

TRENDS IN PULMONARY FUNCTION IN TYPE 1 DIABETIC PATIENTS WITH NEPHROPATHY

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SUMMARY

Reduction of pulmonary function tests may be present in patients with diabetes mellitus. The study included 31 type 1 diabetic patients aged 21-62 years, with diabetes duration of 3-32 years. The protein excretion rate and carbon monoxide diffusion capacity of the lung were assessed as parameters of the severity of complications. Carbon monoxide diffusion capacity was measured by single-breath method and corrected by the measurement of alveolar volume. Proteinuria was found to be the only significant predictor of carbon monoxide diffusion capacity ($R^2=0.46$), forced expiratory flow in the first second ($R^2=0.38$), and forced expiratory flow with 50% of the forced vital capacity exhaled ($R^2=0.32$). Our results suggested diabetes mellitus to be associated with impairment of renal and pulmonary functions. It is postulated that these complications of diabetes might share a similar microangiopathic background.

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INTRODUCTION

Diabetes mellitus is associated with the development of microvascular complications as well as with impairment in the function of many organic systems. Consequently, the kidneys, eyes, cardiovascular system and respiratory system can be damaged (1). The aim of our study was to investigate pulmonary function and its association with renal complications in diabetes mellitus. The development of these complications can be explained by the biochemical alteration of connective tissue constituents, particularly collagen and elastin as well as by microangiopathy due to nonenzymatic protein glycosylation induced by chronic hyperglycemia (2,3).

Pathoanatomical studies in diabetic patients have presented evidence for changes in basal lamina of alveolar epithelium and capillaries (2). In addition to the kidneys, the lungs of diabetic patients are also affected. The consequence is the development of obstructive and restrictive disorders. Collagen is an abundant structural protein of the previously mentioned organic systems. As the result of alveolar-capillary membrane thickening due to collagen and elastin alteration as well as microangiopathy, a reduction of the carbon monoxide diffusion capacity (DLCO) and decline of ventilatory function of the lung can be found in diabetic patients.

Glomerular capillary injuries are usually present in patients with impaired pulmonary function tests. The aim of our study was to assess the presence of lung complications and the connection between renal and lung complications. The values of the protein excretion rate (PER), DLCO and spirometric parameters were compared for this purpose.

PATIENTS AND METHODS

Patients

The study included 31 type 1 diabetic patients (18 male and 13 female, mean age 45 ± 12.09 years, mean diabetes duration 17 ± 7.01 years) without overt lung disease and history of smoking. The duration of the disease was between 3 and 32 years. The effect of the predictor variables of patient age, diabetes duration, systolic and diastolic blood pressure, PER, serum creatinine, creatinine clearance, lipid values and glycated hemoglobin on DLCO and the spirometric parameters of forced vital capacity (FVC), forced expiratory flow in the first second (FEV1), forced expiratory flow with 50% of the forced vital capacity exhaled (FEF50), and peak expiratory flow (PEF) were studied. Because of a possible impact on DLCO, the value of hemoglobin in the blood (Hb) was also measured.

Patients with lung disease and connective tissue disease affecting pulmonary function were excluded from the study. All included patients were in good clinical condition, with no signs of heart failure.

Methods

DLCO was measured by the single breath method and corrected by alveolar volume (VA). Pulmonary function tests were determined by spirometry. PER was determined by the biuret method.

Statistical analysis

Age, diabetes duration, PER, smoking and Hb were included in a stepwise multiple regression model to determine their value in predicting DLCO/VA and spirometric parameters. The normality of the distribution was tested with the Shapiro-Wilk W test. The variables of PER and DLCO were normalized by logarithmic transformation before inclusion in the

regression model (4). Mann-Whitney U test was used to determine the difference in pulmonary function tests according to PER.

RESULTS

PER was found to be the only independent predictor of DLCO values ($R^2=0.46$). Hb and DLCO were found to correlate significantly ($r=0.56$, $p<0.01$), however, the independent effect of Hb on DLCO was not significant, yet almost reaching the conventional significance level of $p=0.05$.

PER, systolic blood pressure and creatinine were the most important variables in the prediction of FEV1 ($R^2=0.38$), and PER and diabetes duration in the prediction of FEF50% ($R^2=0.31$).

A significant difference (Mann-Whitney U test) was found in the lung parameters of DLCO (Fig. 1), FEV1 (Fig. 2), and FEF50 (Fig. 3) between the groups of patients with and without significant proteinuria ($p=0.001$ vs. $p=0.001$ vs. $p=0.039$, respectively) (Table 1). FVC was reduced in the group with $PER \geq 0.15$ g/24 h, but the difference between the groups was not significant ($p=0.241$) (Fig. 4).

Table 1. Characteristics of diabetic patients included in the study (N=31)

	PER <0.15g/24 n=18	PER \geq 0.15g/24 n=13
Age (yrs)	55.2 (15.9)*	46.3 (17.4)*
Diabetes duration (yrs)	24 (19.7)*	22.8 (18.9)*
PER (g/24 h)	0.04 (0.02-0.09) [§]	1.45 (0.45-2.29) [§]
DLCO/VA (%)	79.2 (72-95.5) [§]	58.6 (54-72.2) [§]
DLCO (%)	82 (75-100) [§]	61 (56.5-75.5) [§]
FEV1 (%)	103 (83-111) [§]	84.5 (75-97) [§]
FEF50 (%)	101 (98-126) [§]	78 (65-88.5) [§]
Hb (g/L)	139.3 (20.04)*	125.6 (21.06)*
HbA _{1c} (%)	9,16 (7.48-12.1) [§]	9.47 (8.28-10.97) [§]
Creatinine clearance (mJ/s)	1.49 (1.21-2.03) [§]	0.89 (0.57-1.26) [§]

* mean (SD); [§] median (interquartile range); PER=protein excretion rate; DLCO=carbon monoxide diffusion capacity; VA=alveolar volume; FEV1=forced expiratory flow in the first second; FEF50=forced expiratory flow with 50% of the forced vital capacity exhaled; Hb=hemoglobin; HbA_{1c}=hemoglobin A_{1c}

Figure 1. Correlation of DLCO/VA and PER in diabetic patients

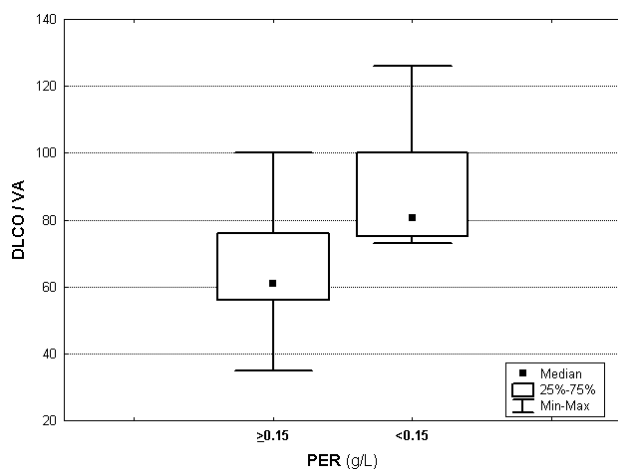


Figure 3. Correlation of FEF50 and PER in diabetic patients

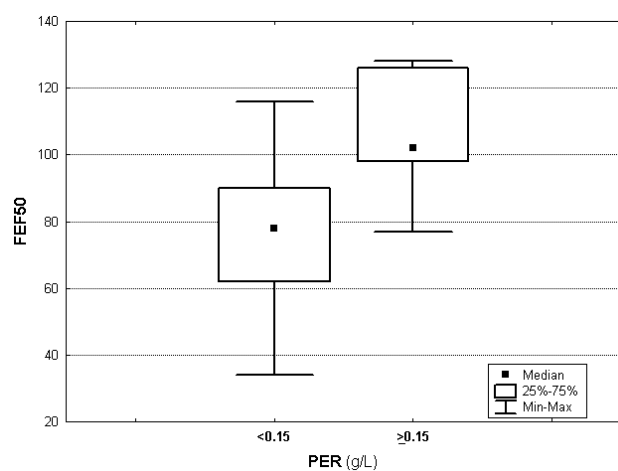


Figure 2. Correlation of FEV1 and PER in diabetic patients

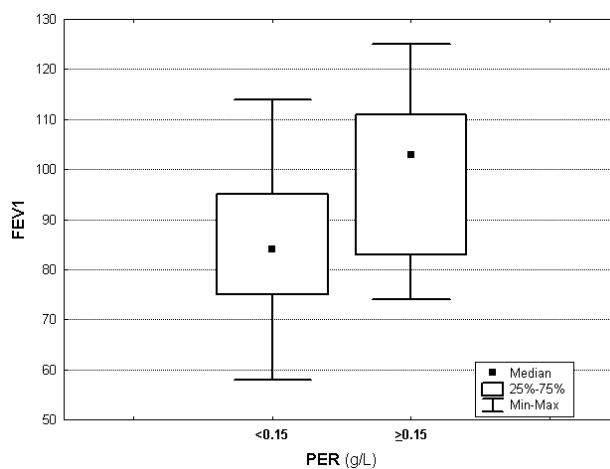
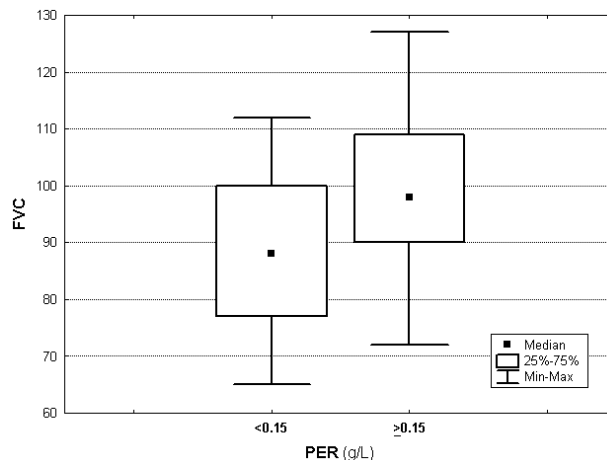


Figure 4. Correlation of FVC and PER in diabetic patients



DISCUSSION

Diabetes mellitus can cause the development of pulmonary complications due to collagen and elastin changes as well as microangiopathy. Connective tissue changes, particularly collagen and elastin changes as well as microangiopathy due to protein nonenzymatic glycosylation induced by chronic hyperglycemia are the main reasons for the development of complications (5,6). The complications in the lungs and kidneys are similar in frequency and severity, which might be due to an identical etiopathogenic mechanism.

Postmortem studies have shown histopathologic changes in the lungs of diabetic patients, specifically connective tissue and small vessel changes (7,8).

Histopathologic evidence of lung involvement has also been described in animal tissues. The observations of morphological and biochemical abnormalities have been reported in the lung of rats with streptozotocin-induced diabetes mellitus (7). A decreased degradation of lung connective tissue might result in an accumulation of connective tissue similar to that occurring in other target organs of patients with diabetes mellitus. If the accumulation of cross-linked collagen occurs in the lung, functional changes resembling mild interstitial fibrosis may follow (7,8). Besides thickened alveolar epithelial and pulmonary capillary basal laminae, ultrastructural changes in pneumocytes have been also found (8-10). The

thickening of the alveolar wall and small vessel wall as an integral structure involved in pulmonary gas exchange may manifest by reduction in the pulmonary diffusing capacity and ventilatory capacity (11).

Thickening of the basal laminae of glomerular capillaries causes impaired selectivity for proteins, specifically, an elevation of the protein excretion rate (7).

Although patients with renal complications suffer from retinopathy more frequently than those without complications, the connection between lung complications and retinopathy is less significant than

that between PER and DLCO. All this confirms the importance of microangiopathic changes as an etiopathogenic mechanism in the development of diabetic complications (5,11).

Proteinuria was the only significant independent predictor of DLCO, FEV1, and FEF50%, showing significant correlation with these parameters as an indicator of the development of lung complications. Our study pointed to the lungs as a target organ for the development of late complications of diabetes mellitus. These findings suggest that both renal and pulmonary complications of diabetes may share a similar microangiopathic background.

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