25-Hydroxyvitamin D and Lipoprotein-Associated Phospholipase A2 Are Correlated with Diabetic Retinopathy Postprint

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Abstract

Objective: To investigate the correlation between 25-hydroxyvitamin D [25(OH)D], lipoprotein-associated phospholipase A2 (LP-PLA2) and diabetic retinopathy (DR). Methods: Clinical data of patients with type 2 diabetes admitted to the Department of Endocrinology, Cangzhou Central Hospital from May 2014 to January 2017 were retrospectively collected and analyzed. Based on fundus photography results, patients were divided into a diabetes without retinopathy (no DR, NDR) group, a background diabetic retinopathy (background DR, BDR) group, and a proliferative diabetic retinopathy (proliferative DR, PDR) group. Healthy individuals undergoing physical examination in the same hospital during the same period were selected as the control group. Relevant biochemical indicator levels among the four groups were compared, and Pearson correlation analysis and multiple logistic regression analysis were performed for each indicator. Results: A total of 340 patients with type 2 diabetes who met the inclusion and exclusion criteria were enrolled in this study, including 125 cases in the NDR group, 118 cases in the BDR group, 97 cases in the PDR group, and 100 cases in the control group. There were no statistically significant differences in gender, age, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose among the four groups (all $P>0.05$). The disease duration progressively increased in the NDR, BDR, and PDR groups. Glycated hemoglobin A1c (HbA1c), glycated albumin (GA), serum cystatin C (Cys-C), LP-PLA2, and 25(OH)D in the NDR, BDR, and PDR groups were all significantly higher than those in the healthy control group (all $P<0.05$). Pairwise comparisons among the NDR, BDR, and PDR groups also showed statistically significant differences in HbA1c, GA, Cys-C, LP-PLA2, and 25(OH)D (all $P<0.05$). Pearson correlation analysis showed that disease

duration, HbA1c, GA, Cys-C, and LP-PLA2 were positively correlated with DR (all P=0.000), while 25(OH)D was negatively correlated with DR (P=0.000). Multiple logistic regression analysis showed that disease duration, HbA1c, Cys-C, and LP-PLA2 were independent risk factors for DR, while 25(OH)D was a protective factor for DR (all P<0.05). Conclusion: Changes in 25(OH)D and LP-PLA2 levels are closely related to the occurrence and progression of DR, with 25(OH)D being a protective factor and LP-PLA2 being a risk factor.

Full Text

Correlation of 25-Hydroxyvitamin D and Lipoprotein-Associated Phospholipase A2 with Diabetic Retinopathy

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Abstract

Objective: To investigate the correlation between 25-hydroxyvitamin D [25(OH)D] and lipoprotein-associated phospholipase A2 (LP-PLA2) with diabetic retinopathy (DR).

Methods: Clinical data of patients with type 2 diabetes mellitus admitted to the Department of Endocrinology at Cangzhou Central Hospital from May 2014 to January 2017 were retrospectively collected and analyzed. Based on fundus photography results, patients were divided into three groups: diabetes without retinopathy (no DR, NDR), background diabetic retinopathy (BDR), and proliferative diabetic retinopathy (PDR). Healthy subjects undergoing physical examination at our hospital during the same period were selected as the control group. Relevant biochemical indices were compared among the four groups, and Pearson correlation analysis and multiple logistic regression analysis were performed for each index.

Results: A total of 340 patients with type 2 diabetes (125 in the NDR group, 118 in the BDR group, and 97 in the PDR group) and 100 control subjects were enrolled. There were no significant differences in sex, age, body mass index, blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or fasting plasma glucose among the four groups (all $P > 0.05$). The disease duration progressively increased from the NDR to BDR to PDR groups ($P < 0.05$). HbA1c, glycated albumin (GA), serum cystatin C (Cys-C), LP-PLA2, and 25(OH)D levels in the NDR, BDR, and PDR groups were significantly higher than those in the control group ($P <$

0.05). Among the NDR, BDR, and PDR groups, HbA1c, GA, Cys-C, LP-PLA2, and 25(OH)D also showed significant differences (all $P < 0.05$). Pearson correlation analysis revealed that disease duration, HbA1c, GA, Cys-C, and LP-PLA2 were positively correlated with DR (all $P < 0.05$), while 25(OH)D was negatively correlated with DR ($P < 0.05$). Logistic regression analysis showed that disease duration, HbA1c, Cys-C, and LP-PLA2 were independent risk factors for DR, while 25(OH)D was a protective factor (all $P < 0.05$).

Conclusions: The levels of 25(OH)D and LP-PLA2 are closely related to the occurrence and development of DR. 25(OH)D is a protective factor, while LP-PLA2 is a risk factor.

Keywords: 25-hydroxyvitamin D; lipoprotein-associated phospholipase A2; type 2 diabetic retinopathy

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1. Materials and Methods

1.1 Study Subjects

We retrospectively analyzed clinical data of inpatients with type 2 diabetes mellitus in the Department of Endocrinology at Cangzhou Central Hospital from May 2014 to January 2017. Inclusion criteria were: (1) diagnosis of type 2 diabetes according to WHO criteria; (2) patients receiving treatment; (3) fundus photography performed using non-mydriatic color fundus photography, with all images read by the same ophthalmologist. Exclusion criteria included: (1) severe cardiac, hepatic, or renal disease; (2) acute diabetic complications; (3) other ocular diseases; (4) vitamin D or bone metabolism-affecting drugs taken within the past year; (5) gestational diabetes; (6) acute or chronic infectious diseases; (7) rheumatic immune diseases. Healthy subjects undergoing physical examination at our hospital during the same period were selected as the control group.

Diagnostic criteria for diabetic retinopathy and diabetic macular edema were based on the 2014 clinical grading standards of the Sydney International Ophthalmology Society. Patients were divided into three groups according to disease severity: diabetes without retinopathy (NDR), background diabetic retinopathy (BDR), and proliferative diabetic retinopathy (PDR).

1.2 Research Methods

General clinical data including gender, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), disease duration, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), glycated albumin (GA), serum cystatin C (Cys-C), LP-PLA2, and 25(OH)D were collected and recorded.

Detection methods: TC and TG were measured by enzymatic methods (Changchun Huili Biotechnology Co., Ltd.). HDL-C and LDL-C were measured by direct methods (Xiamen Haifei Biotechnology Co., Ltd.). FPG was measured by glucose oxidase method. HbA1c was measured by colorimetric method (Roche Diagnostics Shanghai Co., Ltd.). GA was measured by enhanced immunoturbidimetry (Shanghai Jiemei Gene Pharmaceutical Technology Co., Ltd.). Cys-C was measured by immunoturbidimetry (Wuhan Bomaite Biotechnology Co., Ltd.). LP-PLA2 was measured by double-antibody sandwich enzyme-linked immunosorbent assay (Tianjin Kang 尔克 Biotechnology Co., Ltd.). 25(OH)D was measured by electrochemiluminescence (积水医疗科技).

1.3 Statistical Analysis

SPSS 19.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. Inter-group comparisons were performed using one-way ANOVA. Pearson correlation analysis and multiple logistic regression analysis were used for correlation analysis. $P < 0.05$ was considered statistically significant.

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2. Results

2.1 General Clinical Data

There were no statistically significant differences in gender, age, BMI, blood pressure, or other general clinical data among the NDR, BDR, PDR, and control groups (all $P > 0.05$). As the disease severity increased, the disease duration progressively increased from the NDR to BDR to PDR groups ($P = 0.003$).

Comparison of general clinical data between type 2 diabetic retinopathy patients and healthy controls

Group	n	Male/Female	Age (years)	Disease Duration (years)	BMI (kg/m²)	SBP (mmHg)	DBP (mmHg)
NDR	125	64/61	56.8±5.4	2.9±1.1	25.1±2.4	129.7±10.5	82.5±8.1
BDR	118	61/57	57.3±6.2	7.1±1.7	24.6±1.9	134.2±11.8	81.4±8.6
PDR	97	50/47	57.8±5.8	9.2±2.4	25.5±2.1	136.5±12.3	80.8±7.9
Control	100	52/48	58.1±6.5	-	24.3±1.8	112.4±9.5	66.9±5.8

$P > 0.05$ for all comparisons among groups; NDR: diabetes without retinopathy; BDR: background diabetic retinopathy; PDR: proliferative diabetic retinopathy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

2.2 Serological Indicators

There were no significant differences in TC, TG, LDL-C, HDL-C, or FPG among the four groups (all $P > 0.05$). HbA1c, GA, Cys-C, LP-PLA2, and 25(OH)D levels in the NDR, BDR, and PDR groups were significantly higher than those in the control group ($P < 0.05$). Among the NDR, BDR, and PDR groups, HbA1c, GA, Cys-C, LP-PLA2, and 25(OH)D also showed significant differences (all $P < 0.05$).

Comparison of serological indicators between type 2 diabetic retinopathy patients and healthy controls

Group	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	FPG (mmol/L)	HbA1c (%)	GA (%)	Cys-C (mg/L)	LP-PLA2 (g/L)	25(OH)D (nmol/L)
NDR	4.92±1.03	1.81±0.27	2.63±1.02	1.46±0.65	7.69±1.57	7.2±1.8	21.46±3.9	0.94±0.71	73.46±14.72	60.5±7.9
BDR	4.99±1.08	1.75±0.22	2.65±1.01	1.38±0.58	8.25±1.84	8.6±2.1	22.51±3.5	1.72±0.14	145.68±28.53	45.3±5.8
PDR	5.13±1.14	1.88±0.34	2.58±1.04	1.33±0.61	8.81±1.90	10.4±2.2	25.77±4.3	1.52±0.19	191.73±31.6	31.6±5.1
Control	3.86±0.41	1.13±0.25	2.16±0.83	1.75±0.79	4.91±1.35	5.3±1.4	16.74±0.2	0.65±0.20	10.4±4.6	173.59±34.16

$P < 0.05$ compared with control group; $P < 0.05$ for pairwise comparisons among NDR, BDR, and PDR groups; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin A1c; GA: glycated albumin; Cys-C: serum cystatin C; LP-PLA2: lipoprotein-associated phospholipase A2; 25(OH)D: 25-hydroxyvitamin D

2.3 Correlation Analysis of Diabetic Retinopathy

Pearson correlation analysis showed that disease duration ($r = 0.272$, $P = 0.000$), HbA1c ($r = 0.248$, $P = 0.000$), GA ($r = 0.326$, $P = 0.000$), Cys-C ($r = 0.121$, $P = 0.000$), and LP-PLA2 ($r = 0.391$, $P = 0.000$) were positively correlated with DR, while 25(OH)D was negatively correlated with DR ($r = -0.371$, $P = 0.000$).

2.4 Risk Factor Analysis for Diabetic Retinopathy

Logistic regression analysis showed that disease duration, HbA1c, Cys-C, and LP-PLA2 were independent risk factors for DR, while 25(OH)D was a protective factor (all $P < 0.05$).

Risk factor analysis for diabetic retinopathy

Factor		SE	Wald ^{2}	P	OR	95% CI
Disease duration	1.713	0.562	9.514	0.000	6.093	1.763-18.253
HbA1c	1.802	0.571	9.565	0.000	6.184	1.865-18.731
Cys-C	0.473	0.588	0.672	0.359	1.593	0.562-4.775
LP-PLA2	2.316	0.675	8.641	0.001	5.972	1.157-3.026
25(OH)D	-0.601	0.104	16.248	0.000	0.374	0.031-0.391

3. Discussion

Diabetic retinopathy is a highly specific microvascular complication of diabetes and one of the most common chronic microvascular complications in clinical practice. Approximately 30-40% of patients with type 2 diabetes develop retinopathy, which can lead to severe vision impairment and even blindness, significantly affecting patients' quality of life. The pathogenesis of DR involves microcirculatory disturbances, chronic inflammation, hyperlipidemia, and other factors.

25(OH)D is a fat-soluble steroid derivative whose primary function is to regulate calcium and phosphorus metabolism, but it also participates in immune regulation and anti-inflammatory defense. When vitamin D levels are deficient, the regulatory effect on immune function weakens, leading to retinal vascular endothelial damage. Multiple studies have shown that 25(OH)D is closely related to the occurrence and development of diabetes and diabetic vascular complications. 25(OH)D is the main circulating form and storage form of vitamin D in the body, which can effectively reflect endogenous and exogenous vitamin D status. It has strong antioxidant capacity, can reduce free radicals, protect cell membranes, directly inhibit inflammatory responses, and reduce the secretion of inflammatory factors such as interleukin-6. The results of this study showed that 25(OH)D levels in the NDR, BDR, and PDR groups were significantly lower than those in the control group ($P < 0.05$), and 25(OH)D levels progressively decreased with increasing disease severity ($P < 0.05$). Correlation analysis showed that 25(OH)D was negatively correlated with DR ($P < 0.05$), and logistic regression analysis confirmed that 25(OH)D is a protective factor for DR.

LP-PLA2 is a member of the phospholipase superfamily, mainly secreted by macrophages and lymphocytes. It has the function of hydrolyzing platelet-activating factor and can promote the oxidative metabolism of low-density lipoprotein, producing lysophosphatidylcholine and oxidized free fatty acids, which cause vascular endothelial cell dysfunction and promote the formation of new atherosclerotic plaques. LP-PLA2 is a new inflammatory marker of

atherosclerosis and is closely related to blood lipid levels, especially showing the strongest correlation with LDL-C levels. Studies have shown that LP-PLA2 is an independent risk factor for atherosclerosis and is related to its endpoint events. DR and atherosclerosis have similar pathological changes, including inflammatory responses, neovascularization, cell apoptosis, and hypercoagulable states. The results of this study showed that LP-PLA2 levels in the NDR, BDR, and PDR groups were significantly higher than those in the control group ($P < 0.05$), and LP-PLA2 levels progressively increased with increasing disease severity ($P < 0.05$). Correlation analysis showed that LP-PLA2 was positively correlated with DR ($P < 0.01$), and logistic regression analysis confirmed that LP-PLA2 is an independent risk factor for DR.

In conclusion, the changes in 25(OH)D and LP-PLA2 levels are closely related to the occurrence and development of DR. 25(OH)D is a protective factor, while LP-PLA2 is a risk factor. However, this study is a retrospective study, and large-sample prospective studies and randomized controlled trials are needed for further validation in the future.

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Note: Figure translations are in progress. See original paper for figures.