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Original Investigation

The Association of Pulmonary Functions with Glycemic Control and Microvascular Complications in Patients with Type II Diabetes Mellitus

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Abstract

Objective: Pulmonary system is a target organ for microangiopathic damage in patients with diabetes mellitus (DM). In the present study, the relationships of pulmonary functions with glycemic control, duration of diabetes, and microangiopathic complications have been assessed in type II diabetic patients.

Methods: Thirty-one type II diabetic patients with no history of either smoking or cardiopulmonary diseases were enrolled into the study. Blood tests including glycosylated hemoglobin (HbA1c) were performed. Pulmonary functions were assessed with spirometry and carbon monoxide (CO) diffusion capacity.

Results: Pulmonary functions were as follows: FEV_1 (%): 93.88±16.12; FVC (%): 86.48±15.76; FEV_1/FVC: 94.79±12.34; DL_{CO} (mL/min/mmHg): 104.13±15.00; and DL_{VA} (mL/min/mmHg/lt): 103.26±13.00. Eleven patients (35.4%) had diabetic nephropathy, 11 patients (35.4%) had retinopathy, 10 patients (32.3%) had sensorimotor neuropathy, and 10 patients (32.3%) did not have any microangiopathic complications. After adjustment for age, gender, and body mass index, there were significant associations between HbA1c and FEV_1 ($p=0.024$; $r=-0.426$), FVC ($p=0.009$, $r=-0.482$), and FEV_1/FVC ratio ($p=0.028$, $r=0.415$). No association was observed between HbA1c and CO diffusion capacity measurements (for all $p>0.05$). There was no significant relationship between the duration of diabetes and pulmonary functions (for all $p>0.05$). Pulmonary function tests were found similar between patients having microangiopathic complications and those without them.

Conclusion: Poor glycemic control may cause functional alterations of restrictive type in patients with type II DM.

Keywords: Diabetes mellitus, glycemic control, microangiopathic complications, pulmonary functions

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that requires continuous medical attendance along with the education of patients to diminish the risk of acute and chronic complications (1). Cerebrovascular, cardiovascular, and peripheral arterial diseases are well-known chronic macrovascular complications, while nephropathy, retinopathy, and peripheral and/or autonomic neuropathy are the outcomes of microvascular damage in patients with diabetes. The lungs are also the potential targets for diabetes because the pulmonary capillary bed has a wide microvascular network and pulmonary parenchyma is rich in connective tissues. Various histopathological changes have been documented in the pulmonary structures of diabetic patients and animal models such as abnormalities of connective tissue proteins, thickening of alveolar epithelium, and changes in capillary basement membrane (2-4). Studies assessing pulmonary functions in this specific population have been increasingly reported in the recent decade (5, 6). However, results of those studies are inconsistent; while some of the studies revealed decreased pulmonary functions in diabetic patients compared with healthy controls (7-9), some studies reported similar results between diabetic and healthy individuals (10). These discrepancies could probably be attributed to the differences in study populations, such as age and duration of diabetes of the study groups, and confounders, such as status of smoking and presence of cardiovascular diseases, all of which may lead to abnormal measurements of pulmonary functions, while the actual results were in normal limits. Because the number of patients with type II DM tends to increase in developing countries, to point out the changes in pulmonary functions is crucial for subsequent preventive and therapeutical approaches.

The aim of this study was to evaluate the associations of pulmonary functions with glycemic control, duration of diabetes, and microangiopathic complications in type II diabetic patients with no history of either smoking or cardiopulmonary diseases.

Methods

The study protocol was performed in accordance with the principles of Helsinki Declaration, and informed consent was obtained from all of the participants. It was approved by the local medical ethics committee.

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Consecutive type II diabetic patients on oral antidiabetic medications who were admitted to our internal medicine outpatient clinic were enrolled in our study for participation. Patients having symptoms of active respiratory system disorders, positive physical examination findings, and/or abnormal chest X-ray as well as chronic respiratory system diseases were excluded. Additionally, patients with established cardiovascular diseases, cerebrovascular disease, peripheral arterial disease, active malignancy or history of malignancy, hepatitis B and C virus infection, symptoms of active infection or inflammation, and with anemia (Hb<12.0 mg/dL) as well as patients on steroid treatment were not included. Finally, during a 3-month period, a total of 31 type II diabetic patients who never smoked (24 females and 7 males) were recruited into the study.

Age, gender, body weight, and height measurements were recorded for all patients. Weight and height were measured with the same equipments; weight (kg) to the square of height (m) ratio was used for calculation of body mass index (BMI). General physical examinations were performed; arterial blood pressures were measured two times with an appropriate cuff after 10 minutes resting in an upright sitting position and the average value was recorded. Duration of diabetes and actual medications were screened from patients' interviews and hospital charts for each subject and noted down.

Venous blood samples were collected from antecubital vein after an overnight fasting period. Fasting blood glucose, hemoglobin, blood urea nitrogen (BUN), creatinine, glycosylated hemoglobin (HbA1c), and lipid parameters (total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol) were determined by automated procedures conducted at the Biochemistry Department. HbA1c was assessed by high-performance liquid chromatography. Two hours after the breakfast, blood sampling was repeated for assessing the post-prandial blood glucose level.

Diabetic nephropathy was assessed by albumin excretion rates in 24 h urine specimens, and the values over 30 mg/day were accepted as diabetic nephropathy. All participants were assessed by the same ophthalmologist who was blind to the patients' characteristics and laboratory data. Besides the history of laser treatment, the presence of non-proliferative abnormalities (microaneurysm, exudate, or hemorrhage) or proliferative abnormalities with new vessel formations (neovascularization) in fundoscopic examinations were defined as diabetic retinopathy. The peripheral diabetic neuropathy was evaluated with physical examination and nerve conduction studies by the same neurologist blind to the data. Electromyographic nerve conduction studies were performed in the tibial, peroneal, and sural nerves of the non-dominant side lower limbs of the patients. The patients with abnormalities, including both of the motor and sensory nerves, were accepted as having diabetic neuropathy.

The assessment of pulmonary functions was conducted with spirometry and diffusion capacity testing with carbon monoxide (CO). The spirometry was performed in accordance with the American Thoracic Society recommendations (11). Measurements were repeated three times, while the patients were seated upright; the highest ones for forced vital capacity [FVC] (% of predicted value) and the maximum air volume during forced expiration in 1 s [FEV_1] (% of predicted value) were taken into account. Then, the ratio of FEV_1/FVC was computed. The diffusion capacity for CO (DLco; cc/min/mmHg) from inspired air to pulmonary capillary circulation was measured using the single breath method between 08:30 and 10:00 a.m. in sitting position. Corrected DL_{CO} by alveolar ventilation was represented by DL_{CO}/volume of alveoli (VA) (DL_{VA}) ratio.

Statistical analysis

Statistical analysis of the presented data was performed using SPSS software (version 18 SPSS Inc; Chicago, IL, USA). All P values were calculated as two-sided, and values of <0.05 were considered as statistically significant. Normality of distribution for continuous variables was tested using Kolmogorov–Smirnov test and histograms. Normally distributed parametric data were presented as mean±standard deviations (SD) and compared with student t-test between two groups. Non-normally distributed parametric data were presented as median and interquartile range (IQR; the range of values lying between the 25th and 75th centiles) and compared using Mann–Whitney U test. Categorical variables were shown as frequency and percentages and compared using chi-square test. Spearman or Pearson's rank correlation tests were performed to determine correlations between continuous variables. When the linear association was significant, the partial correlation analysis with the corrections of age, gender, duration of diabetes, and BMI was performed.

Results

The general characteristics of the study population are presented in Table 1. The mean age was 57.9±8.5 years, median duration of diabetes was 6 (5–10) years, mean BMI was 29.69±3.58 kg/m^2, and mean HbA1c was 9.2%±2.05% in our study. As comorbid conditions, 17 patients (54%) had hypertension and 5 patients (16.1%) had hyperlipidemia. The results of blood tests and pulmonary assessments are summarized in Table 2.

Among our patients, 10 patients (32.3%) had any of the microangiopathic complications. Diabetic nephropathy was detected in 11 patients (35.4%) (nine of them had microalbuminuria and two of them had overt proteinuria); diabetic retinopathy was detected in 11 (35.4%) patients and diabetic sensorimotor neuropathy was detected in 10 of the 31 patients (32.3%). Pulmonary function tests were found to be similar between patients having microangiopathic complications and those without them. The results are presented in Table 3. HbA1c was higher in patients having complications compared with the ones having no complications (9.74±2.01 vs. 8.17±1.79, respectively; p=0.044).

The correlation analysis revealed reverse associations between HbA1c and mean FEV_1 and FVC values (p=0.034, r=-0.383 and p=0.007, r=-0.471, respectively), while HbA1c had positive correlations with FEV_1/FVC ratio (p=0.018, r=0.424). After adjustment for age, gender, and BMI values, these associations still remained significant. There was no association between HbA1c, DL_{CO}, and DL_{VA} values (for both p>0.05) and the duration of diabetes (p=0.378, r=0.164). A negative correlation was present between fasting blood glucose level and FVC (p=0.035, r=-0.380). There was no association of fasting blood glucose level with FEV_1, FEV_1/FVC, DL_{CO}, and DL_{VA} values (p=0.068, r=-0.332; p=0.582, r=0.103; p=0.329, r=0.181; p=0.633, r=0.089, respectively).

Table 1. General characteristics, laboratory results, and pulmonary functions of the study patients

Age (years)	57.9±8.5
Gender (male; n, %)	24 (77.4%)
BMI (kg/m^2)	29.67±3.58
Systolic blood pressure (mmHg)	127.58±13.28
Diastolic blood pressure (mmHg)	78.39±9.52
Diabetes duration (year)	6 (5–10)
Comorbidities (n, %)	
Hypertension	17 (54.8%)
Hyperlipidemia	5 (16.1%)
Medications (n, %)	
Sulfonylurea	27 (87.1%)
Biguanide	17 (54.8%)
Acarbose	6 (19.4%)
Thiazolidinediones	9 (29.0%)
Renin angiotensin system blockers	8 (25.8%)
Calcium channel blockers	4 (12.9%)
Beta blockers	3 (9.7%)
Statins	4 (12.9%)
Fasting blood glucose (mg/dL)	196.45±54.51
Post-prandial blood glucose (mg/dL)	232.58±57.51
HbA1c (%)	9.24±2.05
Hemoglobin (gr/dL)	13.72±1.22
Blood urea nitrogen (mg/dL)	13.69±4.45
Creatinine (mg/dL)	0.69±0.18
Total cholesterol (mg/dL)	201.61±42.99
Triglyceride (mg/dL)	150 (104–228)
HDL-cholesterol (mg/dL)	43 (37–50)
LDL-cholesterol (mg/dL)	117.70±40.42
FEV_1 (%)	93.88±16.12
FVC (%)	86.48±15.76
FEV_1/FVC	94.79±12.34
DL_{CO} (mL/min/mmHg)	104.13±15.00
DL_{VA} (mL/min/mmHg/lt)	103.26±13.00

Continuous data are presented as mean±SD or median with IQR. Categorical variables are presented as frequencies and percentages. BMI: Body mass index; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FEV_1: Forced expiratory volume in 1 s; %: Percent; FVC: Forced vital capacity; DL_{CO}: Diffusing capacity of the lungs for carbon monoxide; DL_{VA}: Per alveolar diffusion capacity (DL_{CO} adjusted for volume; DL_{CO}/volume of alveoli).

Discussion

In the present study, the associations of glycemic control, duration of diabetes, and extrapulmonary microangiopathic complications with pulmonary functions were assessed in a cohort of non-smoking type II diabetic patients without cardiopulmonary diseases. The main finding of our study was that poor glycemic control was associated with restrictive type of functional alterations determined by spirometry. Pulmonary functions were not associated with duration of diabetes, and they were found to be similar in patients with or without microangiopathic complications.

There have been inconsistent reports concerning the relationship between glycemic control and pulmonary functions of type II diabetic patients (8-13). We have exhibited negative correlations between HbA1c, FEV_1, and FVC and positive correlations between HbA1c and FEV_1/FVC ratio. Although the mean values were in normal limits, correlations of HbA1c with spirometric parameters suggested that patients with poor glycemic control may be prone to restrictive pulmonary alterations. We did not exhibit any association between HbA1c, DL_{CO}, and DL_{VA} values in our study, as in previously reported series (12, 13). Earlier reports exerted non-significant results between HbA1c and measures of lung function (8, 10). However, in the last decade, HbA1c was manifested as a strong and consistent negative predictor of lung functions after adjusting for confounding variables in a follow-up investigation of type II diabetics (14). These discrepant results could be because of some heterogeneities of the study populations. In our study, all participants were non-smoking subjects. Moreover, correlations between HbA1c and spirometric test results remained significant after adjustment by age, gender, and BMI values, all of which may be confounding factors. Barrett-Connor et al. (10) revealed some striking results in their study. They showed that fasting plasma glucose levels were correlated with FEV_1 and FVC values in men without diabetes. Notably, we showed negative correlations of fasting blood glucose level with FVC values in our diabetic cohort. Thus, we considered that glycemic control and the level of glycemia seem to be crucial for pulmonary functions in type II diabetics.

Because of their extended capillary network, lungs could be a target for structural alterations and microvascular damage as a result of advanced glycosylation in type II diabetic patients. One of our expectations in the present study was that patients having microvascular complications of diabetes would also have worse pulmonary functions. However, we found that pulmonary functions did not differ in type II diabetic patients with or without microvascular complications. Similarly, Sinha et al. (4) detected no differences in FEV_1, FVC, and peak expiratory flow values of type II diabetic patients with one or more microangiopathic complications compared with those without any complication. In another study, FEV_1, FVC, and forced expiratory flow values have been reported to be similar in type II diabetics with or without diabetic retinopathy (12). In our study, CO transfer capacity was found to be the same in the setting of microvascular complications of diabetics. Regarding CO transfer capacity, previous reports revealed inconsistent results (15-19). Some studies exerted a decrease in CO diffusion capacity in patients with microvascular damage including retinopathy (15, 16) and nephropathy (16, 20), while, in accordance with our results, others did not find any difference between patients with or without microvascular complications (17, 19). In this setting, Fuso et al. (21) performed a distinctive study. They measured DL_{CO} values separately in sitting and supine positions in type II diabetics and compared these values with those of healthy subjects. DL_{CO} values were found to be increased in supine position in healthy subjects, while it was found to be the same in diabetics. Authors claimed that this postural diffusion testing could be an early method for the evaluation of pulmonary involvement in diabetics (21). In further studies, this point should be evaluated in larger populations.

Table 2. Laboratory results of patients according to microvascular complications

	Any microangiopathy		Nephropathy		Retinopathy		Neuropathy	
	Yes n=21	No n=10	Yes n=11	No n=20	Yes n=11	No n=20	Yes n=10	No n=21
Age (year)	58.3±9.5	57.0±6.4	55.9±10.6	59.0±7.3	60.9±9.8	56.2±7.5	60.6±9.1	56.6±8.1
Diabetes duration (year)	7 (5.5-11.5)	5 (3.75-11.25)	7 (5-13)	6 (5-10)	7 (6-15)	5.5 (5-10)	10 (5.8-16.3)	6 (4.5-9.5)
BMI (kg/m^2)	29.05±2.99	31.02±4.48	29.06±3.06	30.03±3.87	29.56±2.96	29.76±3.95	29.49±3.34	29.78±3.77
Fasting glucose (mg/dL)	200.43±55.94	188.10±53.27	205.73±41.12	19135±61.03	210.18±57.73	188.90±52.62	189.20±64.41	199.90±50.51
PPG (mg/dL)	227.19±59.56	243.90± 54.15	226.27±60.54	236.05±57.07	227.36±63.71	235.45±55.33	228.80±61.62	234.38±56.94
BUN (mg/dL)	13.82± 4.96	13.41±3.37	12.19±4.09	14.51±4.53	15.46±5.35	12.70±3.66	16.26±5.40	12.46±3.43*
Creatinine (mg/dL)	0.70±0.20	0.66±0.13	0.72±0.18	0.67±0.18	0.71±0.22	0.68±0.51	0.74±0.24	0.66±0.14
Hb (gr/dL)	13.51±1.13	14.15±1.36	13.85±1.38	13.65±1.16	12.99±0.78	14.12±1.25*	13.40±0.91	13.87±1.34
HbA1c (%)	9.74±2.01	8.17±1.79*	10.06±2.28	8.78±1.81	10.06±1.76	8.78±2.10	9.70±1.91	9.02 ±2.12
T. Cholesterol (mg/dL)	201.19±35.51	202.50±57.93	204.45±42.56	200.05±44.24	202.09±36.84	201.35±46.94	201.6±31.56	201.62±48.21
Triglyceride (mg/dL)	160 (98-243)	145.5 (121-175.8)	160 (87-253)	145.5 (119-192.75)	125 (94-233)	151.5 (119-219.25)	190.50 (103.5-357.25)	141 (100-188.50)
HDL-Cholesterol (mg/dL)	43 (35-49.50)	45 (39.3-50.3)	40 (35-49)	44 (40-50)	43.4 (35-50)	43 (37.75-49.75)	43.20 (34.25-7.75)	43 (38.5-50.5)
LDL-Cholesterol (mg/dL)	115.29±36.60	122.78±49.26	118.93±41.17	117.03±41.06	120.13±27.87	116.37±46.53	107.54±32.08	122.54±43.72
FEV_1 (%)	92.40±16.09	97.01±16.58	89.53±13.50	96.28±17.24	91.65±13.55	95.11±17.58	98.82±16.73	91.53±15.68
FVC (%)	83.95±13.24	91.80±19.79	81.35±12.02	89.31±17.09	84.09±11.53	87.8±17.8	88.85±13.34	85.36±16.97
FEV_1/FVC	96.86±12.65	90.44±10.99	96.06±15.03	94.09±10.95	97.59±11.97	93.25±12.56	98.56±10.63	93.00±12.92
DL_{CO} (mL/min/mmHg)	104.62±15.46	103.10±14.73	104.45±17.76	103.95±13.76	102.91±15.48	104.80±15.10	106.90±14.93	102.81±15.22
DL_{VA} (mL/min/mmHg/lt)	102.86±10.48	104.10±17.84	103.09±12.17	103.35±13.74	102.45±8.17	103.70±15.2	105.30±8.64	102.29±14.73

Continuous variables are presented as mean±SD or median with IQR depending on the distribution.

BMI: Body mass index; PPG: post prandial glucose; BUN: Blood urea nitrogen; Hb: Hemoglobin; HbA1c: Glycosylated hemoglobin; T. Cholesterol: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s; DL_{CO}: Diffusing capacity of the lungs for carbon monoxide; DL_{VA}: Per alveolar diffusion capacity (DL_{CO} adjusted for volume; DL_{CO}/volume of alveoli).

*p<0.05

Table 3. The associations of HbA1c with pulmonary function tests

	r	p	r_{adj}*	p_{adj}*
FEV_1 (%)	-0.383	0.034	-0.426	0.024
FVC (%)	-0.471	0.007	-0.482	0.009
FEV_1/FVC	0.424	0.018	0.415	0.028
DL_{CO} (mL/min/mmHg)	0.217	0.241	0.250	0.199
DL_{VA} (mL/min/mmHg/lt)	0.147	0.428	0.216	0.270

Associations were calculated by Spearman's correlation analysis. adj*: Adjusted values for age, gender, and BMI values.

FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; DL_{CO}: Diffusing capacity of the lungs for carbon monoxide; DLVA: Per alveolar diffusion capacity (DL_{CO} adjusted for volume; DL_{CO}/volume of alveoli).

We had assumed that we would observe deterioration in pulmonary functions as a result of the prolonged exposure of vascular structures and connective tissue proteins to high blood glucose levels in correlation with duration of diabetes. However, in our study, there was no correlation between duration of diabetes and pulmonary function parameters, neither with spirometry nor with diffusion capacity. In Fremantle's study, decreases in FEV_1, FVC, and vital capacity levels were detected when the duration of diabetes increased (8). Supportively, Barrett et al. (10) showed decreased FEV_1 and FVC values in male type II DM patients for more than 10 years, while the same result could not be manifested in females. On the other hand, Benbassat et al. (22) did not detect a relationship between duration of disease and pulmonary functions. Buckingam et al. (23) claimed that the decrease in vital capacity was neither related to the duration of disease nor to the presence of microvascular complications but to the structure of collagen and distortion of elasticity. Actually, defects in insulin secretion or its actions as well as pathological changes of the disease starts far before the time of diagnosis in type II diabetics. Therefore, the uncertainity in the duration of pathogenetic alterations related to diabetes could also be a confounding factor in such analyses.

Our study had some limitations, one of which was the relatively small study population. The exclusion of the patients with former smoking history leads to a higher female/male ratio. Additionally, a relatively longer median duration of diabetes in our study could have revealed more robust results.

Conclusion

We showed that poor glycemic control was associated with restrictive alterations in the pulmonary function tests of type II diabetics. We did not observe any difference in pulmonary functions in terms of microvascular complications. Our data could support that good glycemic control is essential for the maintenance of pulmonary health in type II diabetics.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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