Turkish Journal of Endocrinology and Metabolism, (1999) 1 : 5-10 **ORIGINAL ARTICLE**

Pulmonary Function Parameters in Patients with Diabetes Mellitus*

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This study is th e preliminary report of a multicentric study conducted to evaluate the possible association between the microvascular complications of diabetes mellitus (DM) and changes in pulmonary functions. 30 non-smoking diabetics having no overt pulmonary or cardiac disease were included. Glycosylated hemoglobin (HbA_{1c}) levels were determined, ophthalmologic examination for diabetic retinopathy was done and microalbuminuria (MAU) was measured in order to evaluate diabetic nephropathy. Pulmonary function tests, including the assessment of diffusing capacity [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1% predicted (FEV_1 %), forced expiratory flow in 25-75% of vital capacity (FEF_{25-75}), carbon monoxide diffusing capacity (DLCO) alveolar volume (VA), DLCO/VA] were performed. The mean age (66.7% male) was 54±9.97yr. Nine patients (30 %) had had DM for more than 10 years. 19 cases (62%) had high HbA_{1c} levels (over 7%), 18 (60%) had a body mass index (BMI) over 27.5 kg/m^2. 70% of patients were using oral antidiabetics (OAD). Diabetic retinopathy was found and degreed in 46.7% of cases. The patient population, subdivided according to HbA_{1c} levels, BMI, type of treatment, retinal findings, duration of DM, microalbuminuria and pulmonary parameters, was compared; statistical analysis was done by SPSS program using Pearson correlation tests. No statistical difference was found between any of these subgroups ($p > 0.05$). So, a possible association between diabetic microvascular pathology and pulmonary functional changes was not detected, this is thought to be due to the insufficient number of patients.

KEY WORDS Diabetes mellitus, pulmonary function test, diffusing capacity

Introduction

Due to an increase in the duration of diabetes mellitus (DM), thickening of the capillary basal membrane, increase in capillary permeability, blood flow and viscosity and disturbances in the functions of platelets may be observed in diabetics, particularly in the ones who are genetically susceptible. As a result of these alterations, capillary protein leakage (microalbuminuria (MAU)), formation of microtrombi and ischemic tissue damage may occur. Microvascular complications are specific for diabetes and these are retinopathy, nephropathy and neuropathy (1).

DM produces damage in small blood vessels characterized by morphologic and biochemical alterations of the capillary basal lamina. These abnormalities have been observed in several organs including the lung. The thickness of both endothelial and epithelial sides of the alveolar-capillary barrier is increased at the expense of alveolar air and blood volume. Carbon monoxide diffusing capacity (DLCO) is so affected by the amount of blood in the lung capillaries so that it could be employed

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as a simple non invasive method to estimate the pulmonary capillary damage in DM patients (2).

In this study, it was aimed to evaluate the possible association between the microvascular complications of DM and the changes in pulmonary functions.

Materials and Methods

In the Department of Endocrinology of Celal Bayar University Hospital, 30 non-smoking patients with diabetes mellitus type II having no overt pulmonary or cardiac disease were included in the study between January 1997- March 1998. Patients with any respiratory or cardiac symptoms and/or physical and radiologic findings were excluded.

HbA_1c was used as an index of diabetic control over the 3-4 month period and determined by the immunoturbidimetric method (using Hitachi 704 otoanalyser). Values over 7.5% were considered as poor glycemic control and ones lower than this level as good glycemic control (3).

Body mass index(BMI) was calculated by the formula of weight/height^2 and according to these values, patients were divided into 3 subgroups as below 25kg/m^2, between 25-27kg/m^2 and over 27kg/m^2 (3).

The study population was divided into two groups according to their drugs as insulin or oral antidiabetics (OAD) and also into three groups based on the duration of DM as 0-5, 6-10 and over 10 years (3).

Diabetic retinopathy was diagnosed by fundoscopic examination by ophthalmologists and classified as normal, background or proliferative retinopathy.

Diabetic nephropathy was diagnosed by measuring microalbuminuria on 24 hour urine collection with the immunoturbidimetric method and values below 30mg/24h were considered as normoalbuminuria (3).

Pulmonary function tests were performed by using a computerized system (Sensor medics 2400 model spirometry) in a sitting position and carbon-monoxide diffusing capacity (DLCO) was measured by the single-breath method using gas chromatographic equipment. Pulmonary function parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1% predicted (FEV_1%), forced expiratory flow in 25-75% of vital capacity (FEF_{25-75}), DLCO, alveolar volume (VA), and DLCO/VA.

The pulmonary parameters of the subgroups mentioned above were compared by SPSS pocket statistical program using Pearson correlation tests.

Results

The mean age of patients(20 female, 10 male) was 54±9.97 (23-74)yr.

HbA_1c levels were normal in 11 patients (37.9%) and high in 19 patients (62.1%), no significant difference between pulmonary function parameters of these 2 groups was found, as summarized in Table 1.

Lung function variations of the groups according to BMI are shown in Table 2.

No significant difference was found among these values. 21 (70%) patients were using OAD, while the other 9 (30%) were insulin dependent diabetes mellitus type II, their pulmonary parameters were also not different ($p > 0.05$) as shown in Table 3.

Pulmonary function variations were not correlated with the duration of DM as summarized in Table 4.

Pulmonary parameters according to ophthalmoscopic findings are shown in Table 5.

MAU levels and their correlations with pulmonary function tests are shown in Table 6, but here there was also no correlation.

Discussion

Microvascular damage on the capillary basal membrane affects many organs including the lungs. Histologic evidence of pulmonary abnormalities in streptozotocin-induced diabetes in rats have included alterations in the ultrastructure of

Tablo 1. Pulmonary function parameters according to HbA_1c levels.

HbA_1c	FVC(L)* (FVC pred.*)	FEV_1(L)* (FEV_1 pred.*)	FEF_{25-75}(L/s)* (FEF_{25-75} pred.*)	DLCO (ml/min/mmHg)* (DLCO pred.*)	DLCO/VA (min/mmHg)* (DLCO/VA pred.*)
Good glycemic control n=11	3.33±0.84 (95.61±9.5)	2.52±0.49 (99.10±9.9)	2.44±0.73 (86.6±25.6)	15.25±4.30 (70.45±15.2)	2.40±0.72 (59.58±17.0)
Poor glycemic control n=19	3.06±0.96 (90.9±14.7)	2.50±0.89 (99.7±17.8)	2.94±1.70 (100.4±42.2)	15.71±7.26 (74.34±28.81)	2.69±1.13 (65.92±25.71)

*P>0.05

Tablo 2. Pulmonary function parameters according to BMI.

BMI	FVC(L) (FVC pred.)	FEV_1(L) (FEV_1 pred.)	FEF_{25-75}(L/s) (FEF_{25-75} pred.)	DLCO (ml/min/mmHg) (DLCO pred.)	DLCO/VA (min/mmHg) (DLCO/VA pred.)
<25 n=9	3.14±0.94 (92.89±10.43)	2.71±0.89 (105±10.59)	3.30±1.58 (110.44±31.16)	14.91±7.29 (75.22±29.09)	2.47±1.04 (60.33±22.92)
25-26.9 n=3	2.94±0.39 (96.67±10.50)	2.30±0.24 (100.33±7.23)	2.35±0.54 (85.67±15.89)	16.56±0.57 (84±6.56)	2.98±0.76 (72±16.37)
>27 n=18	3.11±1.00 (91.39±14.65)	2.40±0.73 (96.50±17.09)	2.40±0.73 (89.28±39.79)	15.33±6.34 (68.28±23.80)	2.56±0.99 (63.83±23.52)

Tablo 3. Pulmonary function parameters according to the treatment type.

Treatment	FVC(L)* (FVC pred.)	FEV_1(L)* (FEV_1 pred.*)	FEF_{25-75}(L/s)* (FEF_{25-75} pred.*)	DLCO (ml/min/mmHg)* (DLCO pred.*)	DLCO/VA (min/mmHg)* (DLCO/VA pred.*)
OAD	3.22±0.95 (94.33±12.89)	2.52±0.76 (99.24±14.05)	2.62±1.32 (90.05±33.31)	15.17±6.05 (74.38±22.69)	2.68±0.91 (65.71±21.04)
INSULIN	2.87±0.84 (87.78±12.36)	2.40±0.77 (99.89±17.51)	2.98±1.61 (107.44±41.96)	13.35±6.45 (66.22±28.59)	2.32±1.10 (58.67±25.71)

*P>0.05

Tablo 4. Pulmonary function parameters according to the duration of DM.

Duration (years)	FVC(L)* (FVC pred.)	FEV_1(L)* (FEV_1 pred.*)	FEF_{25-75}(L/s)* (FEF_{25-75} pred.*)	DLCO (ml/min/mmHg)* (DLCO pred.*)	DLCO/VA (min/mmHg)* (DLCO/VA pred.*)
0-5 n=11	3.11±0.94 (92.64±9.33)	2.50±0.69 (100.64±8.24)	2.61±0.63 (93.36±18.94)	13.70±4.99 (64.45±22.62)	2.39±0.91 (58.27±20.6)
6-10 n=10	3.39±0.93 (101.4±13.3)	2.61±0.71 (105.1±17.46)	2.69±1.22 (94.00±33.4)	17.75±5.73 (81.20±19.96)	2.81±0.73 (69.30±17.8)
>10 n=9	2.82±0.88 (82.00±8.44)	2.30±0.90 (91.67±16.21)	2.91±2.20 (99.00±55.11)	14.62±7.73 (70.78±29.72)	2.54±1.28 (63.78±28.98)

*P>0.05

Tablo 5. Pulmonary function parameters according to diabetic retinopathy.

Retinophaty	FVC(L) (FVC pred.)	FEV_1(L) (FEV_1 pred.)	FEF_{25-75}(L/s) (FEF_{25-75} pred.)	DLCO (ml/min/mmHg) (DLCO pred.)	DLCO/VA (min/mmHg) (DLCO/VA pred.)
Normal	3.18±0.98	2.37±0.66	2.11±0.64	14.6±5.09	2.32±0.66
n=17	(91.81±12.35)	(94.19±12.02)	(75.88±18.86)	(67.75±19.56)	(57.69±14.90)
Background	3.10±1.02	2.71±0.99	3.84±1.83	16.9±8.64	2.99±1.38
n=10	(94.67±12.47)	(109.1±12.76)	(130.1±36.75)	(79.44±33.46)	(73.0±32.46)
Proliferative	2.62±0.50	2.21±0.57	2.61±1.55	12.7±4.63	2.62±0.67
n=3	(81.33±12.34)	(87.67±14.29)	(84.0±39.04)	(65.33±26.63)	(59.33±16.04)

Tablo 6. Pulmonary function parameters according to microalbuminuria levels.

Albuminuria	FVC*(L) (FVC pred.)*	FEV_1*(L) (FEV_1 pred.)*	FEF_{25-75}(L/s)* (FEF_{25-75} pred.)*	DLCO (ml/min/mmHg)* (DLCO pred.)*	DLCO/VA (min/mmHg)* (DLCO/VA pred.)*
Normal	3.20±0.99	2.51±0.78	2.71±1.39	16.1±4.71	3.07±0.60
n=21	(94.4±12.7)	(103.2±15.2)	(93.75±36.41)	(78.41±22.23)	(75±12.54)
High	2.89±0.66	2.40±0.70	2.79±1.49	15.02±6.73	2.39±1.02
n=9	(91.6±13.2)	(98.1±14.82)	(99.51±38.0)	(69.65±25.2)	(59.5±23.9)

*P>0.05

granular pneumocytes in the interalveoler septum of non-ciliated bronchioler epithelial cells and of collagen and elastin in the alveolar wall (4).

Post-mortem studies on diabetic patients have shown the thickening of alveolar epithelial and pulmonary capillary basal laminae, centrilobular emphysema and pulmonary microangiopathy (4). This thickening is because of the expense of alveolar air and blood volume and DLCO is so affected by the amount of blood in the lung capillaries (2). Basal laminal thickening is considered to be the initial lesion in the development of diabetic microangiopathy (4).

Microangiopathy is certainly one of the most important complications in DM and the relationship between microangiopathy and DLCO is well documented but there are conflicting results. Schuyler described significantly diminished transpulmonary pressure at 50 and 60% of total lung capacity (TLC) and decreased TLC in 11 young diabetes mellitus type I patients. He speculated that the observed decreases in lung recoil pressure at these lung volumes were due to premature aging of elastic lung elements and further postulated that the observed decrease in TLC might be due to an altered collagen matrix in the lung. In a study of 23 diabetes mellitus type I patients with limited joint motility (LJM), an association between severe LJM and a significant decrease in lung volumes was found and this was thought to be due to decreased lung compliance or restriction of chest wall expansion as a result of altered collagen metabolism since collagen plays a fundamental role in defining lung structure and function (5). Innocenti (6) concluded that diabetes mellitus type I is characterized by reduced FVC and FEV_1 while a significant decrease in DLCO may be considered as selectively associated with renal disease. In contrast, Schernthaner found no significant abnormalities in pulmonary parameters of 20 diabetic patients (5).

Mori (7) showed that DLCO% decreased significantly as the duration of DM increased and the reduction was greater in patients with diabetic microangiopathy (especially nephropathy) and in those treated with insulin. Other pulmonary function tests showed no relationship. Asanuma (8) showed a negative correlation between DLCO% and the duration of disease. In a cross-section

study, Sandler (5) concluded that 60% of a diabetic population had abnormal pulmonary function, mild reduction of lung elastic recoil and/or a reduction in pulmonary capillary blood volume. The degree of pulmonary dysfunction was correlated with the duration of DM. These changes were not associated with abnormal lung volumes, air flow or gas distribution and there was no association between lung and other organ involvement in diabetic patients. In another study diabetic patients had pulmonary ventilation and perfusion scans and those with defects on perfusion scans showed a decrease in DLCO. The long duration of DM and the presence of high grade retinopathy associated with pulmonary microangiopathy and the decrease in DLCO with diabetes mellitus type 1 were thought to be due to the fact that the patients using insulin usually had a longer duration of disease (9). Mori (7) also concluded that as the duration of DM increased, the DLCO decreased significantly. In this study, no correlation was found between duration and pulmonary functions, but only 9 cases had had DM for more than 10 years so this may be a result of the shortness of disease in this study population.

Glycaemic level and pulmonary parameters also showed no correlation in this study. Since HbA_1c reflects the glycaemic level of the patient for the last 3-4 months, this lack of correlation may not be surprising. Abnormal pulmonary function was reported not to be associated with the index of diabetic control: HbA_1c concentration. However, this finding does not necessarily exclude the influence of blood glucose control on the development of pulmonary dysfunction, since HbA_1c concentration only reflected control during the 3-4 months prior to the study (4). Mori (7) also found no relationship between HbA_1c levels and pulmonary functions but added that it was not adequate to conclude that plasma glucose level is not related to the decreased DLCO%. Lange suggested that an elevated plasma glucose concentration is one of the risk factors for a decrease in FVC and FEV_1. He concluded that over a long observation period, this relationship could be elucidated. Ramirez's data (10) also confirmed that long-term near-normoglycemia may be beneficial in preventing the deterioration of pulmonary function associated with DM.

We did not find any different parameters when we compared the patients according to their treatment. The number of patients treated by OAD was greater than the ones using insulin and this imbalance may explain the above. Kebapçı (11) showed a negative relation between proteinuria and DLCO in diabetes mellitus type 2 while she could not demonstrate a relationship between DLCO and HbA_1c, creatinin clearance, neuropathy and retinopathy in diabetes mellitus type 1 and diabetes mellitus type 2. Most studies based on the comparison the pulmonary functions are conducted on diabetes mellitus type I patients, few studies, however, have focused on the relationship of diabetes mellitus type 2 patients. In one of these studies Mori (8) reported that the reduction in DLCO% was greater in patients with diabetic microangiopathy, especially nephropathy. Barrett (13) reported an absence of an association of diabetes mellitus type 2 with pulmonary dysfunction and thought this to be due to the small number of subjects with severe diabetes or diabetes of prolonged duration as we have in our study and he added that more epidemiological studies were needed to provide further information about the relationship between diabetes mellitus type 2 and lung function.

The abnormalities found in our patients were mild and unlikely to be of clinical significance. This might be due to the different reasons speculated below; 1-The number of some of the subgroups was not sufficient to find a statistical significance. Also the number of patients with complications was low and damage at the level of microangiopathy might not have occurred yet. 2- The use of angiotensin converting enzyme (ACE) inhibitors is known to reduce protein excretion and postpone the onset of persistent proteinuria so their use is recommended to prevent progressive nephropathy (3). Some of our patients were also using ACE inhibitors so this might have caused microalbuminuria values to be less than expected. 3-The most likely explanation is that the single-breath method might not be sensitive enough to detect pulmonary vascular microangiopathy. The low pulmonary vascular pressure determines only minor changes in the pulmonary capillaries of diabetic subjects so the commonly used method of DLCO might not be sensitive enough to discriminate between diabetics and normal subjects (2).

Fuso (2) therefore suggested a change to increase the sensitivity and the diagnostic usefulness of DLCO which could derive from the measurement of posture-related variations of diffusing capacity. It is known that in normal subjects the increase in DLCO in the supine position has been attributed to a recruitment of the upper pulmonary lobe capillaries and to an increase in blood volume. The thickening and the decreased compliance of lung capillaries due to diabetic microangiopathy could negatively affect these changes in diabetes mellitus type I patients. DLCO was significantly increased in normal subjects but not in diabetics by changing the posture of the subject from sitting to the supine position and he suggested this postural test as a screening diagnostic procedure for an early assessment of pulmonary abnormalities in diabetics and the lack of postural increase of pulmonary capillary blood volume in diabetics could reflect the presence of microangiopathy involving the pulmonary small vessels.

So we conclude that longitudinal studies could help to identify a temporal pattern of lung involvement and its possible relationship to other organ involvement and more reliable methods are needed for this.

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