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Correlations of insulin resistance and HbA1c with cytokines IGF-1, bFGF and IL-6 in the aqueous humor of patients with diabetic cataract

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Abstract. – OBJECTIVE: The study aimed to investigate the correlations of insulin resistance and hemoglobin A1c (HbA1c) with cytokines [insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF) and interleukin-6 (IL-6)] in the aqueous humor of patients with diabetic cataract.

PATIENTS AND METHODS: 59 patients with diabetic cataract and 58 patients with simple cataract treated in Jining No. 1 People´s Hospital (Jining, China) from January 2017 to February 2018, were selected randomly. The levels of homeostasis model assessment of insulin resistance (HOMA-IR) and HbAlc, as well as IGF-1, bFGF and IL-6 in the aqueous humor were compared between the two groups. The correlations of HOMA-IR and HbAlc with IGF-1, bFGF and IL-6 were analyzed. In control group, the levels of HOMA-IR and HbAlc, as well as IGF-1, bFGF and IL-6 in the aqueous humor were significantly lower than those in observation group ($p<0.05$).

RESULTS: Compared with the group with HbAlc ≤ 7%, the groups with HbAlc ≥ 9% and 7% <HbAlc< 9% had increased relevant indexes. HbAlc was positively correlated with IGF-1, bFGF and IL-6 (r=0.8309, $p<0.001$; r=0.8968, $p<0.001$; r=0.8205, $p<0.001$). HOMA-IR had positive correlations with IGF-1, bFGF and IL-6 (r=0.9091, $p<0.001$; r=0.9605, $p<0.001$; r=0.8118, $p<0.001$). IGF-1 was positively related to bFGF and IL-6 (r=0.9475, $p<0.001$; r=0.9112, $p<0.001$).

CONCLUSIONS: For patients with diabetic cataract, HOMA-IR and HbAlc were associated with IGF-1, bFGF and IL-6 in the aqueous humor. The measurement of those indexes can help to judge the disease conditions accurately, having good predictive value.

Key Words:
Diabetic cataract, Insulin resistance, Aqueous humor.

Introduction

Diabetic cataract is a common kind of ophthalmic disease, which, if not treated in time, may have the risk of causing blindness, so much attention has been paid to the disease in clinic[1,2]. Clinical studies have found that, as for patients with diabetic cataract, the severity of cataract is related to blood glucose level; in fact, the higher the blood glucose is, the severer the disease will be[3,4]. The major pathogenesis of diabetic cataract is that the injured lens affect the visual acuity. When the blood glucose level in the body is elevated, the osmotic pressure of the lens is increased, and opacity occurs in the fibers due to excessive water absorption. Therefore, early and in-time diagnosis can lower the occurrence of such a disease[5-7]. Homeostasis model assessment of insulin resistance (HOMA-IR) and hemoglobin A1c (HbA1c) are the main evaluation indexes in the body of diabetes mellitus patients[8,9]. Abnormalities of insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF) and interleukin-6 (IL-6) in the aqueous humor occur in most cataract patients[10,11]. In consequence, in order to investigate the correlations of HOMA-IR and HbA1c with IGF-1, bFGF and IL-6, patients with diabetic cataract and simple cataract in our hospital were selected to compare the differences in the indexes in patients between the two groups and analyze the correlations among those indexes, so as to provide more bases for clinical diagnosis, which is conducive to implementing preventive measures for the disease.

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Patients and Methods

Patients

A total of 59 patients with diabetic cataract and 58 patients with simple cataract treated in our hospital from January 2017 to February 2018 were randomly selected as observation group and control group, respectively. Observation group included 29 males and 30 females aged (49.6±4.8) years old, with a body mass index (BMI) of (25.8±2.7) kg/m^2. In control group, there were 25 men and 33 women, aged (50.3±5.7) years old, with a BMI of (24.9±2.8) kg/m^2. Inclusion criteria: 1) patients in both groups meeting the clinical diagnostic criteria of the disease; 2) patients manifesting hypopsia and snowy flake substances in the lens; and 3) patients with good compliance who actively cooperated with the diagnosis and treatment of health-care workers. Exclusion criteria: 1) patients who took drugs for cataract before enrollment; 2) patients complicated with other metabolic diseases; or 3) patients with serious injuries of the heart, liver and kidney.

Methods

Sample collection: the eyeball of the patient was anesthetized, and the eyelid was opened. Next, the anterior chamber was punctured using a 0.45 mm needle, and the eyeball was pressed gently to make the aqueous humor enter into a disposable syringe via the needle. After that, the collected sample of aqueous humor was maintained in a refrigerator.

Observation Indexes

IGF-1, bFGF and IL-6: enzyme-linked immunoassay and kits for IGF-1, bFGF and IL-6 were utilized for measurement. Insulin resistance index: the concentration of fasting blood glucose was multiplied by the concentration of fasting serum insulin, which was divided by 22.5. The higher the numerical value was, the lower the insulin sensitivity would be. Measurement of glycosylated hemoglobin (HbAlc): the fasting serum of the patients was fetched to determine the HbAlc content by virtue of micro-column test.

Statistical Analysis

Statistical Product and Service Solutions 17.0 software (SPSS Inc., Chicago, IL, USA) was applied to record and analyze the data. Measurement data were expressed as ($\bar{x} \pm s$), and *t*-test was conducted. Enumeration data were presented by n, and chi-square test was performed. Analyses of correlations among variables were conducted via Pearson analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of General Clinical Data Between the Two Groups of Patients

Observation group included 29 males and 30 females, with an average age of (49.6±4.8) years old, diastolic blood pressure of (82.5±8.4) mmHg, systolic blood pressure of (135.4±12.5) mmHg and BMI of (25.8±2.7) kg/m^2. In control group, there were 25 men and 33 women, with an average age of (50.3±5.7) years old. The diastolic blood pressure and systolic blood pressure were (85.4±8.4) mmHg and (132.5±13.7) mmHg, respectively, and the BMI was (24.9±2.8) kg/m^2. The differences in the above-mentioned indexes were not significant between the two groups of patients (Table I).

Comparisons of HOMA-IR, HbAlc, IGF-1, bFGF and IL-6 Between the two Groups of Patients

The comparisons of the levels of those indexes between the two groups revealed that control group had remarkably lower index levels than observation group, and the differences were statistically significant ($p<0.05$) (Table II).

Table I. Comparisons of general clinical data between the two groups of patients ($\bar{x} \pm s$).

Index	Observation group	Control group
Gender (male/female)	29/30*	25/33
Age (years old)	49.6±4.8*	50.3±5.7
Diastolic blood pressure (mmHg)	82.5±8.4*	85.4±8.4
Systolic blood pressure (mmHg)	135.4±12.5*	132.5±13.7
BMI (kg/m^2)	25.8±2.7*	24.9±2.8

Note: *$p>0.05$ *vs.* control group.

Table II. Comparisons of HOMA-IR, HbAlc, IGF-1, bFGF and IL-6 between the two groups of patients ($\bar{x} \pm s$).

Index	Observation group	Control group
HOMA-IR	2.73±0.32	1.56±0.12*
HbAlc (%)	8.21±0.87	4.32±0.45*
IGF-1 (ng/ml)	7.59±0.77	4.15±0.56*
bFGF (pg/ml)	7.28±0.79	3.59±0.25*
IL-6 (pg/ml)	59.76±4.97	53.21±4.97*

Note: *p>0.05 *vs.* observation group

Comparisons of HOMA-IR, IGF-1, bFGF and IL-6 Among Different HbAlc Groups

The patients were divided into three groups according to the content of HbAlc. It was discovered that the levels of HOMA-IR, IGF-1, bFGF and IL-6 in the group with HbAlc ≥ 9% were elevated notably compared with those in the groups with 7% <HbAlc< 9% and HbAlc ≤ 7%. Moreover, the group with 7% <HbAlc< 9% had evidently higher levels of the above mentioned indexes than the group with HbAlc ≤ 7%. This indicated that the levels of HOMA-IR, IGF-1, bFGF and IL-6 were increased significantly along with the elevated HbAlc level (Table III).

Analysis of Correlations of HbAlc with IGF-1, bFGF and IL-6

The analysis on the correlations of HbAlc with IGF-1, bFGF and IL-6 manifested that HbAlc was positively correlated with IGF-1, bFGF and IL-6 (r=0.8309, p<0.001, r=0.8968, p<0.001 and r=0.8205, p<0.001), indicating that as the HbAlc content was increased, the secretion and release of IGF-1, bFGF and IL-6 were raised in the body (Figure 1).

Analysis of Correlations of HOMA-IR with IGF-1, bFGF and IL-6

The correlations of HOMA-IR with IGF-1, bFGF and IL-6 were analyzed, and it was demonstrated that HOMA-IR had positive correlations with IGF-1, bFGF and IL-6 (r=0.9091, p<0.001, r=0.9605, p<0.001 and r=0.8118, p<0.001). Thus, the levels of IGF-1, bFGF and IL-6 were elevated constantly with the increased HOMA-IR (Figure 2).

Analysis of Correlations of IGF-1 with bFGF and IL-6

The analysis on the correlations of IGF-1 with bFGF and IL-6 revealed that IGF-1 was positively correlated with bFGF and IL-6 (r=0.9475, p<0.001 and r=0.9112, p<0.001), illustrating that the levels of bFGF and IL-6 in the aqueous humor were increased when excessive IGF-1 was released in the aqueous humor (Figure 3).

Discussion

According to clinical statistics, as the incidence rate is increasing constantly, diabetic cataract becomes one of the leading complications of diabetes mellitus. Moreover, its incidence rate is associated with the course of diabetes mellitus, that is, and the longer the course of diabetes mellitus is, the higher the probability of cataract will be[12,13]. In patients with diabetic cataract, the lowered insulin level and inhibited galactokinase activity can lead to increased content of blood glucose in the body. Such symptoms are able to cause an increase in osmotic pressure of the aqueous humor, as well as swelling, break and

Table III. Comparisons of HOMA-IR, IGF-1, bFGF and IL-6 among different HbAlc groups ($\bar{x} \pm s$).

Index	HbAlc ≤ 7%	7% < HbAlc < 9%	HbAlc ≥ 9%
HOMA-IR	1.97±0.43	2.45±0.43*	2.98±0.34*#
IGF-1 (ng/mL)	4.95±0.34	5.96±0.37*	7.79±0.76*#
bFGF (pg/mL)	4.33±0.42	6.59±0.65*	7.43±0.72*#
IL-6 (pg/mL)	52.31±5.86	58.86±5.87*	62.34±6.87*#
IL-6 (pg/ml)	59.76±4.97	53.21±4.97*	

Note: *p<0.05 *vs.* HbAlc ≤ 7%, #p<0.05 vs. 7% < HbAlc < 9%.

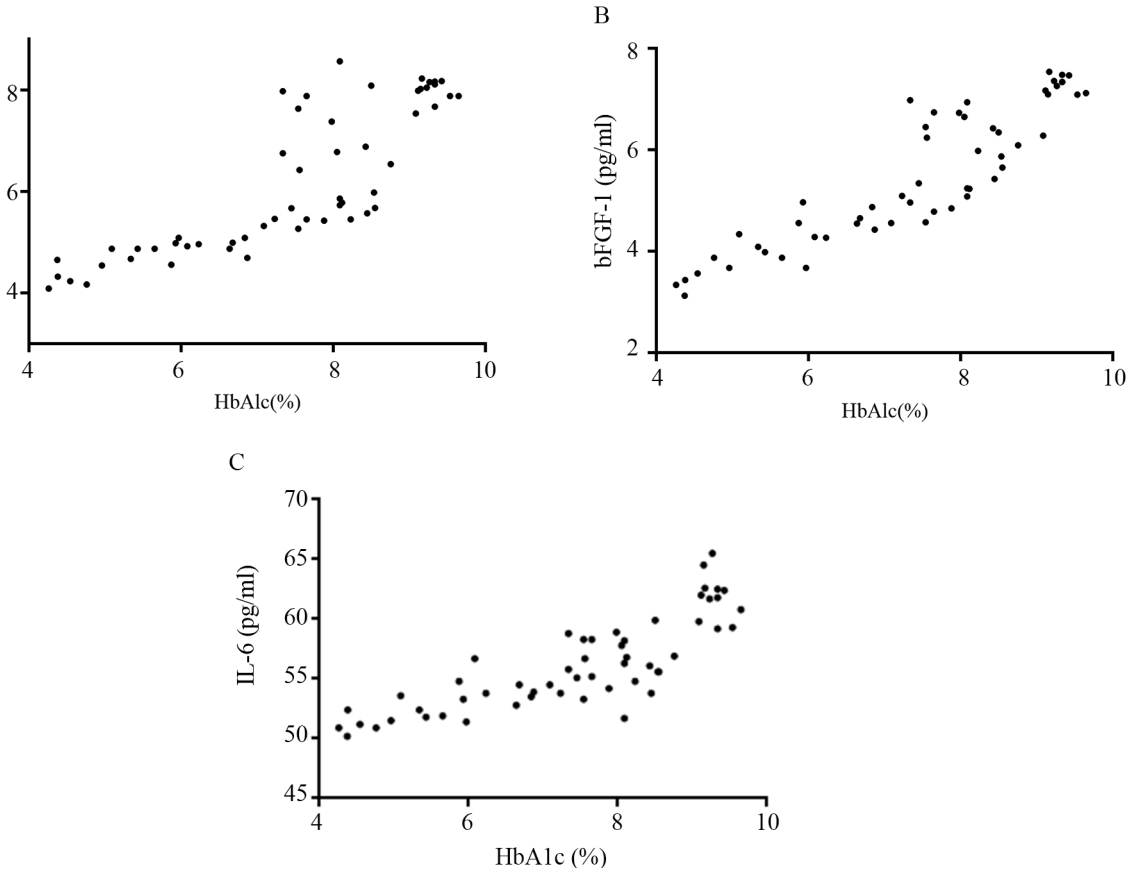

Figure 1. ***A,*** Analysis of correlation between HbAlc and IGF-1. ***B,*** Analysis of correlation between HbAlc and bFGF. ***C,*** Analysis of correlation between HbAlc and IL-6.

opacity of the lens fibers in the patients[14,15]. Most of the previous studies have explored the pathogenesis of diabetic cataract from the aspects of osmotic pressure and protein glycation theories[16,17], and few studies focus on the function indexes of insulin and various functional factors in the aqueous humor. Therefore, patients with diabetic cataract and simple cataract in our hospital were enrolled in this research, aiming to provide more clinical targets and bases for prevention and treatment of diabetic cataract in clinical practices by comparing and analyzing the correlations among insulin resistance, glycosylated hemoglobin and functional factors in the aqueous humor. Clinically, the blood glucose level in the body is judged mainly by virtue of monitoring the indexes HOMA-IR and HbA1c. There are multiple functional factors participating in the functioning of the aqueous humor, of which IGF-1 is a primary one. Ligands that bind to IGF are discovered in the epithelium of the anterior and equatorial regions of the lens, and IGF-1 can conjugate with corresponding binding sites after entering the above mentioned tissue, thus participating in the performing of normal functions by the lens. In addition, relevant research has illuminated that IGF-1 cannot only promote growth but also suppress apoptosis. BFGF can accelerate cell proliferation, and it has been discovered that binding sites of bFGF can be detected in lens epithelial cell (LEC), cornea and other parts. When bFGF binds to its ligands, it can exert the effects on nourishing and promoting cell growth. IL-6 has the functions of anti-inflammation and enhancement of immunity in the aqueous humor. Released mainly by local autocrine and paracrine of the eye, it plays a dual role in promoting both proliferation and apoptosis of LECs, thus exerting regulatory effects[18,19]. According to the findings of this research, the levels of HOMA-IR and HbAlc, as well as IGF-1, bFGF and IL-6 in the aqueous humor in control group were significantly lower than those in observation group ($p<0.05$). Both HbAlc and

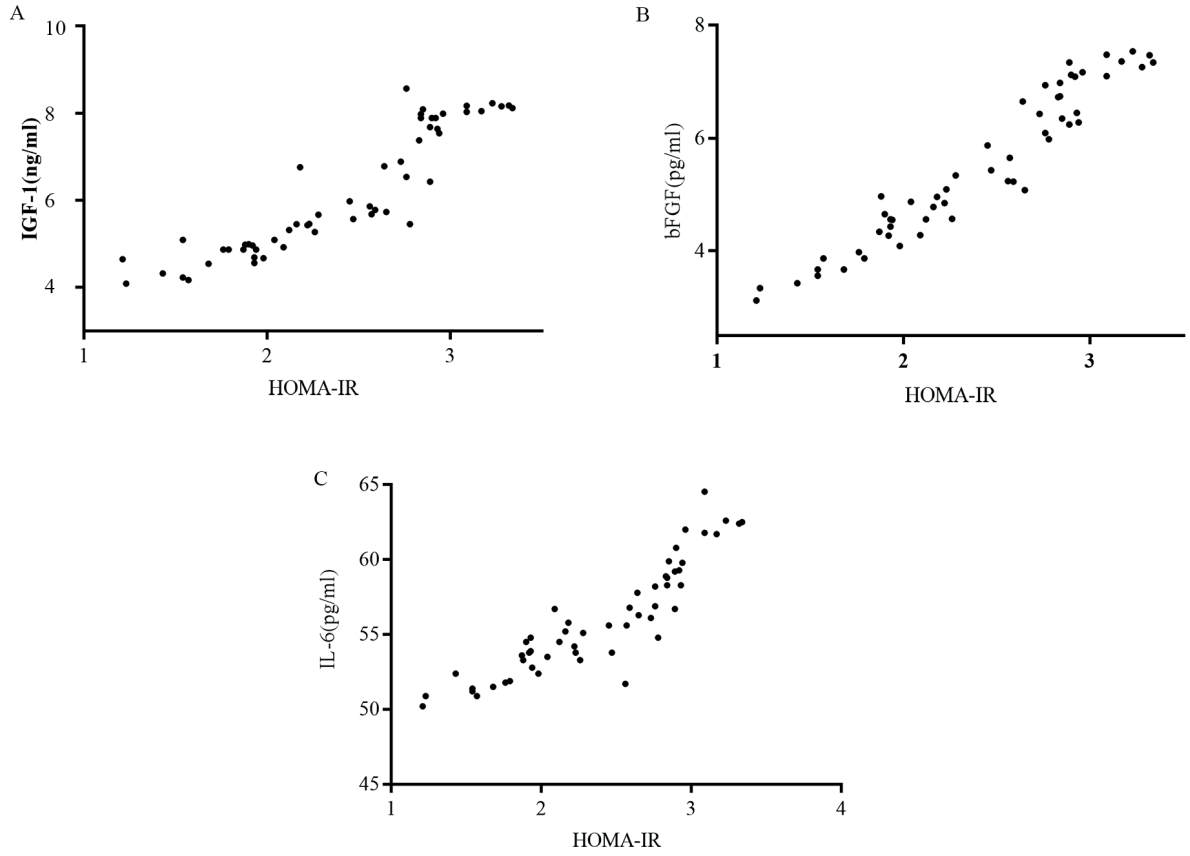

Figure 2. ***A,*** Analysis of correlation between HOMA-IR and IGF-1. ***B,*** Analysis of correlation between HOMA-IR and bFGF. ***C,*** Analysis of correlation between HOMA-IR and IL-6.

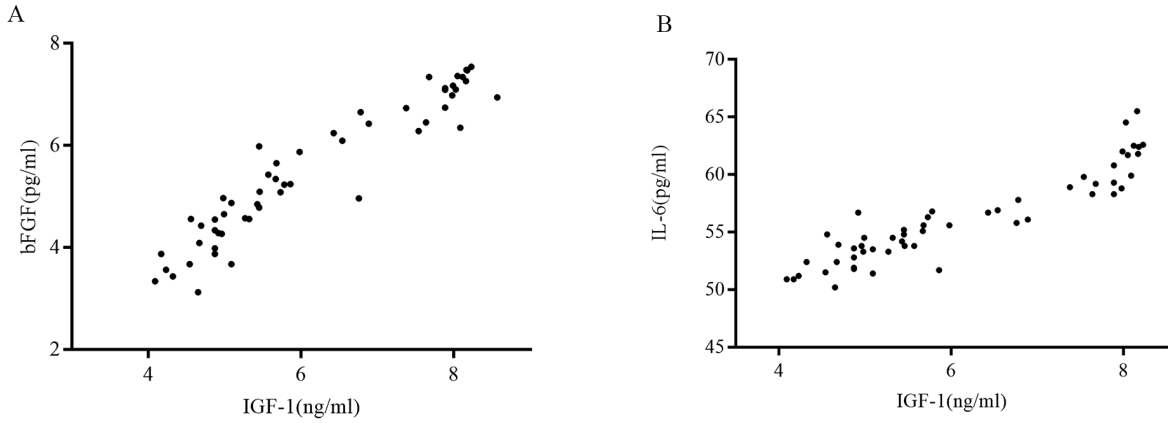

Figure 3. ***A,*** Analysis of correlation between IGF-1 and bFGF. ***B,*** Analysis of correlation between IGF-1 and IL-6.

HOMA-IR had positive correlations with IGF-1, bFGF and IL-6, indicating that when the blood glucose level in the patients is increased, the levels of IGF-1, bFGF and IL-6 in the aqueous humor are changed accordingly, thereby aggravating cataract. Clinical studies have manifested that the abnormally elevated blood glucose level in the patients with diabetes mellitus leads to the apoptosis of LECs. This process is the primary pathologic cause of complications of cata-

ract. Extremely high level of blood glucose may trigger overexpression of bFGF by LECs, and elevated bFGF level in the aqueous humor can induce excessive secretion of endogenous IGF-1 in partial anterior chamber. The increased blood glucose level can affect the normal proliferation and apoptosis of LECs, cause metabolism disorder of the lens, destroy the blood-aqueous barrier, and then make bFGF and IGF-1 enter into the aqueous humor from the blood, which results in the raised levels of bFGF and IGF-1 in the aqueous humor. Relevant research has demonstrated that IL-6 content in the aqueous humor rises when retinopathy occurs in the patients with diabetes mellitus[20], which is similar to the finding of this research, indicating that fundus lesions can induce abnormal increase in IL-6 and play a role in resisting inflammation and strengthening immunity.

Conclusions

As for patients with diabetic cataract, the insulin resistance index HOMA-IR and HbAlc are positively correlated with IGF-1, bFGF and IL-6 in the aqueous humor. When the blood glucose is elevated, the levels of those indexes are increased accordingly, thereby exacerbating the conditions of cataract. The results of this research provide more clinical evidence for the diagnosis and prevention of the disease in clinic, which is worth clinical popularization and application.

Conflict of Interest
The Authors declare that they have no conflict of interest.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
HZ collected general data of patients. HZ and YT analyzed IGF-1, bFGF and IL-6. HZ, YT and YL were responsible for measurement of glycosylated hemoglobin (HbAlc) and Insulin resistance index. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Jining No. 1 People's Hospital and written informed consents were signed by the patients and/or guardians.

Consent for publication
Written informed consents were signed by the patients and/or guardians.

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