Abnormalities of Pulmonary Function in Patients with Non-insulin-Dependent Diabetes Mellitus

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To examine the possible association between the vascular complications of diabetes and changes in pulmonary function, we performed pulmonary function tests including assessment of the diffusing capacity (%DLco) in 80 patients with non-insulin-dependent diabetes mellitus (45 males and 35 females) without overt lung or heart disease. The mean age of the subjects was 57.9 years and the mean duration of diabetes was 10.8 years. The %DLco decreased significantly as the duration of diabetes increased ($r = -0.38$, $p < 0.01$), and the same relationship was also observed in non-smoking subjects ($N = 37$). The reduction in %DLco was greater in patients with diabetic microangiopathy (especially nephropathy) and in those treated with insulin. Other pulmonary function tests (%VC, FEV_{1.0}, PaO₂ and PaCO₂) showed no relationship to the duration of diabetes, the degree of microangiopathy or the type of treatment. These results suggest that diabetic microangiopathy may play an important role in the decrease of %DLco. (Internal Medicine 31: 189–193, 1992)

Key words: diffusing capacity, pulse wave velocity

Introduction

It is well known that diabetes mellitus is associated with an increased susceptibility to infections. With the widespread use of insulin and the advent of newer antimicrobial agents, deaths due to infection have declined considerably among diabetic patients in recent years (1). However, the clinical significance of infections has not yet diminished (2).

Pre-existing pulmonary function disorders are now suspected to be one of the risk factors for respiratory infections in diabetics (3). In this regard, studies of the reduction of the diffusing capacity, forced vital capacity and forced expiratory volume in one second (FEV_{1.0}) have been reported (4–7). These studies have been based on the comparison of the pulmonary function of patients with insulin-dependent diabetes mellitus (IDDM) with that of normal subjects. Few studies however, have focused on the relationship between pulmonary function and the duration of diabetes or the presence of diabetic vascular complications in patients with non-insulin-dependent diabetes mellitus (NIDDM).

Accordingly, in this study NIDDM patients admitted

for glycemic control and education of diabetes underwent pulmonary function tests, including measurement of the diffusing capacity. The possible association between vascular complications of NIDDM and changes in pulmonary function was examined.

Subjects and Methods

The subjects consisted of 80 patients (45 men and 35 women) with NIDDM, none of whom had overt lung or heart disease. None of these subjects had sustained complaints of coughing, sputum or dyspnea (Table 1). Spirography, arterial blood gas analysis, and measurements of the pulmonary diffusing capacity were performed on each subject. We then investigated the relationship between the results of pulmonary function tests and the duration of diabetes, type of treatment, presence of diabetic complications and various other factors. Vital capacity (VC), FEV_{1.0} and carbon monoxide diffusing capacity (DLco) were expressed as a percentage of the corresponding values obtained from age-matched normal subjects (8, 9).

The presence of diabetic microangiopathy was defined

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Table 1. Clinical Profile of the Subjects

Sex	Male 45, Female 35	Smoking	nonsmokers 37, smokers 43
Age	57.9 ± 10.8 yrs	PWV	8.8 ± 1.8 m/s
Height	1.58 ± 0.08 m	Hb	14.0 ± 1.5 mg/dl
Weight	56.4 ± 10.3 kg	HbA1c	8.7 ± 1.9%
Obesity index	7.8 ± 16.3%	%VC	94.9 ± 13.3%
Body surface area	1.56 ± 0.16 m ²	FEV _{1.0} %	81.4 ± 6.9%
Duration of diabetes	10.9 ± 7.1 yrs	PaO ₂	85.1 ± 10.3 mmHg
Diabetic complications		PaCO ₂	38.4 ± 3.6 mmHg
Retinopathy	without 26, with 54	DLco	18.9 ± 4.9 ml/min·mmHg
Nephropathy	without 60, with 20	%DLco	79.7 ± 16.2%
Neuropathy	without 30, with 50		

(mean ± SD)

PWV: aortic pulse wave velocity

as follows: retinopathy was diagnosed by fundoscopic examination by ophthalmologists, nephropathy was diagnosed when proteinuria was present in 2 consecutive examinations or the serum creatinine value exceeded 2 mg/dl, and neuropathy was diagnosed by subjective symptoms or physical examinations. Aortic pulse wave velocity (PWV), as an index for arteriosclerosis, was determined as previously reported (10). Statistical analysis was carried out using Student's t-tests and linear correlation analysis.

Results

1. Duration of diabetes

%DLco was negatively correlated with the duration of diabetes ($r = -0.39$, $p < 0.01$, Fig. 1). Other pulmonary function tests including %VC, FEV_{1.0} or PaO₂ did not correlate with the duration of diabetes (Table 2). As smoking is a well-known factor affecting pulmonary function (11), same procedures were conducted excluding 43 smokers. It was found that %DLco still corre-

Fig. 1. Correlation between %DLco and the duration of Diabetes ($r = -0.39$, $p < 0.001$, $y = -0.90x + 89.54$).

Table 2. Correlation between Duration of Diabetes and Pulmonary Function Tests

	All cases (n = 80)		Nonsmokers (n = 37)	
	r	p value	r	p value
%VC	-0.20	0.08	-0.12	0.5
FEV _{1.0} %	-0.06	0.63	-0.25	0.13
PaO ₂	-0.07	0.52	-0.03	0.86
PaCO ₂	0.10	0.4	0.13	0.45
DLco	-0.33	0.003	-0.40	0.02
%DLco	-0.39	0.0003	-0.37	0.03

lated negatively with the duration of diabetes ($r = -0.37$, $p < 0.05$). There was no significant difference between smokers and non-smokers in mean age, body surface area or the duration of diabetes.

2. Diabetic microangiopathy

Patients with diabetic microangiopathy had a slight decrease in %VC compared to patients without microangiopathy. No relationship was found between diabetic microangiopathy and FEV_{1.0}%, PaO₂ or PaCO₂ (Table 3). Patients with diabetic microangiopathy had a decreased %DLco compared to patients without microangiopathy. In addition, as shown in Fig. 2, %DLco in patients with nephropathy was significantly lower than in those without nephropathy ($72.0 \pm 21.8\%$ vs $82.3 \pm 13.1\%$, $p < 0.05$). The duration of diabetes was 14.4 years for subjects with nephropathy and 9.7 years without nephropathy ($p < 0.01$). There was no significant difference in the hemoglobin levels between subjects with or without nephropathy.

3. Treatment of diabetes

The relationship between the treatment of diabetes with insulin or with oral hypoglycemic agents and/or diet, and the results of the pulmonary function tests was also investigated. Patients treated with insulin had a significant decrease in %DLco compared to patients treated with others drugs ($p < 0.05$, Table 4). No relationship was found between the type of treatment and

Pulmonary Dysfunction in NIDDM Patients

Table 3. Relationship between Diabetic Microangiopathy* and Pulmonary Function Tests

			%VC	FEV _{1.0} %	PaO ₂ (mmHg)	PaCO ₂ (mmHg)
Retinopathy	with (n = 54)		93.0 ± 13.2	82.1 ± 6.0	85.1 ± 10.0	38.7 ± 3.7
	without (n = 26)		98.7 ± 13.1	80.0 ± 8.5	85.1 ± 11.2	37.7 ± 3.4
Nephropathy	with (n = 20)		90.3 ± 15.1	81.7 ± 6.7	85.0 ± 10.6	38.8 ± 2.6
	without (n = 60)		96.4 ± 12.5	81.3 ± 7.0	85.2 ± 10.4	38.2 ± 3.9
Neuropathy	with (n = 50)		93.9 ± 13.7	81.3 ± 6.7	85.0 ± 10.9	39.2 ± 3.5
	without (n = 30)		96.5 ± 13.1	82.3 ± 6.6	85.1 ± 9.5	37.2 ± 3.4

(mean ± SD)

* There was no significant difference between patients with microangiopathy and those without microangiopathy.

Fig. 2. Comparison of %DLco between patients with and without microangiopathy. Solid bars, patients with microangiopathy; hatched bars, patients without microangiopathy. *p < 0.05, comparison of the values between two groups.

%VC, FEV_{1.0}%, PaO₂ or PaCO₂.

4. Macroangiopathy

Our previous study (10) indicated that PWV is increased in patients with diabetic microangiopathy, suggesting a possible association between macroangiopathy and microangiopathy. Here, the %VC and PaO₂ showed

Table 4. Relationship between the Type of Diabetes Treatment and Pulmonary Function Tests

	insulin (n = 30)	others (n = 50)	p value
%VC	92.6 ± 14.0	96.2 ± 12.9	0.24
FEV _{1.0} %	82.0 ± 6.7	81.0 ± 7.1	0.58
PaO ₂	86.4 ± 9.9	84.3 ± 10.6	0.38
PaCO ₂	38.5 ± 3.1	38.3 ± 3.9	0.87
DLco	17.5 ± 4.3	19.8 ± 5.1	0.04
%DLco	74.0 ± 15.3	83.3 ± 15.9	0.02

(mean ± SD)

insulin: patients treated with insulin

others: patients treated with hypoglycemic agents and/or diet

a negative correlation with the PWV values (p < 0.05, Table 5). There was a weak negative relationship between PWV and %DLco (p = 0.05). No correlation was found between PWV and FEV_{1.0}% or PaCO₂.

In addition, PaO₂ was negatively correlated with ΔPWV, which is the difference between PWV values in diabetic patients and the mean PWV values for normal age-matched subjects (r = -0.40, p < 0.01, Fig. 3). The relationship was not significant between ΔPWV and %VC, FEV_{1.0}%, %DLco or PaCO₂.

Discussion

Previous studies concerning pulmonary function

Table 5. Correlation between Aortic Pulse Wave Velocity and Pulmonary Function tests

	PWV		ΔPWV	
	r	p value	r	p value
%VC	-0.3	0.03	-0.26	0.05
FEV _{1.0} %	-0.25	0.07	-0.09	0.53
DLco	-0.27	0.05	-0.07	0.63
%DLco	-0.21	0.13	-0.11	0.42
PaO ₂	-0.36	0.01	-0.4	0.002
PaCO ₂	-0.063	0.65	0.025	0.86

ΔPWV, the difference between the PWV of the patients and the mean PWV of age-matched subjects

Fig. 3. Correlation between PaO_2 and ΔPWV ($r = -0.40$, $p < 0.001$). ΔPWV is the difference between the pulse wave velocity of patients and the mean PWV of age-matched subjects.

abnormalities in diabetics have mainly dealt with IDDM patients (4–7), and only a few studies have been conducted on NIDDM patients. The present study indicates that several types of pulmonary function disorders exist in NIDDM patients.

First, pulmonary diffusing capacity, as determined by %DLco, was found to correlate negatively with the duration of diabetes (Table 2 and Fig. 1). Furthermore, %DLco was reduced in patients with diabetic microangiopathy (Table 3 and Fig. 2). Asanuma et al (3) and Sandler et al (12) have reported that as the duration of diabetes is increased, the pulmonary diffusing capacity is decreased. Asanuma et al also found that patients with diabetic retinopathy have a decreased %DLco compared to patients without retinopathy, but Sandler et al found no relationship between diabetic vascular complications and pulmonary diffusing capacity. Because Asanuma et al studied diabetics of a mean age of 50 years while Sandler et al studied much younger patients with IDDM, this discrepancy in their results seems to be attributable to the differing populations of subjects investigated.

Uchida and co-workers (13) studied ventilation-perfusion scintigrams in diabetic subjects. They observed a decreased pulmonary diffusing capacity in patients with a perfusion defect. As these patients had a longer duration of diabetes and higher incidence of retinopathy, the existence of pulmonary microangiopathy was suggested. These results indicate that, as one manifestation of diabetic microangiopathy, %DLco is reduced by microangiopathic involvement of pulmonary vessels leading to ventilation-perfusion inequalities. In the present results, insulin-treated subjects had significantly lower %DLco values compared to those treated with other vehicles (Table 4). This is partly explained by the

fact that insulin-treated subjects had a longer duration of diabetes compared to the other subjects (12.7 years and 9.7 years, respectively).

Secondly, with an increase in PWV values, it was found that PaO_2 values were decreased (Table 5 and Fig. 3). PWV is considered to be an indicator of macroangiopathy. Sugawara et al (14) explained that 1) an increase in the diffusion distance due to thickening of the pulmonary capillary basement membrane, 2) a decrease in alveolar-capillary matrix, and 3) ventilation-perfusion inequalities due to a decrease in surfactant concomitantly lead to a decreased diffusing capacity, and secondarily to lower PaO_2 values. In this study, we could not observe a correlation between PaO_2 and the duration of diabetes or %DLco. Therefore, we suspect that the mechanism which contributes to decreased PaO_2 might be different from that causing decreased %DLco (possibly ventilation-perfusion inequalities) in diabetic subjects. Further investigation with a larger group is necessary to clarify the relationship of macroangiopathy and decreased PaO_2 .

In the present study, there was no relationship between HbA1c levels at the time of pulmonary function measurements and the results of pulmonary function tests (data not shown). Because HbA1c levels are known as indicators of glycemic control for a short period of 1–2 months, it is not adequate to conclude that the plasma glucose level is not related to the decreased %DLco. In fact, Lange et al (15), who performed multiple regression analysis of their data, suggested that an elevated plasma glucose concentration is one of the risk factors for a decrease in forced vital capacity and $\text{FEV}_{1.0}$.

In future, it seems necessary to repeat pulmonary function tests and to assess the changes of pulmonary function among the same subjects, including the investigation of the risk factors for such changes in the tests. Over a long observation course, the relationship between the plasma glucose concentration and the pulmonary function can be elucidated.

Conclusions

1. Pulmonary diffusing capacity, as determined by %DLco, was found to be negatively correlated with the duration of diabetes. In addition, %DLco was lower in patients with diabetic microangiopathy (nephropathy) or those treated with insulin. These results indicate that decreased pulmonary diffusing capacity may develop as one manifestation of diabetic microangiopathy.

2. Values of PaO_2 were found to correlate negatively with PWV, whereas no definite relationship was observed between PaO_2 and the duration of diabetes or %DLco.

A part of this study was presented at the 27th General Meeting of the Chugoku-Shikoku District of the Japan Diabetes Society (October 1989, Matsue) and at the

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(May 1990, Tokyo).

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