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Original Article

Correlation of retinopathy with serum levels of growth hormones and insulin-like growth factor-1 in patients with diabetic retinopathy

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Abstract: Objective: This study aims to retrospectively analyze the correlation between levels of serum growth hormones and insulin-like growth factor-1 (IGF-1) and severity of retinopathy in type 2 diabetes patients reaching the goal of blood glucose control. Method: A retrospective analysis was adopted for 112 type 2 diabetes patients reaching the goal of blood glucose control in the past 3 years. All patients received fundus fluorescein angiography, based on which the patients were divided into normal fundus group, non-proliferative diabetic retinopathy (DR) group and proliferative DR group. The three groups were compared with regard to the levels of serum growth hormones and IGF-1. Their correlation with severity of DR was assessed using multivariate unconditional logistic regression. Result: In the proliferative DR group, the levels of low density lipoprotein cholesterol (LDL-C), urine micro albumin (UmALB), serum growth hormones and IGF-1 were all significantly higher than those of the normal group and the non-proliferative DR group ($P<0.05$); however, no significant difference was found between the non-proliferative DR group and the normal group ($P>0.05$). The C-peptide (C-P) level in the proliferative DR group was markedly lower than that of the other two groups ($P<0.05$); but no significant difference was found between the non-proliferative DR group and the normal group ($P>0.05$). As indicated by correlation analysis, course of disease, UmALB, IGF-1 and fasting C-P levels were correlated to the severity of DR. Conclusion: The common factors of DR are course of diabetes, systolic pressure, LDL-C, fasting C-R risk and UmALB. In addition to these, higher levels of serum growth hormones and IGF-1 may also contribute to DR, which is speculated to be one mechanism for the progression of DR in type 2 diabetes.

Keywords: Diabetic retinopathy, serum growth hormones, insulin-like growth factor-1

Introduction

Diabetic retinopathy (DR) is a common type of microvascular complication in diabetes and also among the main causes of blindness. The risk factors believed to be associated with DR include course of diabetes, glycated hemoglobin (HhA1c), blood pressure, low density lipoprotein cholesterol (LDL-C), urine micro albumin (UmALB), and possibly vascular endothelial growth factors (VEGF) [1]. However, they cannot explain every aspect of pathogenesis of DR. According to the latest report, growth hormones (GH) and insulin-like growth factor-1 (IGF-1) may be also involved [2]. The present study assessed the correlation between GH and IGF-1 for type 2 diabetes (T2DM) patients combined with different severity of DR, so as to identify other potential risk factors of DR.

Materials and methods

Subjects

From January 2012 to June 2015, 128 T2DM patients treated at our hospital with complete data were included. The diagnosis was based on 1999 WHO criteria [3]. The patients included 78 males and 50 females with an average age of 57.4 ± 11.2 years and course of 12.7 ± 3.2 years. The inclusion criteria were as follows: Confirmed T2DM and having received treat-

Table 1. Comparison of clinical characteristics among three groups of patients ($\bar{x} \pm s$)

Group	Case (n)	Age (years)	Course of disease (years)	Waist circumference (cm)	BMI (Kg/M^2)	SBP (mmHg)	DBP (mmHg)
PDR group	23	56.9 ± 10.42	13.45 ± 4.22	91.54 ± 4.94	23.89 ± 3.86	129.69 ± 13.87	85.55 ± 8.94
NPDR group	31	57.42 ± 9.24	11.63 ± 5.38*	90.15 ± 6.86	24.15 ± 5.14	125.65 ± 10.34	83.83 ± 7.82
N group	74	56.9 ± 13.55	10.81 ± 6.95*	93.25 ± 8.26	24.83 ± 4.82	127.43 ± 9.32	84.51 ± 8.43
F value	-	0.168	11.671	0.285	0.310	0.547	0.675
P value	-	0.506	0.004	0.753	0.734	0.073	0.531

*Compared with the PDR group, the difference was statistically significant (P<0.05).

ment at department of endocrinology of tertiary hospitals with regular follow-up. The treatment protocol conformed to China Guideline for Type 2 Diabetes (2013) [4]; Receiving detection of HbA1c 1 levels in the past 3 years for at least once a year and the result being below 7.5%; without contraindications for fundus fluorescein angiography. Exclusion criteria: grade 2 hypertension or above; abnormalities of the pituitary gland and thyroid; liver diseases or aminotransferase levels two times higher than the normal levels; abnormalities of major organs, including heart, lung, kidney and brain, had been treated with drugs that may affect GH; average number of hypoglycemia onset more than once weekly. All cases signed the informed consent.

Method

All cases received fundus fluorescein angiography. Diagnosis of proliferative DR (PDR) or non-proliferative DR (NPDR) was made according to China Guideline for Type 2 Diabetes (2013). Baseline indicators were measured for all patients: height, weight, waist circumference (WC), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), C-peptide (C-P), plasma glucose 2 h (2hPG) and C-P (2hC-P) after 100 g steamed bun diet, LDL-C, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), urine albumin (UA), GH and IGF-1. All indicators were measured at the Center for Clinical Laboratory of our hospital.

Statistical process

Statistical analysis was conducted using SPSS 18.0 software. Measurements were expressed as x ± s and the difference of the three groups was compared by analysis of variance. t-test was used for comparing the means of the two groups. Risk factors of DR were identified by using multivariate unconditional logistic regression, and P<0.05 was considered significant difference.

Results

According to the result of fundus fluorescein angiography, 128 T2DM patients were divided into 3 groups. PDR group had 23 cases (16 males and 7 females). NPDR group had 31 cases (19 males and 12 females). Normal group (N group) had 74 cases (43 males and 31 females). Of all baseline indicators, the three groups only differed significantly in the course of disease (P<0.05) (**Table 1**).

Blood marker tests of 3 groups indicated that C-P and 2hC-P levels of PDR group were significantly lower than those of NPDR and N groups (P<0.05); however, NPDR group and N group were not significantly different (P>0.05). The levels of LDL-C, UA, GH and IGF-1 were considerably higher in PDR group than in NPDR and N group (P<0.05). But no significant difference was found between NPDR and N groups (P>0.05) (**Table 2**).

Logistic regression

Taking DR as dependent variable and age, course of disease, WC, BMI, LDL-C, HDL-C, TG, TC, C-P, 2hC-P, UA, GH and IGF-1 as independent variables, multivariate logistic regression analysis was performed. The result showed that as far as the 128 T2DM patients were concerned, course of DM, UA, IGF-1 and fasting C-P correlated independently to DR (P<0.05) (**Table 3**).

Discussion

DR is a microvascular complication highly specific to DM. In developing countries, DR is the leading cause of blindness in adults, affecting

Table 2. Comparison of blood markers among three groups of patients ($\bar{x} \pm s$)

Group	GH (ng/ml)	IGF-1 (ng/ml)	C-P (ng/ml)	PC-P (ng/ml)	FPG (mmol/L)	LDL-C (mmol/L)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	UA (mg/L)	PPG (mmol/L)
PDR group	2.61 ± 1.32	158.5 ± 41.42	0.68 ± 0.41	1.43 ± 0.91	7.38 ± 1.54	4.85 ± 1.13	4.15 ± 1.79	5.16 ± 1.31	1.06 ± 0.39	262 ± 49.61	10.14 ± 2.45
NPDR group	1.83 ± 1.14*	132. ± 33.81*	0.93 ± 0.56*	2.66 ± 1.04*	7.85 ± 2.63	3.0 ± 1.10*	3.95 ± 1.31	5.01 ± 1.22	1.11 ± 0.65	221 ± 37.91*	9.96 ± 3.78
N group	1.75 ± 1.06*	129. ± 38.25*	0.99 ± 0.47*	3.11 ± 1.12*	6.93 ± 1.22	3.1 ± 1.24*	3.77 ± 1.21	4.91 ± 0.92	1.13 ± 0.82	218 ± 29.53*	9.63 ± 4.48
F value	*12.822*	*32.762*	*5.068*	*6.048*	*2.206*	*12.823*	*0.445*	*2.207*	*0.056*	*12.820*	*0.057*
P value	*0.002*	*0.013*	*0.014*	*0.005*	*0.063*	0.008	0.643	0.065	0.946	0.012	0.944

*Compared with the PDR group, the difference was statistically significant (P<0.05).

Table 3. Logistic regression analysis of DR-related factors

Variable	β value	Wald X^2 value	*P* value	OR value (95% CI)
Course of DM	0.483	12.181	0.001	1.811 (1.270-2.632)
IGF-1	0.229	7.843	0.033	1.211 (1.121-1.380)
UA	1.420	7.037	0.008	4.137 (1.455-11.211)
C-P	0.186	6.577	0.044	1.049 (1.012-1.098)

2-5% of total population. DR is seen in about 20-40% of T2DM patients, with 8% of them suffering from severe vision loss. By severity, DR is classified into 6 grades consisting of NPDR and PDR [5]. The pathogenesis of DR is very complex and the contributing factors of DR include pericyte loss, endothelial cell proliferation, basement membrane thickening, lumen stenosis and occlusion, retinal ischemia and hypoxia, angiogenesis and traction retinal detachment. Each of the above processes involves assorted array of cytokines. Some researchers believe that activation of VEGF, angiopoietins and specific receptors as well as GH and IGF-1 play a role in DR [6].

Under normal conditions, high blood glucose can inhibit the secretion of GH. But for DM patients, persistent high blood glucose leads to an increase of serum GH, which further aggravates insulin resistance and glucose metabolism disorder. Changes of GH levels may contribute to the occurrence of microvascular lesions. It has been demonstrated by clinical trials that GH levels in DR patients are obviously higher than those in diabetic patients without DR. PDR can be prevented or delayed by resection of the anterior lobe of pituitary gland [7]. In diabetic dwarf with GH deficiency, microvascular lesions may be absent. Merime (1973) studied a population of pituitary dwarfism (caused by GH deficiency) combined with reduced glucose tolerance. As compared with DM patients (increased blood glucose and GH) of the same age, the incidence of DR was 0% vs. 40%, indicating close connection between DR and GH. Higher GH levels will aggravate glucose metabolism disorder, enhancing the activity of glucosidase and galactosidase and thus promoting the synthesis of glycoproteins. With more glycoproteins deposited to the basement membranes of capillaries, diabetic microvascular lesions may be induced. This constitutes one major pathogenesis of DR [8]. Moreover, changes of GH and insulin levels are usually accompanied by increased plasma protein levels, with red blood cell and platelet aggregation and thickened basement membrane of capillaries. As a result, capillary leakage increases, and retinal ischemia, microaneurysm and angiogenesis take place. In the present study, DM patients reaching the goal of blood glucose control still had obviously higher serum GH levels when combined with PDR, as compared with NPDR group and N group. However, the difference between NPDR group and N group was insignificant. From this it can be inferred that GH plays a role in PDR, as is also indicated by many other researches [9]. GH levels showed a significantly positive correlation to the severity of DR, but whether GH levels and severity of DR are causally related or not is unknown. We failed to prove that GH was a risk factor of DR.

IGF-1 originates in the liver. GH acts through IGF-1 and regulates IGF-1, and the latter is used as an indicator of GH levels. As to the correlation between DM and IGF-1, many opposing opinions have appeared. Studies based on larger populations seem to indicate that with the factors of HbAlc, age and course of disease controlled, IGF-1 does not significantly correlate to the occurrence and progression of DR in either teenage or adult DM patients [10]. In other studies, serum levels of IGF-1 increase as DR deteriorates, which agrees with our result. Many scholars hold that IGF-1 levels and severity of DR positively correlate to the course of DM and persistent high blood glucose leads to an increase of IGF-1 levels. This becomes more conspicuous with prolonged course of disease. According to Chante-lau et al. [11], proper blood glucose control does not always lead to the delay of DR and the opposite may occur, especially for simple DR. Before deterioration of DR, the serum level of IGF-1 in these DM patients increased by over 100%. Thus it was concluded that the deterioration of simple DR correlated to reduced retinal tolerance to IGF-1. So IGF-1 is presumed to be one cause of PDR. As found by our study, IGF-1 levels in PDR group were much higher than those in NPDR group and N group and IGF-1 levels correlated to DR, which coincides with the findings of foreign literature.

Though the pathogenesis of DR is still unclear, several risk factors have been reported, including course of DM, systolic pressure, blood glucose control status and urine albumin. These factors are already attended to in clinics [12]. According to our result, DM patients combined with PDR still had higher GH and IGF-1 levels in spite of good blood glucose control status. IGF-1 is a risk factor of DR. For these patients, inhibiting IGF-1 may be one pathway for preventing and treating DR.

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Disclosure of conflict of interest

None.

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