treatment are important for risk reduction [6]. In recent years, laser photocoagulation is considered an effective therapy of DR, highly reducing proliferative risk, and working especially well on severe non-proliferative diabetic retinopathy (NPDR) [7].

Vascular endothelial growth factor (VEGF), a cytokine glycoprotein, is a common vasculogenesis and angiogenesis factor as well [8]. VEGF

can be produced by various retinal cells such as astrocytes, pericytes, and retinal pigment epithelial cells, and high levels of VEGF have been found in active intraocular neovascularization diseases such as proliferative diabetic retinopathy (PDR) [9]. Additionally, VEGF could induce microvascular hyperpermeability and induce breakdown of blood-retinal barrier in humans, especially those with NPDR [10]. Glycosylated hemoglobin (HbA1c) can predict diabetes as well as cardiovascular disease and their mortality, as an indicator of chronic blood glucose concentration [11]. Zehetner et al. reports that poor glycemic control positively correlates with up-regulated VEGF levels in DR patients and the normalization of HbA1c can be an effective way to prevent retinopathy [12]. Sugimoto et al. have been mentioned that photocoagulation treatment in DR might result in decreased VEGF secretion [13], and laser treatment is recommended for diabetic patients in the highest quartile of HbA1c variability [14]. Nevertheless, the association between VEGF and HbA1c with the efficacy and prognosis of laser photocoagulation in patients with DR requires further exploration. Therefore, this study aims to explore whether they are correlative by comparing the changes of VEGF and HbA1c levels in DR patients before and after laser photocoagulation.

Materials and methods

Ethics statement

This study was approved by the Clinical Ethics Committee of Linyi People's Hospital. All patients had a good understanding of this study, and signed the relevant informed consent.

Study subjects

From May 2012 to May 2015, a total of 248 patients with type 2 diabetes mellitus (T2DM) treated in the Department of Endocrinology and the Department of Ophthalmology of Linyi People's Hospital were selected to participate in this study. The patients' ages ranged from 32 to 86 years old (average age: 58.15 ± 9.10 years old), consisting of 122 males and 126 females. Among them, 65 T2DM patients without retinopathy were selected as the control group. Diagnostic criteria for T2DM: HbA1c ≥ 6.5%, fasting blood glucose (FBG) ≥ 7.0 mmol/l (126 mg/dl), oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l (200 mg/dl), random blood sugar (RBS) ≥ 11.1 mmol/l (200 mg/dl) for T2DM patients with typical symptoms of hyperglycemia or acute hyperglycemia. In addition to this, 183 patients with DR were selected as the case group. Inclusion criteria of patients in the case group were as follows: 1) Patients were diagnosed with T2DM by the Department of Medicine. 2) DR was diagnosed using slit lamp microscope, binocular indirect ophthalmoscope, and fundus fluorescein angiography. 3) Fifty-seven cases of patients were confirmed with proliferative diabetic retinopathy (PDR) and 126 cases were confirmed with non PDR (NPDR) according to the diagnosis and staging criteria specified on the international classification system of DR proposed by the Academy of Ophthalmology (AAO) in 2002 [15]. Exclusion criteria: All subjects were diagnosed to be free of diabetic ketosis, acute complications of diabetes (such as hyperosmotic diabetic coma), autoimmune diseases, malignant tumors, systemic chronic diseases (such as severe hepatic, renal, cardiovascular, and cerebrovascular diseases), and eye diseases caused by any other reasons [16].

Sample collection

Fasted venous blood samples from the elbow (3 ml) were collected from all subjects in the morning, and the blood was immediately placed in an ice box and sent to the laboratory. The blood samples were then centrifuged at 3000 r/min for 10 minutes at 4°C, followed by supernatant separation. Afterwards, the samples were packed separately and stored immediately in a refrigerator kept at -20°C for the following experiment.

Serum VEGF and HbA1c detection

Prior to and 4 weeks after laser treatment, changes in VEGF serum and HbA1c levels, visual acuity, and the central macular foveal thickness index of all patients were detected and recorded.

Enzyme-Linked Immuno Sorbent Assay (ELISA) was used to detect the serum level of VEGF. The ELISA Kit was produced by R&D Company, Inc. (Lorton, VA, USA) and consigned by Shanghai Bio Mart Co., Ltd. (Shanghai, China). Fasting blood glucose (FBG) was detected by glucose oxidase method.

Serum HbA1c was detected by micro-column chromatography with a DCA2000 instrument (Bayer Company, Leverkusen, Germany) (reagent was provided by Bayer Company). The detection process was conducted in accordance with the kit instructions for operation.

The best-corrected visual acuity was respectively tested based on the international standard visual acuity chart. The chart consisted of 14 lines of the word "E" in various sizes and opening direction, and the measurements ranged from 0.1-1.5 (or from 4.0-5.2). Each line was labeled, and patients' eyesight was parallel to the 1.0 line. The testing distance was 5 m and the best-corrected visual acuity was recorded using decimal notation. The foveal retinal thickness was inspected and scanned with 3D-OCT (Topcon Medical Systems, Inc., Paramus, NJ, USA) in darkroom conditions. Scanning modes included the horizontal, vertical, and oblique axis, and the scanning length was 4 mm. Based on OCT software, the distance from the inside of the retinal pigment epithelium band to the inside of the strata neuro-epitheliale was measured using an artificial calibration method. After OCT, fundus fluorescein angiography (FFA) was performed by the combined Heidelberg retina angiograph (HRA2). Patients with a negative allergy test were injected 100 g/l sodium fluorescein (5 ml) within 6 seconds through the anterior brachial vein, and FFA was observed for more than 10 minutes. All of the FFA examinations were interpreted by an experienced fundus physician.

Laser photocoagulation therapy

Patients in the case group took an eye examination before laser photocoagulation therapy. Under the guidance of fundus examination and FFA, standard laser treatment was performed by fixed personnel and a 532-frequency doubled semiconductor laser (532 nm) (Zeiss Company, Oberkochen, Germany). Laser parameters were set as such: power 200~700 mW, spot size 100~300 μm, and exposure time 200~300 ms, and laser reactive spot at grade III~IV. The laser parameters for macular edema with clinical significance were: power 100 mW, spot size 50~100 μm, a grid photocoagulation with exposure time of 100~200 ms, and grayish leukoplakia. The exposure interval was 5~7 d/time and the monocular laser photocoagulation therapy was finished within 5 weeks.

Criteria for evaluating therapeutic effect

After laser photocoagulation therapy, DR patients were asked to return to visit the doctor twice a month for visual acuity and fundus examination. FFA examination was done at 3 months, 6 months, and 1 year after laser photocoagulation therapy. DR patients had a follow-up evaluation 1 year after surgery consisting of the following: (1) Vision evaluation standard: a vision improvement ≥ 2 was regarded as improvement, and a vision loss ≥ 2 was regarded as decreased. If visual acuity was lower than 0.1 before treatment, a decrease or increase of 0.02 was set as the standard to determine the decline or improvement in visual acuity, respectively, or regarded as no change. The effective rate was calculated with the improvement plus stability of visual acuity. (2) Assessment of retinopathy progression: the results of FFA indicate that the retinal edema, hemorrhage, and partial or total absorption of exudation were defined as effective after the laser treatment, compared to before the laser treatment. Retinal hemorrhage increased, new blood vessels occurred, and new non-perfusion (NP) areas outside the light coagulation zone were regarded as lesion aggravated. No above changes were regarded as lesion stable. The effective rate was calculated with the effective level plus stability.

Statistical analysis

All data were analyzed using SPSS 21.0 statistical software (IBM Corp. Armonk, NY, USA), and tested by bilateral statistical test. Measurement data was expressed as mean ± standard deviation (SD), and comparisons between two groups were analyzed with *t* test. Enumeration data was expressed as percentage or rate. χ^2 test and Spearman correlation method was used for correlation analysis. The predictive value of VEGF serum and HbA1c levels on the treatment effect was evaluated by receiver operating characteristic (ROC) curves. Factors influencing the efficacy of laser photocoagulation in DR patients were analyzed by multi-factor logistic regression analysis. $P < 0.05$ indicates statistical significance.

Results

Baseline characteristics of study subjects among the control, NPDR, and PDR groups

The control group consisted of 65 patients with 130 eyes, including 38 males with 76 eyes and

Table 1. The baseline characteristics of subjects with NPDR, PDR and normal diabetes

	Control group (65 cases)	NPDR group (126 cases)	PDR group (57 cases)	F/t	*P*
Age	56.55 ± 10.72	58.53 ± 8.37	59.12 ± 8.55	1.444	0.238
Gender					
Male	38	58	26		
Female	27	68	31	3.030	0.220
Course of diabetes (years)	5.45 ± 1.64	8.74 ± 2.41*	9.98 ± 3.17*,#	59.410	< 0.001
Retinal thickness (um)	289.46 ± 80.27	363.38 ± 85.06*	401.62 ± 86.76*,#	28.940	< 0.001
Visual acuity	0.54 ± 0.14	0.32 ± 0.13*	0.21 ± 0.09*,#	114.700	< 0.001
VEGF level (ng/L)	357.35 ± 113.61	479.11 ± 99.12*	660.63 ± 134.53*,#	122.600	< 0.001
HbA1c (%)	5.15 ± 1.24	7.16 ± 2.18*	10.35 ± 2.35*,#	85.98	< 0.001
Macular type					
Ischemic lesions	0	9	3	1.130	0.770
Cystoid macular edema	0	20	12		
Regional macular edema	0	65	30		
Diffuse macular edema	0	32	12		

Note: *indicates $p < 0.05$ compared with the control group; #indicates $p < 0.05$ compared with the NPDR group; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor; HbAlc, glycosylated hemoglobin.

27 females with 54 eyes, whose ages ranged from 32 to 86 years with a mean age of 56.55 ± 10.72 years. The case group included 183 patients with 366 eyes, and was classified in accordance with different phases into two groups: the NPDR group and the PDR group. The NPDR group was composed of 126 patients with 58 males with 116 eyes and 68 females with 136 eyes, ranging from 32~85 years old with a mean age of 58.53 ± 8.37 years. In that same group, there were 9 patients with ischemic lesions, 20 patients with cystoid macular edema, 65 patients with regional macular edema, and 32 patients with diffuse macular edema. The PDR group was made up of 57 patients, including 26 males with 52 eyes and 31 females with 62 eyes whose ages were between 34~85 years with a mean age of 59.12 ± 8.55 years. In the PDR group, there were 3 patients with ischemic lesions, 12 patients with cystoid macular edema, 30 patients with regional macular edema, and 12 patients with diffuse macular edema. No statistical differences existed between the control group and the case group in age, gender, and macular type (both $P > 0.05$). Before treatment, there were remarkable differences in disease course, visual acuity, retinal thickness, serum VEGF, and HbA1c levels between the case group and the control group (all $P < 0.05$). Compared with the NPDR group, the PDR group had a longer disease course, weakened visual acuity, thicker retina, and higher serum VEGF and HbA1c levels (all $P < 0.05$) (**Table 1**). Correlation analysis between course of diabetes with VEGF serum and HbA1c levels revealed a correlation coefficient of 0.392 and 0.308 (both $P < 0.05$), respectively, demonstrating that VEGF serum and HbA1c levels positively correlate to the development and progression of DR (**Figure 1**).

Efficacy and predictive value of VEGF and HbA1c levels on DR patients after laser photocoagulation

After treatment, VEGF serum and HbA1c levels in the NPDR and PDR groups were significantly lower than their indexes while prior to treatment (both $P < 0.05$). No statistical differences in VEGF serum and HbA1c levels between the NPDR group and the control group (both $P > 0.05$) were found post-treatment. However, VEGF serum and HbA1c levels were higher in the PDR group than those in the control group (both $P < 0.05$). Higher levels of VEGF serum and HbA1c levels were found in the PDR group compared with the NPDR group (both $P < 0.05$), post-treatment.

Patients in the case group were classified into the effective group (n = 138) and the ineffec-

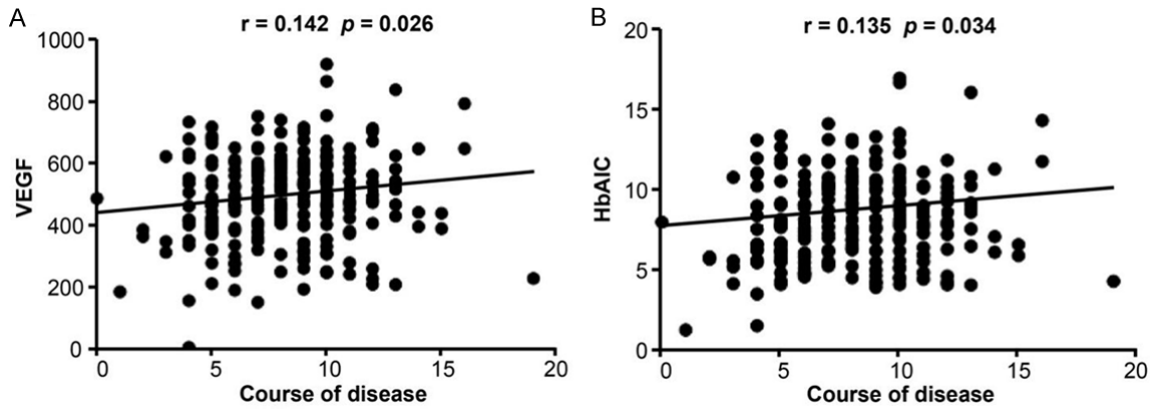

Figure 1. Correlation analysis between course of diabetes with serum VEGF and HbA1c levels. Note: (A) Correlation analysis between course of diabetes and serum VEGF level; (B) Correlation analysis between course of diabetes and HbA1c level; VEGF, vascular endothelial growth factor; HbA1c, glycosylated hemoglobin.

Table 2. Pro-/post-treatment serum VEGF and HbA1c levels in the control and case groups

	VEGF level		HbA1c level	
	Pro-treatment	Post-treatment	Pro-treatment	Post-treatment
Group 1				
Control group (n = 65)	357.35 ± 113.61		6.15 ± 1.24	
NPDR (n = 126)	535.46 ± 108.66	352.26 ± 121.24*	9.52 ± 2.47	5.94 ± 1.60*
PDR (n = 57)	579.93 ± 126.89	401.62 ± 125.31$^{*,\&}$	9.82 ± 2.64	6.65 ± 1.21$^{*,\&}$
Group 2				
Effective group (n = 138)	361.81 ± 128.12$^{\#}$	325.69 ± 118.10$^{*,\#}$	5.48 ± 2.75$^{\#}$	5.31 ± 2.81$^{*,\#}$
Ineffective group (n = 45)	553.61 ± 126.52	550.25 ± 121.32	9.43 ± 2.25	9.34 ± 2.25

Note: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor; HbA1c, glycosylated hemoglobin. *indicates $P < 0.05$ compared with pro-treatment; $^{\&}$indicates $P < 0.05$ compared with the control group; $^{\#}$indicates $P < 0.05$ compared with ineffective group.

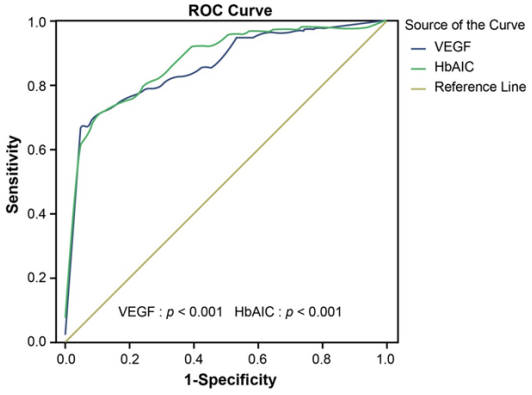

Figure 2. ROC curve of therapeutic effect judged by VEGF and HbA1c levels of diabetic retinopathy patients after laser photocoagulation. Note: ROC, receiver operating characteristic; VEGF, vascular endothelial growth factor; HbA1c, glycosylated hemoglobin.

tive group (n = 45) according to their efficiency of treatment. Analysis (**Table 2**) indicates that VEGF serum and HbA1c levels after treatment in the effective group were lower than those before treatment (both $P < 0.05$). The ineffective group also exhibited the same trend in VEGF serum and HbA1c levels, but without significant difference (both $P > 0.05$). VEGF serum and HbA1c levels, either pre- or post-treatment, were lower in the effective group than in the ineffective group (both $P < 0.05$). VEGF serum and HbA1c levels pre-treatment in both the effective and ineffective groups were employed for ROC curve analysis (**Figure 2**). Those results of ROC curve analysis show that the area under the curve (AUC) of VEGF was 0.734 (95% confidence interval (CI) = 0.655-0.812, $P < 0.05$), and when optimal cutoff value was at 562.31, the sensitivity and specificity reached their peak at 66.7% and 74.6%, respectively. ROC curve analysis results of HbA1c show AUC of e0.714 (95% CI = 0.628-0.801, $P < 0.05$), and when optimal cutoff value was at 9.725,

Table 3. Visual acuity and therapeutic effect of diabetic retinopathy in patients with different VEGF and HbA1c levels

Group	Visual acuity			*P*	Therapeutic effect of diabetic retinopathy			*P*
	Increase (%)	Stable (%)	Decrease (%)		Effective (%)	Stable (%)	Ineffective (%)	
High-level VEGF	34 (22.37)	77 (50.66)	41 (26.97)	0.048	23 (15.13)	87 (57.24)	42 (27.63)	< 0.01
Low-level VEGF	13 (41.94)	14 (45.16)	4 (12.90)		24 (77.42)	4 (11.42)	3 (11.16)	
High-level HbA1c	37 (23.42)	79 (50.00)	42 (26.58)	0.123	27 (17.09)	88 (55.70)	43 (27.22)	< 0.01
Low-level HbA1c	10 (39.5)	12 (48.00)	3 (12.48)		20 (78.43)	3 (13.41)	2 (8.16)	

Note: VEGF, vascular endothelial growth factor; HbA1c, glycosylated hemoglobin.

Table 4. Regression analysis of factors affecting therapeutic effect of laser photocoagulation in DR patients

Factor	*B*	*SE*	*Wald*	*P*	Exp (B)	95% CI	
						Lower limit	Upper limit
Age	1.391	0.274	25.904	< 0.001	< 0.001	2.348	6.883
Gender	-0.972	0.736	1.742	0.187	0.187	0.089	1.602
Course of disease	-3.552	0.737	23.254	< 0.001	< 0.001	0.007	0.121
Retinal thickness	-0.020	0.006	10.845	0.001	0.001	0.969	0.992
Visual acuity	-9.079	5.639	2.592	0.107	0.107	0.000	7.191
VEGF level	-0.011	0.005	5.749	0.016	0.016	0.980	0.998
HbA1c level	-0.250	0.215	1.353	0.245	0.245	0.511	1.187

Note: VEGF, vascular endothelial growth factor; HbA1c, glycosylated hemoglobin. B, regression coefficient; S.E., standard error; Wald is the statistical interference of partial regression coefficients; OR, odds ratio; 95% CI, 95% confidence interval.

the sensitivity peaked at 50.9% and specificity peaked at 86.5%.

Association of VEGF and HbA1c levels with visual acuity and retinopathy in DR patients after laser photocoagulation

The optimal cutoff value obtained from the ROC curve was set as the standard; values below optimal cutoff value was regarded as low-level, while values over or equal to the optimal cutoff value was regarded as high-level. The results demonstrate that visual recovery and therapeutic effects of DR patients were worse in patients with high levels of VEGF, while patients with high HbA1c levels displayed worse outcomes than those with low HbA1c levels in therapeutic effect of retinopathy (see **Table 3**).

Regression analysis of factors affecting therapeutic effect of laser photocoagulation in DR patients

The therapeutic effect of the case group was set as the dependent variable, and patients' age, gender, disease course, retinal thickness, visual acuity, VEGF, and HbA1c levels before treatment were set as independent variables. Multi-factor regression analysis revealed that age, disease course, visual acuity, and VEGF levels were independent risk factors affecting the therapeutic effect of laser photocoagulation treatment in DR patients (see **Table 4**).

Discussion

Over the last several decades, laser photocoagulation has been gaining momentum as an important treatment strategy for DR. The treatment effect released by Diabetic Retinopathy Study (DRS) demonstrates a 50% reduced rate of severe vision loss, making it the standard treatment for patients with DR [17]. However, there is no definite standard to assess its therapeutic effect in individual patients. Thus, it is of great importance to find effective biomarkers to evaluate the examination of the therapeutic effects.

This study observed that VEGF serum and HbA1c levels were higher in the NPDR group and the PDR group than those in the control group, and that VEGF serum and HbA1c levels were also higher in the PDR group than those in the NPDR group, indicating that serum VEGF

and HbA1c levels have a positive correlation to the onset and progression of DR. VEGF, a mitogen for endothelial cells, is a key angiogenic factor for stimulating new vessel formation and vascular hyper-permeability in DR, and due to its expression both *in-vivo* and *in-vitro* can be induced by retinal hypoxia [18]. DR results in a series of changes, including increased retinal vascular permeability, chronic retinal hypoxia and extensive retinal ischemia; the processes of which are thought to be mediated by various growth factors such as VEGF [19]. HbA1c is regarded as a biochemical model for the pathogenesis of DR through glycosylation reactions [20]. The metabolic control, reflected by blood glucose level and HbA1c value, accounts for an important factor for the onset and progression of DR, making HbA1c varying with DR progression [18]. Early epidemiologic studies show a critical relationship between HbA1c levels and the incidence of DR, making it feasible to avoid progression of DR with tight glycemic control [21]. Cavusoglu et al. [22] argue that progressively increasing VEGF serum and HbA1c levels bear a correlation with the degree of DR, which is in agreement with our results. Therefore, VEGF serum and HbA1c levels are associated with the severity of DR in patients.

The same study also argues that VEGF serum and HbA1c levels are down-regulated after laser photocoagulation in DR patients, and that VEGF serum and HbA1c levels in the NPDR group were significantly lower when compared to the PDR group. Laser photocoagulation, in which laser burns are placed over the entire retina except the central macula, is an established technique for treating severe DR [23]. It promotes regression and arrests progression of retinal neovascularisation while ameliorating retinal ischemia and hypoxia, thus inhibiting VEGF activity and causing a reduction in ischemia-driven VEGF production, which eventually causes VEGF serum levels to decrease [24]. The same result was observed by Lip et al. in their pilot study, where they suggest that the angiogenic stimuli responsible for increased VEGF appeared to decrease during laser photocoagulation [9]. Qiao et al. found that laser photocoagulation can reduce VEGF serum and HbA1c levels [25], which is in agreement with our studies. In addition, it was found that the lower the VEGF and HbA1c levels were, the better the visual acuity recovery and therapeutic effects of DR. Therefore, the use of an intravitreal anti-VEGF agent such as Ranibizumab is proposed as an effective method for initial management of patients with high-risk PDR [26]. In this study, we found that VEGF and HbA1c levels after treatment in the effective group were significantly lower than those before treatment, and VEGF and HbA1c levels in the effective group were also lower than those in the ineffective group both before and after treatment. These results are in accordance with the above investigations.

In conclusion, this study discovered that lower VEGF and HbA1c levels in DR patients had better efficacy of laser photocoagulation, providing potential guidance for clinical treatment in DR patients. However, despite taking as many influential factors as possible (such as age and gender) into consideration, sample sizes were not large enough, resulting in varying VEGF serum and HbA1c levels. Additionally, we failed to make long-term follow-ups of patients treated with laser photocoagulation, rendering the outcome less convincible. Finally, due to the time and funding allotted for the experiment, the roles of APC/Wnt complex on VEGF and retina were not discussed in our study. Therefore, more studies with larger samples and frequent follow-ups should be carried out so as to substantiate the result and to further elucidate the roles of APC/Wnt complex on VEGF and retina.

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Disclosure of conflict of interest

None.

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