Diabetes mellitus and Lung Function

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Key Words
Diabetes mellitus · Lung diffusing capacity · Pulmonary volumes

Abstract
Objectives: To assess the nature of pulmonary dysfunction in type 1 diabetes and the relationship of pulmonary function tests to diabetic factors and complication. Subjects and Methods: Sixteen type 1 diabetic patients and 26 control subjects matched for age and sex were studied. We performed spirometry measurements and measured pulmonary diffusing capacity (DLCO) in sitting and supine position by the single-breath method corrected by alveolar volume (VA). Glycosylated hemoglobin (HbA1c), retinopathy and microalbuminuria were included as parameters of metabolic control and diabetic complications. Results: Diabetic patients showed a significant reduction of the following pulmonary function tests (% predicted value) as compared with control subjects: total lung capacity (TLC, 92.6 ± 14.5 vs. 113.9 ± 17.5, p < 0.001), lung diffusing capacity in sitting position (DLCO, 90.4 ± 21.1 vs. 107.7 ± 15.6, p = 0.004), lung diffusing capacity in supine position (DLCO, 88.3 ± 19.3 vs. 111.9 ± 19.9, p = 0.001). The differences in diffusing capacity corrected by alveolar volume in sitting and supine position (DLCO/VA) were not significant. By changing the posture from sitting to supine position both diabetic patients and control subjects significantly increased DLCO/VA (103.4 ± 17.7 vs. 112.7 ± 22.3, p = 0.046 and 99.5 ± 13.4 vs. 114.4 ± 13, p < 0.001, respectively). There was no correlation between pulmonary function tests and diabetic complications. Conclusion: These data indicate that type 1 diabetic patients showed reduced TLC and DLCO, features of pulmonary restrictive dysfunction. There was no correlation between abnormal pulmonary function and the presence of other diabetic complications.

Introduction

Diabetes mellitus is associated with widespread metabolic, hormonal and microvascular abnormalities as well as with disturbances of the function of many organic systems [1]. Abnormalities of pulmonary function have been described in type 1 diabetic patients. The development of these complications could be explained by the biochemical alteration of connective tissue constituents, particularly collagen and elastin, as well as microangiopathy of pulmonary vessels due to a nonenzymatic glycosylation of proteins induced by chronic hyperglycemia [2, 3]. Patients develop obstructive and restrictive disorders and,
as a result of alveolar-capillary membrane thickening due to microangiopathy and collagen and elastin alteration, the capacity for the diffusion of carbon monoxide (DLCO) is reduced [2]. The commonly used single-breath DLCO method [4] might not be sensitive enough to investigate diabetic pulmonary microangiopathy as the low pulmonary vascular pressure determines only minor changes in the pulmonary capillaries of diabetic subjects. A chance to increase the sensitivity and the diagnostic usefulness of DLCO in the assessment of lung vascular damage in type 1 diabetic patients could derive from the measurement of posture-related variations of DLCO. In normal subjects, the increase of DLCO in supine position has been attributed to a recruitment of the upper pulmonary lobe capillaries and to an increase in blood volume [5–8]. Pulmonary microangiopathy could negatively affect these changes in type 1 diabetic patients [8].

The aim of this study was to assess the nature of pulmonary dysfunction in type 1 diabetic patients and the relation of pulmonary dysfunction to diabetic factors and complications (age, duration of diabetes, metabolic control, retinopathy, microalbuminuria).

Materials and Methods

Sixteen type 1 diabetic patients aged 37.3 ± 12.8 years were studied. All patients were insulin-dependent from the time of diagnosis. They were treated with a standard insulin regimen consisting of 2 daily insulin injections. Glycosylated hemoglobin (HbA1c) was measured using the DCA 2000® system device (Bayer, Elkhart, USA). The same system was used to identify the presence of microalbuminuria in a random urine specimen (microalbumin normal range 5–37 mg/l and albumin-to-creatinine ratio normal range <30 mg/g). The presence of retinopathy (as determined by ophthalmoscopy) was graded as follows: 0 = none; 1 = nonproliferative; 2 = preproliferative; 3 = proliferative.

The control group consisted of 26 healthy volunteers aged 44.8 ± 13.1 years. Levels of hemoglobin were evaluated in all subjects. None of the subjects were smokers or had a history of respiratory symptoms or pulmonary diseases or heart failure. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Informed consent was obtained from all of the participants after the purpose of the study was fully explained to each subject. Informed consent was obtained from all of the participants after the purpose of the study was fully explained to each subject. Both diabetic and normal subjects underwent pulmonary function tests with spirometry and measurement of lung volumes (helium dilution method). DLCO was measured by the single-breath method [9]. Four DLCO measurements, two in sitting and two in supine position, were performed in each subject, according to the method used in a previous study [10]. The subjects were asked to assume the appropriate position 5 min before the test with an interval of at least 15 min between each DLCO measurement (the best value as a percentage of predicted values). Alveolar volume (VA) was determined by the single-breath dilution method for each DLCO measurement. Coefficient of diffusion (DLCO/VA) was obtained by dividing the absolute values of each variable by the respective value of VA (the best value as a percentage of predicted values).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control subjects</th>
<th>Diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.8 ± 13.1</td>
<td>37.3 ± 12.8</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/15</td>
<td>9/7</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>14.3 ± 1.3</td>
<td>13.8 ± 1.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.9 ± 3.4</td>
<td>24.5 ± 3.1</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, %</td>
<td>-</td>
<td>9.4 ± 1.8</td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>-</td>
<td>16.6 ± 8.8</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of study groups

<table>
<thead>
<tr>
<th>Test</th>
<th>Control subjects</th>
<th>Diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>105.2 ± 1.4</td>
<td>98.5 ± 13.1</td>
</tr>
<tr>
<td>FVC</td>
<td>96.4 ± 11.6</td>
<td>92.6 ± 12.6</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>92.5 ± 6.3</td>
<td>90.2 ± 9.6</td>
</tr>
<tr>
<td>VC</td>
<td>94.5 ± 12.3</td>
<td>90.3 ± 12.0</td>
</tr>
<tr>
<td>TLC</td>
<td>113.9 ± 17.5</td>
<td>92.6 ± 14.5*</td>
</tr>
<tr>
<td>DLCO sitting position</td>
<td>107.7 ± 15.6</td>
<td>90.4 ± 21.1*</td>
</tr>
<tr>
<td>DLCO supine position</td>
<td>111.9 ± 19.9</td>
<td>88.3 ± 19.3*</td>
</tr>
<tr>
<td>DLCO/VA sitting position</td>
<td>99.5 ± 13.4</td>
<td>103.4 ± 17.7</td>
</tr>
<tr>
<td>DLCO/VA supine position</td>
<td>114.4 ± 13.0</td>
<td>112.7 ± 22.3</td>
</tr>
<tr>
<td>VA, sitting position, liters</td>
<td>6.5 ± 1.5</td>
<td>5.5 ± 1.3**</td>
</tr>
<tr>
<td>VA, supine position, liters</td>
<td>6.1 ± 1.6</td>
<td>4.8 ± 0.9*</td>
</tr>
</tbody>
</table>

Table 2. Lung function data and diffusing capacity in sitting and supine position (% predicted values)

Values are expressed as mean ± SD; *p < 0.01, ** p < 0.05 versus control group. VC = Vital capacity. The differences between means were evaluated by independent samples t test and Mann-Whitney test.

Statistical Analysis

The differences between means were evaluated by paired t test (normal distribution of the data) and Wilcoxon signed rank test for the change of DLCO from sitting to supine position; independent samples t test (normal distribution of the data) and Mann-Whitney test were used for comparison of the values of the pulmonary function tests and DLCO in sitting and supine position. Correlation coefficients were calculated between DLCO/VA, forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), total lung capacity (TLC) and age of the patients, diabetes duration, levels of HbA1c, degree of retinopathy, and albumin-to-creatinine ratio, using Spearman correlation; p < 0.05 was chosen as the value indicating significance (SPSS 8.0 statistical software).
Table 3. Comparison between sitting and supine position in diabetic patients and in control subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects sitting</th>
<th>supine</th>
<th>p value</th>
<th>Diabetic patients sitting</th>
<th>supine</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO, % predicted</td>
<td>107.7±15.7</td>
<td>111.9±19.9</td>
<td>NS</td>
<td>90.4±21.1</td>
<td>88.3±19.3</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO/VA, % predicted</td>
<td>99.5±13.4</td>
<td>114.4±13.0</td>
<td>&lt;0.001</td>
<td>103.4±17.7</td>
<td>112.7±22.3</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD; NS = not significant. The differences between means were evaluated by paired t test and Wilcoxon signed ranks test.

Results

The clinical characteristics of the diabetic and control groups are shown in table 1. Diabetic and control groups did not differ by age, gender, BMI or hemoglobin levels.

Table 2 shows lung function test results in diabetic patients and control subjects. Statistical differences between the two groups were found for TLC (92.6 ± 14.5 vs. 113.9 ± 17.5), DLCO in sitting position (90.4 ± 21.1 vs. 107.7 ± 15.6) and in supine position (88.3 ± 19.3 vs. 111.9 ± 19.9), VA in sitting (5.5 ± 1.3 vs. 6.5 ± 1.5) and VA in supine position (4.8 ± 0.9 vs. 6.1 ± 1.6). The values for the above measurements were significantly higher in the control group (p < 0.05). The differences between the two groups for DLCO/VA in sitting and supine position were not found to be significant. The ratio of FEV1 to FVC was similar in diabetic patients and control subjects.

The posture-related changes of DLCO and DLCO/VA are reported in table 3. Control subjects, as expected, showed a significant increase in supine position for DLCO/VA (99.5 ± 13.4 vs. 114.4 ± 13.0, p < 0.001). Diabetic patients also showed a significant increase in supine position for DLCO/VA (103.4 ± 17.7 vs. 112.7 ± 22.3, p = 0.046), whereas a decrease was found for DLCO (not significant).

In diabetic patients, no significant correlations were found between DLCO/VA, pulmonary volumes, age, duration of diabetes, levels of HbA1c, retinopathy and microalbuminuria.

Discussion

Lung function in diabetic patients has been described in previous clinical studies, the results of which are contradictory. Previous spirometric studies on subjects with diabetes mellitus have been conducted on highly selected patients with type 1 diabetes. Although the majority of the investigators have reported changes in the elastic properties of the lungs and reduced pulmonary diffusing capacity [11–14], FEV1 and FVC have mostly been within normal ranges [11–15]. However, in the study of Asanuma et al. [16] the subjects with type 1 diabetes had slightly but significantly reduced FEV1 and FVC compared to control subjects. In another study, Schnapf et al. [17] were only able to demonstrate a reduction of lung volumes in type 1 diabetic patients when the patients also had limited joint mobility. Consequently, it has been suggested that nonenzymatic glycosylation of connective tissue, especially the collagen, might be responsible for both lung and joint abnormalities [18, 19].

Our results show that the predominant abnormality in type 1 diabetic patients was a reduction in TLC and in DLCO (% predicted) in sitting and supine position. There was not found to be any association between pulmonary dysfunction and diabetic complications or metabolic control. The pattern of abnormal pulmonary function observed in our study, low TLC, DLCO and preserved FEV1/FVC, is suggestive of a restrictive type of lung disease. In addition to lung disease, chest wall disorders, obesity, neuromuscular diseases and pleural diseases can all cause a similar restrictive pattern of pulmonary function. Since these patients were not obese and had no evidence of any pleural, chest wall or neuromuscular problems, we believe that the restrictive changes in pulmonary function present in our study were due to lung tissue derangement. The possibility exists that the reduced TLC could be the result of increased chest wall stiffness, but it seems more likely that the alteration of lung connective tissue at a biochemical level is responsible for the development of abnormal lung mechanics. Histologic evidence of pulmonary abnormalities in streptozotocin-induced diabetes in rats has included alterations in the ultrastructure of granular pneumocytes in the interalveolar septum [20], of nonciliated bronchiolar epithelial (Clara) cells [21] and of colla-
gen and elastin in the alveolar wall [22]. It is possible that some of these ultrastructural abnormalities could be the result of direct toxic effects of streptozotocin although Kida et al. [22] argued that they were the consequence of the lack of insulin. Autopsy findings in diabetic subjects, however, have included thickening of epithelial and capillary basal laminae of alveoli, the latter being suggestive of existing pulmonary microangiopathy [23] and centrilobular emphysema [24]. Evidence of diabetic microangiopathy has also been presented in the capillaries of alveolar septa and in the alveolar and pleural arterioles [13, 25].

Collagen is the major connective tissue of the lung parenchyma and both qualitative and quantitative abnormalities in collagen can cause restrictive pulmonary disease [24]. Increased nonenzymatic glycosylation of various proteins, including collagen, is known to occur in diabetes mellitus [26]. Advanced glycosylation products form on molecules having low physiologic turnover rates [27]. Nonenzymatically glycosylated diabetic collagen is considerably more resistant to digestion by pepsin and collagenase than nondiabetic collagen [28]. Thus, a likely explanation of pulmonary dysfunction in diabetes mellitus is that chronic hyperglycemia causes an increase in the glycosylation of collagen in the lungs and a decrease in its normal turnover, resulting in less compliant pulmonary parenchyma and the observed restrictive changes in pulmonary function. However, against this hypothesis is the finding of Sandler et al. [13] of reduced pulmonary elastic recoil in type 1 diabetic patients that was not associated with accelerated aging of collagen.

Regarding DLCO, previous studies showed that the lower DLCO in diabetics was due to a lower pulmonary capillary blood volume and not due to either diminished membrane diffusing capacity or lower hemoglobin concentration [14]. The lung capillary damage in patients with diabetes was supported by the study of Fusco et al. [8] in which postural variations of DLCO and pulmonary capillary blood volume were measured. In contrast to control subjects, patients with diabetes showed normal pulmonary volumes but did not show significant increases of DLCO and pulmonary capillary blood volume in the supine position. The thickening of the basal lamina and the increase in rigidity of small vessels that characterize diabetic microangiopathy can be accepted as the main reason for this reaction [8]. In our study, we observed reduced pulmonary volumes and DLCO in diabetic patients compared to control subjects. There was no relationship between DLCO and the presence of microangiopathy elsewhere. Although lung volumes and DLCO may be reduced in type 1 diabetic patients the pattern of pulmonary dysfunction is not uniform. This may reflect either the relatively small sample size or, alternatively, the almost random pattern of organ involvement which is a feature of diabetes mellitus.

Since the available data on pulmonary function type 1 diabetes are still conflicting, further studies are needed to confirm the mechanisms of multiple end-organ dysfunction seen in diabetes. Hyperglycemia is an important factor in the initiation and progression of microvascular complications in type 1 diabetes [30, 31] and vigorous control of blood glucose concentration is associated with a lower incidence of systemic complications including nephropathy, retinopathy, neuropathy and probably pulmonary dysfunction.

References