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The Association of Physiological Factors and Biochemical Factors with Different Progress Phage of Diabetic Retinopathy in Type 2 Diabetes Patients

Songhe Li[1]* and Dacheng Wen[2]*

[1]Department of Gastrointestinal Nutrition and Hernia Surgery, The 2nd Hospital of Jilin University, China

[2]Department of Ophthalmology, The 1st Hospital of Jilin University, Changchun, China

Abstract

Diabetic Retinopathy (DR) stands as a prevalent and consequential microvascular complication of Diabetes Mellitus (DM), holding the unfortunate distinction of being the primary cause of blindness in individuals affected by DM. As such, a pressing need exists to thoroughly investigate the implications of various physiological and biochemical risk factors across distinct phases of the disease. This exploration is crucial for shaping the diagnostic and therapeutic strategies employed in the management of DR. While prior research has established connections between DR and factors such as Body Mass Index (BMI), blood glucose levels, Glycated Hemoglobin (HbA1c), Serum Creatinine (Scr), Uric Acid (UA), and β2 Microglobulin (β2-MG), the exact influence of these factors on varying stages of DR progression remains unclear.

Our study constitutes a pioneering effort to delve into the divergent manifestations of DR across its different progression stages, specifically regarding physiological and biochemical elements. The implications of this study hold tremendous promise in terms of reducing both the incidence rate and the potential for vision loss among patients grappling with DR. Our findings indicate that the severity of Moderate Non-Proliferative DR (NPDR) is notably exacerbated by increased BMI, Scr, and β2-MG levels. Similarly, the progression to Severe NPDR is closely associated with advancing age, elevated blood glucose levels, heightened Scr, and UA concentrations. Furthermore, the risk of Proliferative DR (PDR) escalates with rising BMI, blood glucose levels, HbA1c, and β2-MG concentrations. Notably, age, blood glucose, HbA1c, Scr, UA, and β2-MG have all been identified as prominent risk factors shaping the trajectory of DR in patients.

Keywords: Physiological factors and biochemical factors; Diabetic retinopathy; Type 2 diabetes

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Correspondence:
Songhe Li, Department of Ophthalmology, The 1st Hospital of Jilin University, Chaoyang District, Changchun 130021, China, Dacheng Wen, Department of Gastrointestinal Nutrition and Hernia Surgery, The 2nd Hospital of Jilin University, Nanguan District, Changchun 130041, China, Tel: (+86) 13578995888;

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Introduction

Diabetes stands as one of the most prevalent chronic diseases encountered in clinical practice. As the disease progresses, its impacts extend to diverse areas, including the eyes, brain, heart, kidneys, nerves, and blood vessels, inflicting varying degrees of damage. Among the complications affecting the eyes, Diabetic Retinopathy (DR), diabetic cataracts, oculomotor nerve palsy, and vitreous hemorrhages manifest. Of these, Diabetic Retinopathy (DR) emerges as a particularly common and severe microvascular complication associated with Diabetes Mellitus (DM), contributing significantly to blindness within the diabetic population. In fact, DR ranks as a leading cause of blindness among individuals with diabetes, making it a critical concern in both Europe and the United States.

Concurrently, Diabetic Nephropathy (DN) constitutes a pivotal complication within the spectrum of diabetic microvascular diseases, with its progression often culminating in renal failure, thus becoming a major contributor to diabetic patient mortality. Recognizing the intricate relationship between DR and renal function, alongside exploring how different stages of DR intersect with renal function within DM patients, holds paramount significance in mitigating the incidence of DR and curbing its associated rates of blindness.

Prior investigations have illuminated certain aspects of the DR landscape. For instance, studies have revealed an association between Body Mass Index (BMI) and an elevated risk of Proliferative Retinopathy (POR) in individuals with DM [1]. Likewise, a link has been established between heightened blood glucose levels and a greater propensity for DR in cases of proliferative retinopathy

compared to instances of Non-Apparent Diabetic Retinopathy (NPDR) [2,3]. Glycated Hemoglobin (HbA1c), serving as a marker of blood glucose control, has also been implicated) [4]. Additionally, serum creatinine (Scr) [5], Uric Acid (UA) [6], and β2 Microglobulin (β2-MG) [7], have been identified as factors, albeit the full extent of their impact on different DR progressions remains enigmatic.

In this study, we rigorously examined both physiological and biochemical factors, discerning variations among each progression phase of DR in comparison to its preceding phase. This comprehensive analysis also encompassed an assessment of the diverse risk factors associated with the severity of DR. Notably, our findings illuminated distinct patterns: the severity of Moderate NPDR escalated with increasing BMI, Scr, and β2-MG levels, while Severe NPDR exhibited a correlation with advancing age, elevated blood glucose, heightened Scr, and UA levels. Similarly, Proliferative DR demonstrated a correlation with elevated BMI, blood glucose, HbA1c, and β2-MG levels. Collectively, age, blood glucose, HbA1c, Scr, UA, and β2-MG emerged as pivotal risk factors in shaping the trajectory of DR progression.

In summation, this study represents a significant contribution to our understanding of the intricate relationship between physiological and biochemical factors and the various stages of DR progression. Our insights not only enhance our grasp of the mechanisms underlying DR but also hold the potential to inform more effective strategies for diagnosis, management, and prevention.

Materials and Methods

Participants

In strict adherence to our approved protocol (2011-034), we meticulously conducted an exhaustive analysis encompassing individual subjects from all cases spanning the period of December 2011 to December 2020 within the Department of Ophthalmology and Endocrinology at the First Hospital of Jilin University. The cohort under scrutiny exhibited a duration of diabetes ranging from 10 to 15 years, while their ages ranged between 35 and 76 years, with a mean age of (52.78 ± 7.52) years. Each patient received comprehensive care, including a balanced dietary regimen, exercise routines, and fundamental treatments. Moreover, blood sugar, blood pressure, and blood lipid levels were diligently managed through standard pharmaceutical interventions, ensuring that they remained within optimal parameters.

To effectuate a meticulous analysis, we segregated subjects based on their diabetic status and duration of the condition. This categorization yielded two distinct groups: a control group comprising 249 individuals free from diabetes, and a diabetic group encompassing 1251 patients. Within the diabetic cohort, further categorization was predicated on the observed retinal alterations within patients' eye fundus, resulting in the formation of five subgroups: Non-Proliferative Diabetic Retinopathy (NPDR) (251 cases), Mild NPDR (259 cases), Moderate NPDR (257 cases), Severe NPDR (246 cases), and Proliferative Diabetic Retinopathy (PDR) (238 cases).

In order to ascertain a robust and relevant study population, we employed stringent inclusion and exclusion criteria. Inclusion criteria stipulated that subjects be aged ≥18 years and provide informed consent. Conversely, exclusion criteria encompassed: (1) exclusion of individuals with type 1 diabetes and secondary diabetes mellitus; (2) individuals with clear diagnoses of primary glomerular disease, autoimmune diseases, connective tissue disorders, blood disorders, cancer, or drug-induced renal damage; (3) exclusion of those who had experienced critical events such as myocardial infarction, cerebrovascular accidents, malignant hypertension, or diabetic ketoacidosis within the last six months; (4) individuals with concurrent severe respiratory, digestive, or blood-related primary diseases, ongoing infections, or mental health conditions; (5) individuals with congestive heart failure; (6) exclusion of cases involving cancer, pregnancy, or breastfeeding; (7) exclusion of individuals with conditions such as glaucoma, retinal artery occlusion, retinal vein occlusion, age-related macular degeneration, or optic neuropathy; (8) individuals with conditions such as corneal opacity, cataracts, or vitreous opacity that could impact fundus observations; (9) individuals who had previously undergone laser or endoscopic eye surgery; and (10) individuals with angle-closure glaucoma, as they were deemed unsuitable for mydriasis examination.

Definition of diabetes mellitus and diabetic retinopathy

Diabetes Mellitus (DM) was characterized by the criteria of a fasting plasma glucose level ≥7.0 mmol/L, utilization of diabetic medication, or confirmation via a physician's diagnosis of diabetes. In the context of type 2 diabetes, diagnosis was established through self-reported medical history of physician diagnosis. The categorization of diabetic retinopathy was in accordance with the international clinical classification, as outlined in Table 1 [8].

Examination

Clinical data collection of relevant indicators: For the purpose of data harmonization, the clinical information was systematically gathered in adherence with a standardized observation Table 2. Subsequently, this data was uniformly input into the designated data acquisition system. The information encompassed the following aspects: Basic Information: Patient particulars, including name, gender, age, date of birth, nationality, occupation, concurrent medical conditions, personal history, allergy history, family medical history, diabetes duration, medication regimen, dietary particulars, height, weight, and Body Mass Index (BMI) calculation.

Study and analytical components: Laboratory assessments were conducted, necessitating fasting periods of 10 hours to 12 hours prior to morning venous blood collection for fasting blood glucose measurement. The Body Mass Index (BMI) was calculated by dividing weight by the square of height (kg/m²). Serum creatinine, blood uric acid, and fasting blood glucose were quantified utilizing an automated biochemical analyzer (Hitachi 7600-210, Hitachi, Tokyo, Japan). HbA1c levels were determined using the Glycosylated Hemoglobin Assay Meter (Bio-Rad VARIANT-II, USA), while β2 microglobulin was assessed through nephelometry (Siemens, BN II).

Ophthalmic examination: A comprehensive ophthalmic examination encompassed several critical aspects: Uncorrected visual acuity and best corrected visual acuity. Intraocular pressure measurement utilizing a non-contact tonometer (CT-80A Co., Ltd. Topcon, Japan), with a standard intraocular pressure threshold of ≤21 mm Hg, slit lamp examination, Mydriatic fundus photography, which may entail fundus fluorescein angiography, Visual acuity assessment was conducted employing the internationally recognized 5-meter vision chart. Patients with refractive errors underwent optometry examination. Fundus examination employed mydriasis and 90D indirect ophthalmoscopy, complemented by fundus color photography. This approach facilitated the observation of various lesions, including retinal microvascular anomalies, retinal hemorrhage range and count, retinal bead extent, retinal

Table 1: International clinical classification of diabetic retinopathy.

Property Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No Apparent Retinopathy	€ No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just Microaneurysms but less than severe NPDR
Severe Non-Proliferative Diabetic Retinopathy	Any of the following: € More than 20 intraretinal hemorrhages in each of 4 quadrants € Definite Venous beading in 2+ quadrants € Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or more of the following: € Neovascularization € Vitreous/preretinal hemarrhage

microvascular abnormalities, retinal neovascularization, vitreous hemorrhage, and pre-retinal hemorrhage.

Statistical analysis

Statistical methodologies were systematically applied for robust analysis: One-way ANOVA analysis was utilized to detect significant differences among distinct groups. Pearson's test was employed for comparisons between two groups. Ordinal logistic regression analysis was conducted, employing the severity of Diabetic Retinopathy (DR) as the dependent variable. This facilitated an assessment of the relationship between various risk factors and the progression of DR.

Result

Analyzing the Impact of Physiological and Biochemical Factors on Different Progress Phases of Diabetic Retinopathy in T2DM Patients.

To investigate the influence of physiological and biochemical factors on renal function across distinct phases of Diabetic Retinopathy (DR) in Type 2 Diabetes Mellitus (T2DM) patients, we undertook an extensive analysis employing one-way ANOVA and Pearson's test. Our study encompassed 1500 subjects distributed across control, NPDR, Mild-NPDR, Moderate NPDR, Severe NPDR, and PDR groups.

Physiological Factors

Age and DR progression: Employing one-way ANOVA and Pearson's test, we scrutinized the relationship between age range and DR severity progression. The analysis was carried out within age brackets of 35-44, 45-54, 55-64, and >64. The findings indicated that within the Severe PDR group, the number of subjects within the age range of 55-64 and >64 was significantly higher than in the preceding groups ($p<0.01$) (Figure 1A).

BMI and DR Progression: We evaluated the association between Body Mass Index (BMI) and DR progression (Figure 1B). A comparative analysis showed that the BMI of patients in the Moderate NPDR group was significantly higher than those in the Mild NPDR group ($p<0.05$). Furthermore, patients in the PDR group demonstrated significantly higher BMI than those in the Severe NPDR group ($p<0.05$). When considering the BMI ranges of <25, 25-29.9, and >29.9, Moderate NPDR and Severe NPDR groups displayed higher BMI values compared to the preceding group within the 25-29.9 range ($p<0.05$). Severe NPDR and PDR groups exhibited elevated BMI values compared to the preceding group within the >29.9 range ($p<0.05$).

Blood glucose and HbA1c levels: In terms of blood glucose control, we measured blood glucose and HbA1c levels. ANOVA

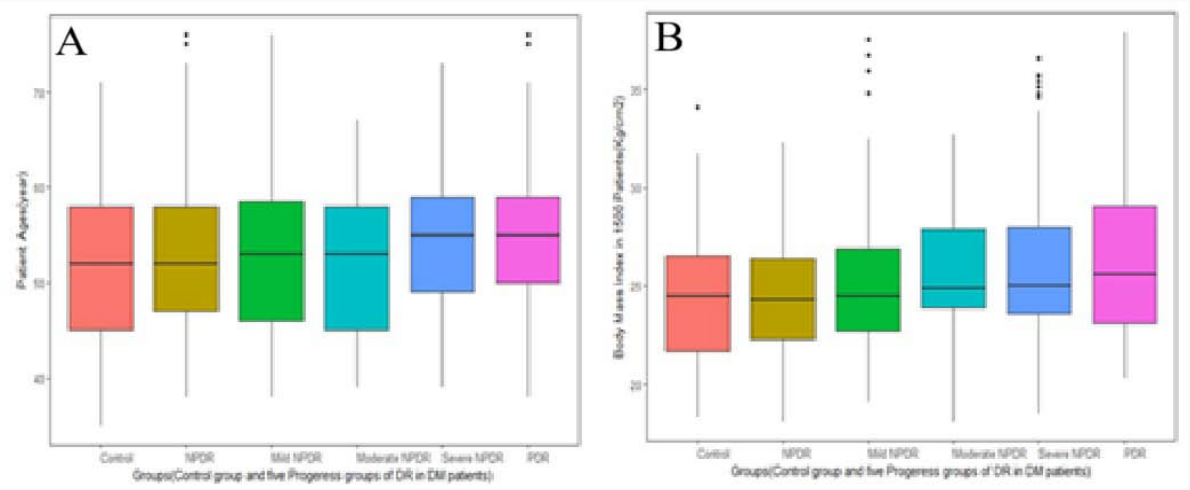

Figure 1: Physiological factors (Age and BMI) in control, NPDR, Mild NPDR, Moderate NPDR, Severe NPDR and PDR groups in 1500 patients. Median, minim value, maxim value and outliers are shown in the graphs.
A. Patient ages. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed patients with Severe PDR group were significantly older than Moderate NPDR groups ($p<0.01$).
B. BMI in patients. ANOVA analysis showed that it has significant difference among these groups. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed patients with Moderate NPDR group were significantly higher than Mild NPDR groups ($p<0.05$), and patients with PDR group were significantly higher than Severe NPDR group ($p<0.05$).

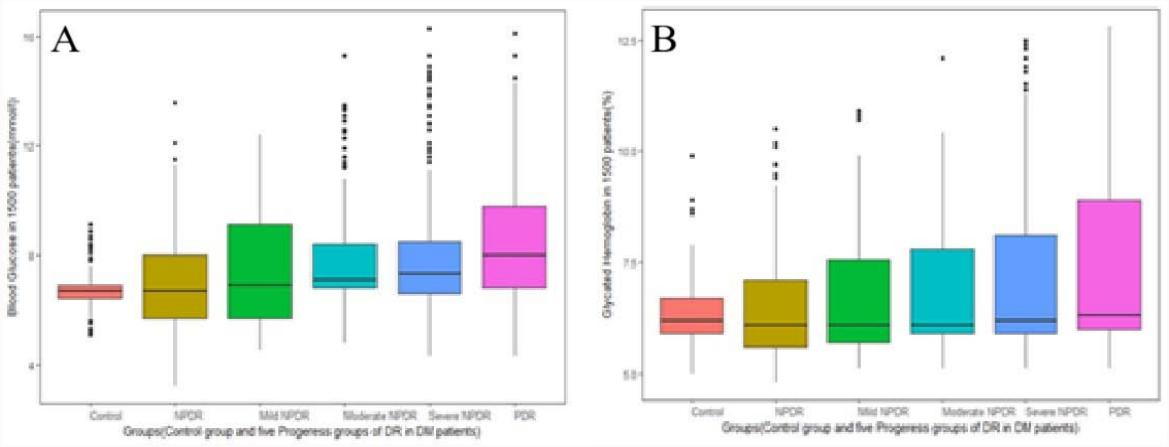

Figure 2: Reaction to control situation of Blood Glucose (Blood Glucose and HbA1c) in control, NPDR, Mild NPDR, Moderate NPDR, Severe NPDR and PDR groups in 1500 patients. Median, minim value, maxim value and outliers are shown in the graphs.
A. Blood Glucose in patients. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed that Mild NPDR group were significantly higher than NPDR group ($p<0.05$), Severe NPDR group were significantly higher than Moderate NPDR group ($p<0.05$), and PDR group were significantly higher than Severe NPDR groups ($p<0.05$).
B. HbA1c in patients. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed that Severe NPDR group were significantly higher than Moderate NPDR group ($p<0.05$), and PDR group were significantly higher than Severe NPDR groups ($p<0.05$).

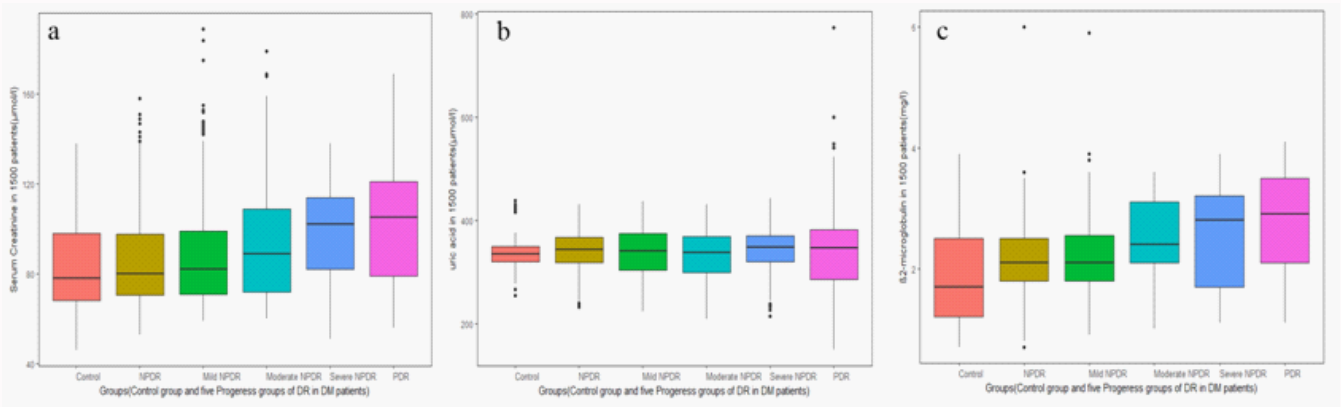

Figure 3: Biochemical factors (Ser, UA and B2-MG) in control, NPDR, Mild NPDR, Moderate NPDR, Severe NPDR and PDR groups in 1500 patients. Median, minim value, maxim value and outliers are shown in the graphs. A. Ser in patients. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed that Moderate NPDR group were significantly higher than Mild NPDR group ($p<0.05$), and Severe NPDR group were significantly higher than Moderate NPDR groups ($p<0.05$).
B. UA in patients. ANOVA analysis showed that it has no significant difference among these groups. However, based on Pearson analysis, compared each group with the previous one group showed that Severe NPDR group were significantly higher than Moderate NPDR groups ($p<0.05$).
C. B2-MG in patients. ANOVA analysis showed that it has significant difference among these groups ($p<0.01$). And based on Pearson analysis, compared each group with the previous one group showed that Mild NPDR group were significantly higher than NPDR group ($p<0.01$), Moderate NPDR group were significantly higher than Mild NPDR group ($p<0.05$), Severe NPDR group were significantly higher than Moderate NPDR groups ($p<0.05$), and PDR group were significantly higher than Severe NPDR groups ($p< 0.05$).

analysis demonstrated significant differences among the groups. Pearson analysis revealed specific differences between each group and its predecessor. For blood glucose, Mild NPDR group exhibited significantly higher levels compared to the NPDR group ($p<0.05$), Severe NPDR group displayed significantly higher levels than Moderate NPDR group ($p<0.05$), and PDR group showcased significantly higher levels compared to Severe NPDR group ($p<0.05$) (Figure 2A). Regarding HbA1c levels, Severe NPDR group recorded significantly higher levels than the Moderate NPDR group ($p<0.05$), and the PDR group exhibited significantly higher levels than the Severe NPDR group ($p<0.05$) (Figure 2B).

Biochemical factors

Renal Function Impact: Employing one-way ANOVA and Pearson's test, we evaluated the impact of varying degrees of diabetic retinopathy on renal function, particularly Scr, UA, and β2-MG. The analysis revealed significant differences in Scr levels. Moderate NPDR group displayed significantly higher levels compared to the Mild NPDR group ($p<0.05$), and Severe NPDR group exhibited significantly higher levels than the Moderate NPDR group ($p<0.05$) (Figure 3A). Regarding UA, the Severe NPDR group exhibited significantly higher levels than the Moderate NPDR group ($p<0.05$) (Figure 3B). In terms of β2-MG, the Mild NPDR group demonstrated significantly higher levels than the NPDR group ($p<0.01$), Moderate NPDR group recorded significantly higher levels than the Mild NPDR group ($p<0.05$), Severe NPDR group exhibited significantly higher levels than the Moderate NPDR group ($p<0.05$), and PDR

Table 2: Descriptive data and frequency analysis for general, clinical and biochemical characteristics of 1500 patients. This P-value is based on one-way ANOVA analysis. We also perform Pearson analysis between each two groups when P-value is showed statistic difference among each group.

	None Diabetes Mellitus	Diabetes Mellitus (DM) (n=1251)					
	Control (n=249)	No apparent retinopathy (NPDR) (n=251)	Mild non-proliferative (Mild NPDR) (n= 259)	Moderate non-proliferative diabetic (Moderate NPDR) (n=257)	Severe non-proliferative diabetic retinopathy (Severe NPDR) (n=246)	Proliferative diabetic retinopathy (PDR) (n=238)	One way ANOVA P-value
Age (years)	53.56 ± 7.90	53.91 ± 8.00	54.69 ± 10.06	55.61 ± 7.65	55.72 ± 7.49	56.29 ± 7.41	<0.01
	(Mean ± SD) n(%)	(Mean ± SD) n(%)	(Mean ± SD) n(%)	(Mean ± SD n (%)	(Mean ± SD) n(%)	(Mean ± SD) n(%)	
35-44	39.6 ± 2.32 15(6.02%)	40.12 ± 3.12 13(5.18%)	39.64 ± 2.34 55(21.23%)	39.61 ± 2.43 14(5.45%)	39.13 ± 2.26 15(6.10%)	42.00 ± 2.34 13(5.04%)	<0.01
45-54	47.66 ± 2.66 107(42.97%)	49.44 ± 3.71 107(42.63%)	48.07 ± 2.81 43(16.60%)	47.66 ± 2.66 77(29.96%)	49.81 ± 3.06 70(28.46%)	49.75 ± 2.95 92(38.66%)	<0.01
55-64	58.38 ± 3.08 100(40.16%)	58.02 ± 2.47 100(39.84%)	59.06 ± 2.69 122(47.10%)	58.38 ± 3.08 137(53.31%)	61.62 ± 1.43 132(53.66%)	58.03 ± 2.67 124(52.10%)	<0.01
≥65	66.81 ± 0.56 27(10.84%)	70.48 ± 3.81 31(12.35%)	66.96 ± 0.94 39(15.05%)	67.10 ± 1.16 29(11.28%)	69.56 ± 5.17 246(11.79%)	68.02 ± 3.20 9(3.78%)	<0.01
DM duration (years)	0	11.80 ± 1.71	11.67 ± 1.53	11.71 ± 1.67	11.92 ± 1.58	11.68 ± 1.35	NS
Sex (% male)	53.4	58.6	57.5	59.5	59.3	61.8	
Blood glucose	4.96 ± 0.91	7.39 ± 0.73	8.29 ± 1.87	8.87 ± 0.68	10.08 ± 1.20	11.30 ± 0.52	<0.01
Glycated hemoglobin (HbA1c)(%)	5.12 ± 1.09	5.23 ± 1.18	7.70 ± 0.53	8.17 ± 0.70	9.05 ± 0.61	9.73 ± 0.86	<0.05
Body Mass Index (BMI) (Kg/cm^2)	19.03 ± 1.60	23.10 ± 1.68	24.53 ± 1.30	25.96 ± 1.54	27.75 ± 1.42	29.57 ± 1.44	<0.01
Serum creatinine (Scr) (μmol/l)	66.29 ± 11.90	67.10 ± 10.59	72.21 ± 5.76	90.09 ± 8.39	91.44 ± 6.51	111.03 ± 10.73	<0.01
Uric acid (UA)(μmol/l)	231.61 ± 42.93	255.78 ± 24.50	307.65 ± 26.35	329.37 ± 24.48	371.855 ± 21.43	401.71 ± 38.23	<0.01
β2 microglobulin (β2-MG)(mg/l)	2.86 ± 16.52	1.11 ± 0.42	2.05 ± 0.36	2.69 ± 0.42	3.05 ± 0.55	3.50 ± 0.35	<0.01

Table 3: Univariate Odd ratio and 95% confidence intervals for risk factors of all patients were estimated by using multinomial logistic regression.

	NPDR		Mild NPDR		Moderate NPDR		Severe NPDR		PDR	
Risk factors	OR (95%CI)	P-valve	OR (95%CI)	P-valve	OR (95%CI)	P-valve	OR (95%CI)	P-valve	OR (95%CI)	P-valve
Age ≥ 45 years	1.84 (1.21-2.79)	p<0.01	1.32 (0.89-1.95)	0.17	1.09 (0.74-1.60)	0.67	1.94 (1.27-2.97)	p<0.01	1.81 (1.19-2.77)	p<0.01
Male gender	0.81 (0.57-1.16)	0.24	0.85 (0.60-1.20)	0.35	0.78 (0.55-1.11)	0.17	0.79 (0.55-1.12)	0.18	0.72 (0.50-1.04)	0.08
Blood glucose (≥ 7.0 mmol/l)	0.79 (0.54-1.16)	0.23	0.7 (0.48-1.02)	0.06	1.46 (0.98-2.20)	0.06	1.83 (1.20-2.81)	p<0.01	2.66 (1.67-4.25)	p<0.0001
HbA1c (≥ 8.5%)	1.25 (0.88-1.78)	0.21	1.12 (0.79-1.59)	0.51	1.42 (1.00-2.01)	p<0.05	2.4 (1.67-3.45)	p<0.0001	2.55 (1.76-3.69)	p<0.0001
BMI (≥ 25 Kg/cm^2)	0.91 (0.63-1.30)	0.6	1.21 (0.85-1.73)	0.29	1.39 (0.98-1.99)	0.07	3.64 (2.51-5.29)	p<0.0001	1.7 (1.19-2.44)	p<0.01
Scr (≥ 133 μmol/l)	1.4 (0.438-4.47)	0.57	2.16 (0.74-6.32)	0.15	6.45 (2.46-16.91)	p<0.0001	0.81 (0.21-3.04)	0.75	6.61 (4.36-10.05)	p<0.0001
UA (≥ 356 μmol/l)	4.27 (2.57-7.08)	p<0.0001	5.6 (3.40-9.21)	p<0.0001	5.86 (3.56-9.64)	p<0.0001	8.35 (5.08-13.72)	p<0.0001	13.56 (8.22-22.36)	p<0.0001
β2-MG (≥ 2.4 mg/l)	0.53 (0.34-0.85)	p<0.01	0.62 (0.40-0.97)	p<0.05	2.98 (4.06-9.96)	p<0.01	9.77 (6.48-14.75)	p<0.0001	10.96 (7.19-16.69)	p<0.0001

OR: Odds Ratios; CI: Confidence Interval

group showcased significantly higher levels than the Severe NPDR group (p<0.05) (Figure 3C).

Risk Factors for DR

As outlined in Table 3, our analysis of the ordinal logistic regression unveiled key risk factors associated with various DR groups. These findings underscore the significance of age, blood glucose, Scr, UA, and β2-MG in predicting the severity of DR in different patient cohorts.

Discussion

Global Impact of Diabetes Mellitus and the Significance of Investigating Physiological and Biochemical Factors in Diabetic Retinopathy

The worldwide prevalence of Diabetes Mellitus (DM) among adults has surged to 9%, emerging as a formidable global health concern [9]. Currently, an estimated 3.18 billion individuals are afflicted with diabetes, and this number is escalating at a rate exceeding 8.3% [10]. Hence, investigating the impact of physiological and biochemical factors on the severity scale of Diabetic Retinopathy (DR) in Type 2 diabetes (T2DM) patients holds profound implications for mitigating the incidence and blindness rates among DR patients.

BMI's relationship with DR

BMI's influence on DR has yielded contradictory outcomes in prior research [11,12]. Nevertheless, studies have demonstrated a positive correlation between elevated BMI and Waist-to-Hip Ratio (WHR) [13]. Our study concurs, revealing significantly higher BMI values in the Moderate and PDR phases compared to their preceding phases. Although BMI's role in DR remains complex, maintaining optimal BMI and WHR in diabetic patients is paramount to stalling

DR progression and related complications.

Hyperglycemia's impact

Hyperglycemia is a pivotal factor in DR pathogenesis; inadequate blood glucose control heightens DR risk, whereas sustained glycemic control curbs complication emergence (Galicia-Garcia et al., 2020). Vigilant blood glucose control is pivotal in preventing and delaying DR, with studies demonstrating that early control yields better outcomes than subsequent intervention [14]. Enhanced glycemic control substantially reduces DR risk [14] and its severity [15]. Our findings align, indicating that elevated blood glucose levels correspond to escalated retinal lesions and an augmented risk of DR progression.

HbA1c and DR

HbA1c emerges as a pivotal factor in DR progression, reflecting average blood glucose levels over 2 to 3 months [16]. Our study indicates significantly elevated HbA1c levels in Severe NPDR and PDR phases, highlighting the correlation between suboptimal blood glucose control and heightened retinopathy.

Renal function and DR

This study made several significant findings related to Diabetic Retinopathy (DR) and its associations with kidney function markers. Here is an improved version of your text with enhanced clarity and flow:

The findings of this study revealed notable insights into the progression of Diabetic Retinopathy (DR) and its relationship with kidney function markers. Notably, the levels of Serum Creatinine (Scr) in patients with Moderate Non-Proliferative Diabetic Retinopathy (NPDR) and Severe NPDR were found to be significantly higher than those in the preceding phase. Additionally, Uric Acid (UA) levels were significantly elevated in the Severe NPDR phase compared to the previous phase.

Furthermore, β2-Microglobulin (β2-MG) levels in NPDR patients were significantly higher than in non-diabetic patients ($p<0.01$). When examining specific DR phases, β2-MG levels were found to significantly increase in Moderate NPDR, Severe NPDR, and Proliferative Diabetic Retinopathy (PDR) phases when compared to their respective preceding groups.

Scr is a reliable indicator of renal function, primarily reflecting changes in glomerular filtration. When Scr levels exceed 124 μmol/L, it is indicative of renal dysfunction [17]. β2-MG is a crucial marker for assessing renal function [17,18].

Hyperuricemia is a common occurrence in individuals with diabetes, with a prevalence ranging from 6.79% to 41.46% in the Chinese population, notably higher in coastal areas and urban settings [19]. This condition is primarily linked to reduced uric acid excretion. Diabetes patients often experience insulin resistance, which affects the reabsorption of uric acid by renal transporters, ultimately leading to elevated UA levels [20].

In our study, the Odds Ratios (OR) for β2-MG, Scr, and UA demonstrated an increased risk of DR with advancing stages of DR. Our results align with previous research, such as the finding that every 1 μmol/L increase in UA raised the risk of diabetes by 1.11 times [21]. Furthermore, studies conducted in the United States indicated that individuals with diabetic nephropathy had a 2.14 times higher risk of elevated UA levels compared to those with normal UA levels [22]. It has also been demonstrated that UA can contribute to early diabetic nephropathy in Type 2 diabetes patients, and maintaining lower UA levels can reduce the progression of diabetic nephropathy [23]. In conclusion, while renal function assessment cannot rely solely on Scr, UA, and other clinical parameters within normal ranges, the identification of abnormal levels of Scr, UA, and β2-MG underscores the importance of timely monitoring of renal function. Such vigilance plays a crucial role in preventing and delaying the onset and progression of diabetic retinopathy. Our study is pioneering in its approach to exploring the influence of physiological and biochemical factors across various DR progression phases. The implications are far-reaching, potentially reducing DR incidence and blindness rates, thereby addressing a pressing global health concern.

This study represents the first comprehensive investigation into the diverse progressions of individuals afflicted with Diabetic Retinopathy (DR), with a specific focus on evaluating their physiological and biochemical factors. The results of this research hold significant promise, with the potential to substantially diminish both the occurrence and the prevalence of blindness among DR patients.

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