Pulmonary Function and Retrobulbar Hemodynamics in Subjects With Type 2 Diabetes Mellitus

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BACKGROUND: The primary goals of this study were to evaluate early changes in pulmonary function and retrobulbar hemodynamics and to examine the correlation between these parameters in patients with type 2 diabetes during the preclinical stages of diabetic retinopathy. METHODS: For the single-time point measurements, 63 subjects with type 2 diabetes without diabetic retinopathy (diabetes group) and 32 healthy subjects (control group) were selected to evaluate any early changes in pulmonary function and retrobulbar hemodynamics and to examine the correlation between these parameters. In the longitudinal follow-up study, 32 subjects who were newly diagnosed with type 2 diabetes were divided into 2 groups according to their resistivity index (≤0.7 and >0.7). Early changes in pulmonary function and retrobulbar hemodynamics were studied in these groups and compared with the previous values. RESULTS: For the single-time point measurements, the fasting plasma glucose, 2-h postprandial blood glucose, glycosylated hemoglobin A1c, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels as well as the pulmonary function parameters were significantly higher in the diabetes group than in the control group. The pulmonary function parameters were negatively and significantly correlated with glycosylated hemoglobin A1c and the duration of diabetes. The retrobulbar hemodynamics were positively correlated with glycosylated hemoglobin A1c and diabetes duration; in contrast, the correlation between retrobulbar hemodynamics and glycosylated hemoglobin A1c. In the longitudinal follow-up study, the pulmonary function of the 2 groups categorized by their resistivity index levels indicated that subjects with resistivity index levels ≤0.7 showed significantly better pulmonary function, and the pulmonary function of this group showed improvement and a significantly smaller decrease. The incidence of diabetic retinopathy in the group with resistivity index levels ≤0.7 (9 of 22, 40.9%) was significantly lower than that in the group with resistivity index levels >0.7. CONCLUSIONS: Pulmonary function and retrobulbar hemodynamics changed during the preclinical stages of diabetic retinopathy. Regulating glycemia may improve retrobulbar hemodynamics in the retrobulbar arteries (ie, central retinal artery, posterior ciliary artery, and arteria ophthalmica). By detecting the retrobulbar resistivity index and the levels of glycosylated hemoglobin A1c, we could predict future changes in pulmonary function during the preclinical stages of diabetic retinopathy as well as the degree of retinopathy. (ClinicalTrials.gov registration NCT02774733.) *Key words: type 2 diabetes; pulmonary function; retrobulbar hemodynamics; ultrasound; resistivity index.* [Respir Care 2017;62(5):602–614. © 2017 Daedalus Enterprises]

Introduction

The prevalence of type 2 diabetes is increasing worldwide, particularly in Asian countries.[1] Patients with type 2 diabetes develop abnormal glucose and lipid metabolism, both of which are associated with multiple organ dysfunc-

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tion syndromes. Type 2 diabetes is an independent risk factor that accounts for a 2-fold increase in the development of cardiovascular disease[2] and induces vascular complications such as diabetic nephropathy and diabetic retinopathy.[3] Indeed, these conditions are the leading causes of end-stage renal failure and acquired blindness, respectively.[4]

Patients with type 2 diabetes have a reduced alveolar gas exchange capacity compared with that of healthy adults.[5] However, pulmonary vascular injury induced by hyperglycemia has been overlooked in the current treatment of type 2 diabetes. Obesity, smoking, vascular disease, and the duration of diabetes also markedly contribute to reduced lung function, and smokers (current and former) exhibit chronic air flow obstruction.[6] Color Doppler imaging is used to evaluate blood flow velocity based on a shift in the Doppler ultrasound and has been widely used in various medical fields.[7] Compared with healthy individuals without concomitant diabetes and systemic hypertension, patients with hyperglycemia and uncontrolled blood pressure have significantly increased blood flow as estimated by color Doppler imaging.[8] The retrobulbar resistivity index can be used to assess hemodynamic changes in diabetic retinopathy.[9,10]

To the best of our knowledge, there are no reports on the correlation between pulmonary function and the bilateral retrobulbar resistivity index in patients with type 2 diabetes and without diabetic retinopathy. We believe that by using noninvasive color Doppler imaging combined with evaluation of pulmonary function in adults during the preclinical stages of diabetic retinopathy, we can determine the importance of this correlation and whether it could help predict diabetic complications and early pulmonary changes.

QUICK LOOK

Current knowledge

Diabetic nephropathy and retinopathy are the leading causes of end-stage renal failure and acquired blindness, respectively. However, clinicians seldom consider the pulmonary vascular injury induced by glycemia in diabetic patients. Studies have shown that pulmonary function and retrobulbar hemodynamics change during the preclinical stages of diabetic retinopathy. The literature shows that, compared with healthy individuals, patients with type 2 diabetes have a reduced alveolar gas exchange capacity. The retrobulbar resistivity index can be used to assess the hemodynamic changes in the retrobulbar arteries during the preclinical stages of diabetic retinopathy.

What this paper contributes to our knowledge

Regulating glycemia can improve retrobulbar hemodynamics in the retrobulbar arteries (central retinal artery, posterior ciliary artery, and arteria ophthalmica). This study suggests that detecting the retrobulbar resistivity index and glycosylated hemoglobin A1c would allow for the prediction of changes in pulmonary function during the preclinical stages of diabetic retinopathy and the degree of retinopathy in the future.

Methods

Subjects

We assessed 82 patients with type 2 diabetes (46 males and 36 females) without diabetic retinopathy from the diabetic out-patient clinic at the Fourth Hospital of the People in Shenyang; we also assessed 38 healthy individuals (21 males and 17 females) to serve as a control group. Sixty-three subjects (34 males and 29 females) with diabetes and 32 healthy subjects (17 males and 15 females) were enrolled in our study. All of the participants were of Han descent and were provided a diet and exercise regimen by professional nutritionists. There was no statistically significant difference between groups regarding sex ratio or age (range 34–68 y). The diabetes duration (range 3–12 y), body mass index (range 23–31 kg/m^2), glycosylated hemoglobin A1c levels (range 7% [53 mmol/mol] to 10% [86 mmol/mol]), pulmonary function parameters, retrobulbar hemodynamic parameters (bilateral resistivity index), serum lipid parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride), and blood pressure were recorded (Table 1). Type 2 diabetes was diagnosed in accordance with the guidelines of the American Diabetes Association[11] using the following criteria: (1) symptoms of diabetes (thirst, polydipsia, diuresis, and unexplainable weight loss); (2) random blood sugar ≥11.1 mol/L, fasting plasma glucose ≥7.0 mol/L, or an oral glucose tolerance test outcome (2-h postprandial blood glucose) ≥11.1 mol/L; or (3) no symptoms of diabetes but either random blood sugar ≥11.1 mol/L or fasting plasma glucose ≥7.0 mol/L.

The inclusion criteria were: (1) diagnosis of type 2 diabetes according to the guidelines of the American Diabetes Association[11]; (2) no history of smoking (never smoked), pulmonary disease, or pulmonary infection (during the treatment or recovery period); (3) no hepatopathy,

The authors have disclosed no conflicts of interest.

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Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Control Group (n = 32)	Diabetes Group (n = 63)	P
Sex, n (%)			
Male	17 (53.13)	34 (53.97)	.94
Female	15 (46.87)	29 (46.03)	
Age, mean ± SD y	52.00 ± 7.96	53.02 ± 8.63	.58
Diabetes duration, mean ± SD y	NA	7.79 ± 1.73	NA
BMI, mean ± SD kg/m^2	23.91 ± 2.92	27.68 ± 2.05	<.001
FBG, mean ± SD mmol/L	4.98 ± 0.56	7.94 ± 0.81	<.001
2hPBG, mean ± SD mmol/L	7.19 ± 0.31	10.93 ± 1.12	<.001
HbA1c			
%	5.18 ± 0.58	8.00 ± 0.73	<.001
mmol/mol	46.13 ± 6.31	63.86 ± 8.27	<.001
Baseline HbA1c, n (%)			
≤7% (53 mmol/mol)	32 (100)	8 (12.70)	<.001
>7% (53 mmol/mol)	0 (0)	55 (87.30)	
TC, mean ± SD mg/dL	188.31 ± 15.08	200.03 ± 20.18	<.001
HDL cholesterol, mean ± SD mg/dL	45.63 ± 4.75	40.22 ± 4.69	<.001
LDL cholesterol, mean ± SD mg/dL	111.94 ± 9.34	122.37 ± 11.41	<.001
TG, mean ± SD mg/dL	141.56 ± 8.15	148.97 ± 11.69	<.001
Cholesterol-lowering drugs, n (%)			
Use	5 (15.63)	26 (41.27)	.01
No use	27 (84.37)	37 (58.73)	
SBP, mean ± SD mm Hg	124.81 ± 6.80	128.49 ± 5.82	.07
DBP, mean ± SD mm Hg	89.54 ± 4.48	86.98 ± 5.76	.08
IOP, mean ± SD mm Hg			
Right eye	15.94 ± 1.48	16.59 ± 1.83	.09
Left eye	16.00 ± 1.32	16.46 ± 1.67	.18
% predicted VC (L), mean ± SD	87.28 ± 4.35	79.06 ± 2.80	<.001
% predicted FVC (L), mean ± SD	79.06 ± 3.84	71.71 ± 3.56	<.001
% predicted FEV_1 (L), mean ± SD	78.59 ± 2.21	77.03 ± 3.79	.034
% predicted PEF (L/s), mean ± SD	58.13 ± 2.88	52.41 ± 3.18	<.001
% predicted MVV (L), mean ± SD	89.16 ± 2.14	86.86 ± 2.78	<.001
% predicted TLC (L), mean ± SD	96.03 ± 2.16	93.76 ± 5.24	.02
% predicted FEV_1/FVC, mean ± SD	77.72 ± 2.90	74.59 ± 3.19	<.001
% predicted D_{LCO} (mL/min/mm Hg), mean ± SD	87.22 ± 2.74	85.03 ± 2.66	<.001
% predicted D_{LCO}/V_A (mL/min/mm Hg), mean ± SD	91.88 ± 1.56	90.13 ± 2.45	<.001
CRA, mean ± SD			
Right RI	0.61 ± 0.03	0.73 ± 0.05	<.001
Left RI	0.61 ± 0.02	0.73 ± 0.05	<.001
PCA, mean ± SD			
Right RI	0.61 ± 0.02	0.73 ± 0.05	<.001
Left RI	0.62 ± 0.04	0.73 ± 0.06	<.001
OA, mean ± SD			
Right RI	0.62 ± 0.02	0.73 ± 0.05	<.001
Left RI	0.62 ± 0.03	0.73 ± 0.05	<.001

NA = not applicable
BMI = body mass index
FBG = fasting plasma glucose
HbA1c = glycosylated hemoglobin A1c
2hPBG = 2-h postprandial blood glucose
TC = total cholesterol
HDL = high-density lipoprotein
LDL = low-density lipoprotein
TG = triglycerides
SBP = systolic blood pressure
DBP = diastolic blood pressure
IOP = intraocular pressure
VC = vital capacity
PEF = peak expiratory flow
MVV = maximum voluntary ventilation
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
CRA = central retinal artery
PCA = posterior ciliary artery
OA = arteria ophthalmica

nephropathy, or gastrointestinal disease; and (4) a high likelihood of good compliance and the ability to visit our hospital for periodic assessments. The exclusion criteria were: (1) diagnosis of type 1 diabetes; (2) pregnancy and/or active lactation; (3) intensive care with insulin treatment; (4) renal inadequacy, hypohepatia, or heart disease; (5) pneumonia, influenza (during the treatment or recovery period), phthisis, or other pulmonary infection; (6) presence of multiple pulmonary cysts, bullae of the lung, or diffuse pulmonary calcifications confirmed via CT; (7) combined diabetic retinopathy and hypertension (for which antihypertensive drugs are used); (8) eye conditions that could affect hemodynamics, such as a high degree of myopia, maculopathy of any origin, glaucoma, or a history of laser treatment or intraocular surgery; (9) inadequate control of serum lipid parameters by cholesterol-lowering drugs; (10) body mass index $\geq$32 kg/m^2; and (11) the use of systemically injected glucocorticoids within 3 months before our study. This trial was conducted in compliance with the Declaration of Helsinki and was approved by the Medical Ethics Committee (approval ICE20150712) at our hospital. Either an independent ethics committee or institutional review board at each research site reviewed the study protocol. Each subject and his or her family members provided written informed consent.

Study Design

For the single-time point measurements, 82 patients (46 males and 36 females) with type 2 diabetes and 38 healthy individuals (20 males and 18 females) were recruited, all of whom were examined by slit-lamp biomicroscopy to exclude diabetic retinopathy in either eye. Diabetic retinopathy was staged according to the Fukuda classification as follows: no signs of diabetic retinopathy (A0), nonproliferative diabetic retinopathy (mild) (A1), nonproliferative diabetic retinopathy (moderate) (A2), or nonproliferative severe/preproliferative diabetic retinopathy (B1).[12] After this examination, we excluded 8 patients with type 2 diabetes (5 with A1 stage and 3 with A2 stage diabetic retinopathy). Among the healthy individuals, 3 were excluded because of the presence of a cold. After the slit-lamp biomicroscopy assessment, 74 patients with type 2 diabetes and 35 healthy individuals were further examined. After the subjects fasted for $\geq$8 h, 5 mL of venous blood was collected, and pulmonary function tests, the intraocular pressure, and the retrobulbar hemodynamics (resistivity index) were evaluated by color Doppler imaging. During this evaluation, our ophthalmologist could not locate the retrobulbar blood vessels in 9 patients with type 2 diabetes. Three healthy individuals were excluded because they chose not to undergo color Doppler imaging for personal reasons. Thus, 63 subjects with type 2 diabetes (34 males and 29 females) and 32 healthy subjects (17 males and 15 females) were included in the study. During the longitudinal follow-up, 134 subjects with type 2 diabetes (70 males and 64 females) were initially diagnosed with type 2 diabetes in 2000 and were divided into 2 groups based on their resistivity index ($\leq$0.7 or $>$0.7); however, only 53 of these subjects (29 males and 24 females) could be located in 2015. The pulmonary function and resistivity index were measured again in 2015 and compared with the values observed in 2000.

Study Assessments and End Points

For blood specimen collection and laboratory tests, venous blood was collected between 6:00 and 8:00 AM following a fast of $\geq$8 h and was used to measure fasting plasma glucose, glycosylated hemoglobin A1c, and serum lipid parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides). Plasma glucose levels were determined by using the glucose oxidase method, and the oral glucose tolerance test method administered 75 g of oral glucose (7.5 bottles of a 50% anhydrous glucose solution were added to 150 mL of warm water). Venous blood was collected to measure the 2-h postprandial blood glucose. In addition, 5 mL of venous blood was collected into a glass tube, left to separate for $\geq$10 min, and centrifuged (3,000 rpm) for 10 min to obtain the serum, which was subsequently stored in a -70°C freezer until further use. The serum lipid parameters were measured according to the manufacturer's instructions, and all samples were measured within 1 week of collection.

To determine the blood pressure, systolic and diastolic blood pressure tests were conducted using an electronic sphygmomanometer. Blood pressure was measured with the subject in a sitting position with an automatic device at the brachial artery after a 5-min rest period.

Pulmonary function tests were performed using a spirometer (model HI-101, Jaska Corp, Tokyo, Japan). We used the ratio of the measured values and expected values (which yielded the percentage of the predicted value) to eliminate the influence of age, height, and weight on the obtained values. Before testing, individuals sat quietly for $\geq$30 min. The pulmonary function tests were performed 3 times at 15-min intervals, and the best of 3 acceptable readings was used in the analysis. Diffusing capacity of the lung for carbon monoxide (D_{LCO}), alveolar gas volume (V_A), D_{LCO}/V_A, and total lung capacity (TLC) were determined by the single-breath CO diffusion test, which was performed using a gas mixture of 10% helium, 0.3% CO, and 21% oxygen; the remaining volume consisted of nitrogen. The diffusion capacity was defined as the volume of gas (1 mL) that diffused through the alveolar capillary membrane under a certain pressure gradient (1 mm Hg) within a certain period of time (10 s). Because CO has a high

affinity for hemoglobin, the integrity of the alveolar-capillary membrane is the primary factor that affects CO diffusion. D_{LCO}/V_A was used to assess the alveolar membrane permeability.[13] Spirometry and analysis of pulmonary function were performed by trained professionals. Intraocular pressure was measured with a fully automated tonometer (model TX-F, Canon, Tokyo, Japan), and bilateral eyes were included in the study.

The retrobulbar hemodynamic parameters (resistivity index) in the retrobulbar arteries (central retinal artery, posterior ciliary artery, and arteria ophthalmica) were detected by color Doppler imaging (Powervision SSA-380A with a 7-MHz transducer, Toshiba, Tokyo, Japan). To measure the peak systolic velocity and end-diastolic velocity of the retrobulbar arteries, the measurements were obtained with the subject in a sitting position according to a previously published method.[14] The resistivity index was subsequently calculated [(arteria ophthalmica − end-diastolic velocity)/arteria ophthalmica] for each vessel measured. These procedures were performed by the same ophthalmologist.

Statistical Analysis

Categorical data are expressed as the mean ± SD, and continuous data are expressed as percentages. The statistical analysis was conducted using SPSS 17.0 (SPSS, Chicago, Illinois). Pearson's correlation coefficient was used to evaluate the linear correlation between the following sets of variables: the pulmonary function parameters and both the glycosylated hemoglobin A1c and diabetes duration, the retrobulbar hemodynamic parameters and both the glycosylated hemoglobin A1c and diabetes duration, and the pulmonary function parameters and the retrobulbar hemodynamic parameters. In the multiple linear regression analysis, the pulmonary function parameters were the dependent variables, and the bilateral eye resistivity indexes were the independent variables. Differences in the continuous variables between the 2 groups (resistivity index ≤ 0.7 and >0.7) were evaluated using the independent samples *t* test, and within-group differences between 2000 and 2015 were assessed with the paired-sample *t* test. $P < .05$ was considered statistically significant.

Results

Subject Disposition and Baseline Characteristics

The baseline demographic and clinical characteristics of the remaining 63 type 2 diabetes subjects and 32 healthy subjects were recorded. The control and diabetes groups had a mean age of approximately 52 and 53 y, respectively ($P = .58$). The ratio of males to females in the control and diabetes groups were 17:15 and 34:29, respectively ($P = .94$). The control and diabetes groups had a mean systolic blood pressure of 124.81 ± 6.80 and 128.49 ± 5.82 mm Hg, respectively ($P = .07$), and a mean diastolic blood pressure of 89.54 ± 4.48 and 86.98 ± 5.76 mm Hg, respectively ($P = .08$). The control group and the diabetes group had a mean intraocular pressure in the right eye of 15.94 ± 1.48 and 16.59 ± 1.83 mm Hg, respectively, and in the left eye of 16.00 ± 1.32 and 16.46 ± 1.67 mm Hg, respectively; neither of these pressure comparisons were significantly different ($P = .09$ and $P = .18$, respectively). The control and diabetes groups had a mean body mass index of 23.91 ± 2.92 and 27.68 ± 2.05 kg/m^2, respectively, which was significantly different ($P < .001$). The control group and the diabetes group had significantly different mean fasting plasma glucose levels (4.98 ± 0.56 and 7.94 ± 0.81 mmol/L, respectively, $P < .001$) and significantly different mean 2-h postprandial blood glucose levels (7.19 ± 0.31 and 10.93 ± 1.12 mmol/L, respectively, $P < .001$). The control group and the diabetes group had mean glycosylated hemoglobin A1c levels of 5.18 ± 0.58% (46.13 ± 6.31 mmol/mol) and 8.00 ± 0.73% (63.86 ± 8.27 mmol/mol), respectively, which were significantly different ($P < .001$). The control group and the diabetes group had mean total cholesterol levels of 188.31 ± 15.08 and 200.03 ± 20.18 mg/dL, respectively, which were significantly different ($P = .005$). The control group and the diabetes group had mean high-density lipoprotein cholesterol levels of 45.63 ± 4.75 and 40.22 ± 4.69 mg/dL, respectively, which were significantly different ($P < .001$). The control group and the diabetes group had mean low-density lipoprotein cholesterol levels of 111.94 ± 9.34 and 122.37 ± 11.41 mg/dL, respectively, which were significantly different ($P < .001$). The control group and the diabetes group had mean triglyceride levels of 141.56 ± 8.15 and 148.97 ± 11.69 mg/dL, respectively, which were significantly different ($P = .002$). The rates of use of cholesterol-lowering drugs in the control and diabetes groups were 15.63 and 41.27%, respectively, which were significantly different ($P = .01$) (Table 1).

Correlation of Pulmonary Function Parameters With Both Glycosylated Hemoglobin A1c and Diabetes Duration

The VC was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration ($r = -0.36$ and -0.27, respectively). The FVC was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration ($r = -0.73$ and -0.52, respectively). The FEV_1 was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration ($r = -0.55$ and -0.39, respectively). The peak expiratory flow (PEF) was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration ($r = -0.64$ and -0.55, respectively). The max-

Table 2. Correlation of Pulmonary Function Parameters With Glycosylated Hemoglobin A1c and Diabetes Duration in the Diabetes Group

Pulmonary Function Parameters	HbA1c		Diabetes Duration	
	r	*P*	r	*P*
VC	−0.36	.004	−0.27	.030
FVC	−0.73	.01	−0.52	<.001
FEV_1	−0.55	<.001	−0.39	.002
PEF	−0.64	<.001	−0.55	<.001
MVV	−0.46	<.001	−0.35	.005
TLC	−0.81	<.001	−0.62	<.001
FEV_1/FVC	−0.56	<.001	−0.40	<.001
D_{LCO}	−0.30	.02	−0.40	<.001
D_{LCO}/V_A	−0.65	<.001	−0.52	<.001

HbA1c = glycosylated hemoglobin A1c
VC = vital capacity
PEF = peak expiratory force
MVV = maximal voluntary ventilation
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
D_{LCO}/V_A = diffusing capacity of the lung for carbon monoxide/alveolar gas volume

Table 3. Correlation of Retrobulbar Hemodynamics With Diabetes Duration and Glycosylated Hemoglobin A1c in the Diabetes Group

Retrobulbar Hemodynamics	HbA1c		Diabetes Duration	
	r	*P*	r	*P*
CRA				
Right RI	0.82	<.001	0.74	<.001
Left RI	0.82	<.001	0.77	<.001
PCA				
Right RI	0.75	<.001	0.73	<.001
Left RI	0.81	<.001	0.74	<.001
OA				
Right RI	0.82	<.001	0.73	<.001
Left RI	0.80	<.001	0.77	<.001

HbA1c = glycosylated hemoglobin A1c
CRA = central retinal artery
RI = resistivity index
PCA = posterior ciliary artery
OA = arteria ophthalmica

imum voluntary ventilation (MVV) was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.46 and −0.35, respectively). The TLC was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.81 and −0.62, respectively). The FEV_1/FVC was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.56 and −0.40, respectively). The D_{LCO} was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.30 and −0.40, respectively). The D_{LCO}/V_A was negatively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.65 and −0.52, respectively) (Table 2). In contrast, none of these correlations were significantly different in the control group.

Correlation of the Retrobulbar Hemodynamics With Glycosylated Hemoglobin A1c and Diabetes Duration

The right resistivity index of the central retinal artery was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.82 and −0.74, respectively). The left resistivity index of the central retinal artery was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.82 and −0.77, respectively). The right resistivity index of the central retinal artery was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.75 and −0.73, respectively). The left resistivity index of the central retinal artery was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.81 and −0.74, respectively). The right resistivity index of the arteria ophthalmica was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.82 and −0.73, respectively). The left resistivity index of the arteria ophthalmica was positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (r = −0.80 and −0.77, respectively) (Table 3). In contrast, the correlation between the retrobulbar parameters and glycosylated hemoglobin A1c showed no significant differences in the control group.

Correlation Between the Pulmonary Function Parameters and the Retrobulbar Hemodynamic Parameters

The vital capacity (VC) was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.39, −0.31, and −0.27, respectively). The VC was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.31, −0.33, and −0.31, respectively). The FVC was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.60, −0.59, and −0.54, respectively). The FVC was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.59, −0.63, and −0.62, respectively). The FEV_1 was negatively and significantly correlated with the right resistivity index of

Table 4. Correlation Between Retrobulbar Hemodynamics Parameters and Pulmonary Function in the Diabetes Group

Pulmonary Function	Retrobulbar Hemodynamics											
	Right RI (CRA)		Right RI (PCA)		Right RI (OA)		Left RI (CRA)		Left RI (PCA)		Left RI (OA)	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
VC	−0.39	.002	−0.31	.013	−0.27	.033	−0.31	.01	−0.33	.009	−0.31	.01
FVC	−0.60	<.001	−0.59	<.001	−0.54	<.001	−0.59	<.001	−0.63	<.001	−0.62	<.001
FEV_1	−0.45	<.001	−0.48	<.001	−0.38	.002	−0.45	<.001	−0.50	<.001	−0.43	<.001
PEF	−0.59	<.001	−0.55	<.001	−0.47	<.01	−0.56	<.001	−0.56	<.001	−0.56	<.001
MVV	−0.33	.008	−0.25	.045	−0.25	.051	−0.30	.02	−0.26	.037	−0.26	.039
TLC	−.66	<.001	−0.68	<.001	−0.62	<.001	−0.65	<.001	−0.70	<.001	−0.65	<.001
FEV_1/FVC	−0.49	<.001	−0.49	<.001	−0.50	<.001	−0.53	<.001	−0.54	<.001	−0.53	<.001
D_{LCO}	−0.27	.035	−0.26	.038	−0.30	.02	−0.30	.02	−0.29	.02	−0.33	.009
D_{LCO}/V_A	−0.49	<.001	−0.44	<.001	−0.43	<.01	−0.50	<.001	−0.43	<.001	−0.50	<.001

RI = resistivity index
CRA = central retinal artery
PCA = posterior ciliary artery
OA = arteria ophthalmica
VC = vital capacity
PEF = peak expiratory force
MVV = maximal voluntary ventilation
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
D_{LCO}/V_A = diffusing capacity of the lung for carbon monoxide/alveolar gas volume

the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.45, −0.48, and −0.38, respectively). The FEV_1 was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.45, −0.50, and −0.43, respectively). The PEF was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.59, −0.55, and −0.47, respectively). The PEF was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.56, −0.56, and −0.56, respectively). The MVV was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.33, −0.25, and −0.25, respectively). The MVV was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.33, −0.25, and −0.25, respectively). The TLC was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.66, −0.68, and −0.62, respectively). The TLC was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.65, −0.70, and −0.65, respectively). The FEV_1/FVC was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.49, −0.49, and −0.50, respectively). The FEV_1/FVC was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.53, −0.54, and −0.53, respectively). The D_{LCO} was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.27, −0.26, and −0.30, respectively). The D_{LCO} was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.30, −0.29, and −0.33, respectively). The D_{LCO}/V_A was negatively and significantly correlated with the right resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.49, −0.44, and −0.43, respectively). The D_{LCO}/V_A was negatively and significantly correlated with the left resistivity index of the central retinal artery, central retinal artery, and arteria ophthalmica (r = −0.50, −0.43, and −0.50, respectively) (Table 4); however, this correlation was not significantly different in the control group. The multiple linear regression analysis between pulmonary function and the retrobulbar hemodynamic parameters was significant for all parameters except for MVV (*P* = .15) and D_{LCO} (*P* = .24). The maximum standard coefficient of regression was 1.517 (right resistivity index, central retinal artery) for VC, 0.779 (right resistivity index, arteria ophthalmica) for FVC, 0.836 (right resistivity index, arteria ophthalmica) for FEV_1, 1.144 (right resistivity index, arteria ophthalmica) for PEF, 0.655 (left resistivity index, central retinal artery) for TLC, 0.612 (left resistivity index,

Table 5. Multiple Regression Analysis Between Pulmonary Function and Retrobulbar Hemodynamics in the Diabetes Group

Dependent Variable	Coefficient			Typical Coefficient						*P*
	R	R^2	F	Right RI (CRA)	Right RI (PCA)	Right RI (OA)	Left RI (CRA)	Left RI (PCA)	Left RI (OA)	
VC	0.51	0.26	3.246	−1.517	.320	.540	.823	−.441	.063	<.001
FVC	0.68	0.46	7.998	−.328	.101	.779	.175	−.707	−.647	<.001
FEV_1	0.56	0.31	4.235	−.093	−.282	.836	−.122	−.751	−.056	<.001
PEF	0.67	0.45	7.610	−.737	−.154	1.144	−.077	−.286	.464	<.001
MVV	0.39	0.15	1.649	−.838	.297	.327	−.274	−.008	.194	.15
TLC	0.71	0.51	9.587	−.163	−.262	.429	.074	−.655	−.118	<.001
FEV_1/FVC	0.57	0.33	4.573	.510	.239	.229	−.612	−.518	−.382	<.001
D_{LCO}	0.36	0.13	1.382	.393	.260	−.064	−.213	−.094	−.586	.24
D_{LCO}/V_A	0.56	0.31	4.182	−.173	−.063	.611	−.680	.495	−.674	.002

RI = resistivity index
CRA = central retinal artery
PCA = posterior ciliary artery
OA = arteria ophthalmica
VC = vital capacity
PEF = peak expiratory force
MVV = maximal voluntary ventilation
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
D_{LCO}/V_A = diffusing capacity of the lung for carbon monoxide/alveolar gas volume

central retinal artery) for FEV_1/FVC, and 0.680 (left resistivity index, central retinal artery) for D_{LCO}/V_A (Table 5).

Longitudinal Follow-Up

The pulmonary function of the 2 groups of type 2 diabetes subjects was analyzed based on their resistivity index levels. Subjects with resistivity index levels ≤0.7 had significantly better pulmonary function (VC%, FVC%, FEV_1%, PEF%, MVV%, TLC%, FEV_1/FVC%, D_{LCO}%, and D_{LCO}/V_A%) in 2000, and their pulmonary function showed further improvement in 2015 and a significantly smaller decrease from 2000 to 2015 except for the change of FEV_1/FVC, which was greater than that of the group with resistivity index levels >0.7; however, no significant difference was observed ($P = .85$, Table 6). The incidence of diabetic retinopathy in the group with resistivity index levels ≤0.7 (9 of 22, 40.91%) was significantly lower than that in the group with resistivity index levels >0.7 (22 of 31, 70.97%) ($P = .03$). The incidence of proliferative diabetic retinopathy in the group with resistivity index levels ≤0.7 (2 of 9, 22.22%) was lower than that in the group with resistivity index >0.7 (8 of 22, 36.36%), although this difference was not significant ($P = .45$, Table 6).

Discussion

This study demonstrated that the pulmonary function and retrobulbar hemodynamics (resistivity index) changed during the preclinical stages of diabetic retinopathy. Regulating glycemia can improve not only pulmonary function but also the retrobulbar hemodynamics in the retrobulbar arteries. By detecting the resistivity index, we could predict changes in pulmonary function during the preclinical stages of diabetic retinopathy and determine the level of retinopathy.

Glycosylated hemoglobin A1c is an indicator of diabetes control. Higher glycosylated hemoglobin A1c levels are correlated with reduced diabetic control and elevated concentrations of circulating glucose. If circulating glucose is constantly elevated for 3 months (as measured by glycosylated hemoglobin A1c), it can lead to increased nonenzymatic glycosylation of proteins in the tissue.[15] The consistency of these results is on par with those of other studies, although the current study enrolled patients with glycosylated hemoglobin A1c levels as low as 7% (53 mmol/mol), whereas other studies excluded patients with baseline glycosylated hemoglobin A1c levels <7.5% (58 mmol/mol).[15] This distinction is important because the efficacy of antidiabetic agents appears to be greater in patients with higher baseline glycosylated hemoglobin A1c levels.[15] A major contributing factor to poor adherence in maintaining glycosylated hemoglobin A1c <7% (53 mmol/mol) is a lack of patient awareness.[15] Prabhu et al[16] showed that only 23 subjects (11.5%) were aware of glycosylated hemoglobin A1c, and 10 subjects (5%) misinterpreted this parameter as a level of glycosylated hemoglobin A1c. Additionally, approximately 164 subjects (82%) were unaware of the significance or terminology relating to glycosylated hemoglobin A1c, and the percentage of subjects achieving the target level of <7% (53 mmol/mol) remained low among individuals with diabetic retinopathy. In our study,

Table 6. Changes of the Resistivity Index Values in the Central Retinal Artery and the Pulmonary Function From Baseline to Year 15

Content	Group (Mean RI in CRA)		*P*
	≤0.7 (*n* = 22)	>0.7 (*n* = 31)	
Sex, *n* (%)			.98
Male	12 (54.55)	17 (54.84)	
Female	10 (45.45)	14 (45.16)	
Age in 2000, mean ± SD y	49.64 ± 5.81	52.77 ± 6.67	.08
BMI in 2000, mean ± SD kg/m^2	27.55 ± 1.60	27.52 ± 1.79	.95
DR in 2015, *n* (%)			.03
Yes	9 (40.91)	22 (70.97)	
No	13 (59.09)	9 (29.03)	
PDR in 2015, *n* (%)			.45
Yes	2 (22.22)	8 (36.36)	
No	7 (77.78)	14 (63.64)	
Mean RI in CRA, mean ± SD			
Baseline	0.67 ± 0.03	0.75 ± 0.02	<.001
Year 15	0.71 ± 0.03	0.79 ± 0.03	<.001
% predicted VC, mean ± SD			
Baseline	80.45 ± 1.65	75.74 ± 1.90	<.001
Year 15	77.05 ± 1.53	70.48 ± 1.67	<.001
Change	−3.41 ± 1.59	−5.26 ± 2.18	<.001
% predicted FVC, mean ± SD			
Baseline	73.05 ± 1.65	68.16 ± 2.33	<.001
Year 15	70.00 ± 1.54	63.10 ± 2.51	<.001
Change	−3.04 ± 1.70	−5.06 ± 2.83	.004
% of predicted FEV_1, mean ± SD			
Baseline	79.64 ± 1.26	73.45 ± 1.21	<.001
Year 15	75.91 ± 0.92	68.52 ± 2.32	<.001
Change	−3.73 ± 1.42	−4.93 ± 1.67	.008
% predicted PEF, mean ± SD			
Baseline	53.05 ± 1.65	48.97 ± 1.52	<.001
Year 15	49.36 ± 1.53	43.94 ± 1.93	<.001
Change	−3.68 ± 2.03	−5.03 ± 1.66	.01
% predicted MVV, mean ± SD			
Baseline	89.36 ± 1.73	84.42 ± 1.73	<.001
Year 15	83.18 ± 1.84	76.61 ± 2.28	<.001
Change	−6.18 ± 1.76	−7.81 ± 2.75	.02
% predicted TLC, mean ± SD			
Baseline	94.86 ± 1.75	88.74 ± 2.08	<.001
Year 15	91.68 ± 1.64	83.74 ± 2.89	<.001
Change	3.18 ± 0.96	−5.00 ± 2.03	<.001
% predicted FEV_1/FVC, mean ± SD			
Baseline	75.23 ± 1.45	70.94 ± 1.15	<.001
Year 15	72.00 ± 1.60	67.77 ± 1.59	<.001
Change	−3.23 ± 0.92	−3.16 ± 1.61	.85
% predicted D_{LCO}, mean ± SD			
Baseline	85.95 ± 1.43	81.55 ± 2.19	<.001
Year 15	83.50 ± 1.26	76.32 ± 2.29	<.001
Change	−2.45 ± 1.65	−5.23 ± 2.00	<.001
% predicted D_{LCO}/V_A, mean ± SD			
Baseline	90.18 ± 2.20	82.77 ± 1.78	<.001
Year 15	88.45 ± 1.79	78.35 ± 2.15	<.001
Change	−1.73 ± 1.45	−4.42 ± 2.11	<.001

RI = resistivity index
CRA = central retinal artery
BMI = body mass index
DR = diabetic retinopathy
PDR = proliferative diabetic retinopathy
VC = vital capacity
PEF = peak expiratory flow
MVV = maximum voluntary ventilation
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
D_{LCO}/V_A = diffusing capacity of the lung for carbon monoxide/alveolar gas volume

the rate (8 of 63, 12.70%) of achieving this glycosylated hemoglobin A1c standard (<7.0% [53 mmol/mol]) was also low in the diabetes group. Most type 2 diabetes subjects inadequately control their glycemia, so the mean levels of fasting plasma glucose (7.94 mmol/L) and 2-h postprandial blood glucose (10.93 mmol/L) were higher than the target levels (7 and 10 mmol/L, respectively).

Mechanisms underlying lung damage in individuals with diabetes are not fully known, but glycemic control appears to play a key role in the association between reduced lung function and diabetes. Interestingly, collagen is less susceptible to proteolysis due to the nonenzymatic glycosylation of proteins in the lungs and chest wall, leading to its accumulation in lung connective tissue. This process is primarily triggered by hyperglycemia and is thus more pronounced in patients with poor metabolic control. In addition, the nonenzymatic glycosylation of proteins in the lungs decreases pulmonary compliance.[17] A characteristic of the alveolar-capillary system is a large microvascular reserve where oxidative damage can occur; therefore, hyperglycemia can damage the lung.[18] The loss of this microvascular reserve in the lung may be clinically associated with an increased risk of hypoxia in acute or chronic pathological lung conditions such as pneumonia, asthma, COPD, and congestive heart failure. Moreover, microvascular abnormalities frequently contribute to histological changes in the lung parenchyma, such as nodular fibrosis. Our group found that glycemic control can improve oxidative/antioxidative imbalances and pulmonary function. Pulmonary function parameters are positively correlated with glutathione peroxidase and superoxide dismutase activity and negatively correlated with reactive oxygen species and malondialdehyde levels.[19]

Systemic inflammation is another concern of diabetic patients, because oxidative stress-induced systemic inflammation is associated with endothelial dysfunction in diabetic patients.[20-22] Additionally, insulin resistance could alter lung volume and mechanical function via mediators such as leptin[18] as well as independently lead to air flow obstruction in a manner similar to that in which peripheral airway inflammation causes air flow obstruction in asthma.[23] The CO transfer capacity of the lungs is remarkably affected by the integrity of the lung capillary endothelium, which supports the need to focus more on pulmonary vascular changes. Reports on lung function tests in diabetic subjects over the last 15 y have predominantly comprised pulmonary microangiopathy results. Lung function tests related specifically to pulmonary microangiopathy include pulmonary capillary blood volume and CO transfer capacity.[24] Niranjan et al[25] observed significantly lower TLC, FVC, FEV_1, and VC in type 1 diabetic subjects than in healthy subjects. However, our study only selected individuals with type 2 diabetes ranging in duration from 3 to 12 y, and the population was smaller than that in studies by Niranjan et al.[25] Our results showed that the pulmonary function parameters were significantly negatively correlated with glycosylated hemoglobin A1c and diabetes duration (Table 2); in contrast, the correlation between pulmonary function parameters and glycosylated hemoglobin A1c was not significant in the control group. Previous studies were inconsistent regarding the correlations between the glycosylated hemoglobin A1c and pulmonary function parameters: 3 studies described weak or absent associations between glycosylated hemoglobin A1c and spirometric measurements, which was consistent with our results.[6,26,27] Another cross-sectional population study revealed a negative correlation between plasma glucose levels and FVC and/or FEV_1.[28] In our study, we did not observe microangiopathy in the lung, but the pulmonary function improved concomitant with a reduction in glycosylated hemoglobin A1c levels (negatively correlated). However, it is noteworthy that good glycemic control and regular antidiabetic treatment positively affected lung function in subjects with type 2 diabetes.

The pathophysiological mechanism of diabetic retinopathy remains a challenge in medical research. Although the exact pathogenesis of the disease has yet to be elucidated, several studies have proposed that processes that affect ocular blood flow contribute to in diabetic retinopathy. Several researchers have focused on hemodynamic changes in the diabetic retina and choroid. As in other vascular beds, ocular blood flow is measured as blood flow velocity multiplied by the cross-sectional area. In terms of abnormal ocular blood flow in the different stages of diabetic retinopathy, some significant deviations have been documented in different reports. However, presumably due to the various techniques used to measure retinal blood flow, the exact nature of these deviations is somewhat controversial.[29,30] Little research has addressed hemodynamic changes in patients without diabetic retinopathy; thus, we studied the hemodynamic changes in type 2 diabetes subjects without diabetic retinopathy with the goal of inhibiting the progress of diabetic retinopathy during the treatment period. Diabetic retinopathy is one of the leading causes of preventable blindness in developed countries and is becoming a primary cause of blindness in middle-income countries.[31] Up to 39% of patients who are newly diagnosed with type 2 diabetes have signs of diabetic retinopathy.[32] Population-based diabetic eye screening programs have been initiated in several western European countries. Compared with populations where organized population-based screening has not been implemented, populations that have access to these screening programs have a lower incidence and prevalence of blindness.[33] However, because of the relatively poor economic conditions in China, population-based diabetic eye screening programs cannot be widely initiated. The frequency of diabetic retinopathy, which is the most common micro-

vascular complication of diabetes, increases with age and disease duration. An overwhelming majority of patients with type 1 diabetes and >60% of patients with type 2 diabetes will develop diabetic retinopathy within 20 y of diagnosis[34]; therefore, in our longitudinal follow-up study, the quantum was 15 y (from 2000 to 2015). Because diabetic retinopathy was an exclusion criterion, we chose subjects with a diabetes duration ranging from 3 to 12 y, yet 8 of the 82 patients (9.76%) had diabetic retinopathy but still enrolled in our study. Color Doppler imaging is used to evaluate the circulatory parameters of the retrobulbar blood vessels, and scanning laser Doppler flowmetry (a useful method to evaluate blood flow in the retinal tissue) has been widely applied in ophthalmic pathology for many years.[35,36] A study by Dimitrova et al[8] showed a positive correlation between the recordings of scanning laser Doppler flowmetry of retinal tissue and the retrobulbar circulatory parameters of the color Doppler imaging in diabetes patients without diabetic retinopathy. Dimitrova reported a significantly increased arteria ophthalmica, end-diastolic velocity, and resistivity index in the central retinal vein due to the progression of the retinopathy over a 21-month period; however, no significantly altered circulatory parameters in the central retinal artery or posterior ciliary artery were recorded after the progression of diabetic retinopathy.[37] In our longitudinal follow-up study, the incidence of diabetic retinopathy in the group with resistivity index levels ≤0.7 (9 of 22, 40.91%) was significantly lower than that in the group with resistivity index levels >0.7 (22 of 31, 70.97%, $P = .03$), and the incidence of proliferative diabetic retinopathy in the group with resistivity index levels ≤0.7 (2 of 9, 22.22%) was lower than that in the group with resistivity index levels >0.7 (8 of 22, 36.36%), although this difference was not significant ($P = .45$). The resistivity index level increased gradually and significantly over 15 y, which was similar to the results of the 10-y follow-up study by Neudorfer et al.[38]

Hirose et al[39] demonstrated that glycosylated hemoglobin A1c values may better predict the development of retinopathy if metabolic memory-free data are involved. Our results showed that the retrobulbar hemodynamics were positively correlated with glycosylated hemoglobin A1c and diabetes duration (Table 3); in contrast, the correlation between retrobulbar hemodynamics and glycosylated hemoglobin A1c was not significant in the control group. Furthermore, several studies have shown the correlation between the severity of retinopathy and the decrease in the extent of blood flow. Hyperglycemia enhances blood flow and intervenes with retinal autoregulation, and retinal blood flow is regulated through changes in ocular vascular resistance. Therefore, the resistivity index plays an important role in the assessment of hemodynamic changes in diabetic retinopathy.[9,10] Systemic inflammation associated with hyperglycemia can induce endothelial dysfunction in diabetic patients[18,20,21] and may reduce the arteria ophthalmica and end-diastolic velocity in the retrobulbar arteries.

In the present study, not all correlations were significantly different. This may be because our population ($n = 63$) was too small or because both assessed parameters were approximations. The correlation between the pulmonary function parameters and circulatory parameters of retrobulbar arteries could be influenced by not only the circulatory characteristics in the measured areas but also other known or unknown factors. Changes in the 2 parameters above could influence our outcome. Our results showed that the retrobulbar hemodynamics were positively and significantly correlated with glycosylated hemoglobin A1c and diabetes duration (Table 3); in contrast, the correlation between renal parameters and glycosylated hemoglobin A1c was not significant in the control group. The pulmonary function parameters were negatively correlated with the resistivity index, with most of these correlations defined as significant; therefore, we chose the resistivity index to evaluate the interaction between pulmonary function and the circulatory parameters of retrobulbar blood vessels in subjects with type 2 diabetes. Additionally, Neudorfer et al[38] also reported that resistivity index values were lower in subjects without diabetic retinopathy compared with those with diabetic retinopathy. The resistivity index can be used as an index of diabetic retinopathy progression in patients with type 2 diabetes. Moreover, multiple linear regression analysis between the chosen indicators of pulmonary function and retrobulbar hemodynamics parameters was significant except for MVV and D_{LCO}. The maximum standard coefficient of regression was 1.517 (right resistivity index [central retinal artery]) for VC, 0.779 (right resistivity index [arteria ophthalmica]) for FVC, 0.836 (right resistivity index [arteria ophthalmica]) for FEV_1, 1.144 (right resistivity index [arteria ophthalmica]) for PEF, 0.655 (left resistivity index [central retinal artery]) for TLC, 0.612 (left resistivity index [central retinal artery]) for FEV_1/FVC, and 0.680 (left resistivity index [central retinal artery]) for D_{LCO}/V_A (Table 5). Therefore, our multiple linear regression analysis revealed that the bilateral retrobulbar resistivity index may serve as an early predictor of changes in pulmonary function during the preclinical stages of diabetic retinopathy. The longitudinal follow-up study showed that subjects with resistivity index levels ≤0.7 showed significantly better pulmonary function in 2000, and their pulmonary function was better and showed a significantly smaller decrease in 2015 except for the changes in FEV_1/FVC. The change in FEV_1/FVC in the group with resistivity index levels ≤0.7 was greater, albeit not significantly, than that in the group with resistivity index levels >0.7 ($P = .85$). These results strengthen the argument of the use of the resistivity index as a predictor of pulmonary function in patients with type 2 diabetes. Chen et al[40] showed that compared with a

moderate decline in glomerular filtration rate, microalbuminuria had a greater impact on predicting the development and progression of diabetic retinopathy among subjects with type 2 diabetes. In our study, we demonstrated that the pulmonary function parameters were negatively correlated with the resistivity index in all 3 retrobulbar blood vessels; thus, we may combine microalbuminuria with the retrobulbar hemodynamics parameters to better predict the development and progression of diabetic retinopathy.

However, there were several limitations that will be resolved in future studies. First, we did not observe morphological changes in alveolar tissue and did not identify the proteins responsible for the alveolar tissue damage. Because all subjects did not undergo a lung biopsy, we will adopt an animal model to study alveolar tissue changes. Second, we failed to assess the long-term changes in pulmonary function and the circulatory parameters of retrobulbar blood vessels. Moreover, we studied subjects with type 2 diabetes without diabetic retinopathy but did not study the correlations during the different phases (eg, proliferative diabetic retinopathy and nonproliferative diabetic retinopathy). Therefore, we recommend that clinicians and patients monitor lung damage in patients with type 2 diabetes similar to the monitoring protocol for patients with diabetic nephropathy and diabetic retinopathy.

Conclusions

To the best of our knowledge, this is the first study to examine the correlation between pulmonary function and the circulatory parameters of retrobulbar blood vessels in subjects with type 2 diabetes without diabetic retinopathy. Our results show that the resistivity index was negatively correlated with pulmonary function and that poor glycemic control can compromise pulmonary function and retrobulbar hemodynamics. This finding indicates that patients and physicians should monitor lung function as well as the eye base. The resistivity index as well as the retina may predict the degree of injury in pulmonary function during the preclinical period. Because the sample size in our study was small (particularly in the 15-y follow-up study), we will enroll more subjects in future experiments. In addition, the technical relationship between detecting pulmonary function and retrobulbar hemodynamics requires further investigation in type 2 diabetes patients.

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