Brief report

Reduced lung diffusion capacity in type 2 diabetes is independent of heart failure

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A B S T R A C T

In a case–control analysis comparing 303 patients with diabetes and 303 without (matched on age, race, sex and height), diabetics had reduced lung diffusion (DLCO) independent of smoking, obesity, clinical heart failure, asymptomatic left ventricular systolic and diastolic dysfunction: DLCO (mean ± SE: 15.5 ± 0.9 vs. 16.4 ±0.9, p = 0.01).

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1. Introduction

Diabetes is a debilitating disease in large part due to its microvascular complications. Since the lungs contain an extensive microvascular circulation, the possibility that DM causes glycosylation of alveolar-capillary proteins leading to microangiopathy has been raised [1]. Experimental studies performed on lung tissue from diabetic rats [2–4], as well as autopsy [5] and transbronchial biopsy studies [6] confirmed this hypothesis, reporting increased thickness of the alveolar-capillary [2–5] and bronchial-capillary [6] basement membranes in adults with DM.

These biological changes may translate into clinical findings. Clinical studies have shown a reduction in diffusion capacity for carbon monoxide (DLCO) in patients with DM independent of other potential risk factors such as smoking and obesity [7,8]. The reduction in DLCO was found to correlate with DM control, duration and presence of other microangiopathic complications [9]. A recently published meta-analysis found a difference of 9.3% predicted in the mean DLCO, between 3182 patients with DM and 27,080 subjects without [10].

Although heart failure (HF) is present in up to 15% of patients with DM [11] and is associated with gas transfer abnormalities [12], none of the prior studies examined HF as potential link between DM and reduced DLCO. In our previous work, we found that DLCO was reduced in patients with DM independent of HF, when HF was defined by ICD9 codes [13]. In addition, impaired ventricular function (either systolic or
diastolic) increases the pulmonary capillary wedge pressure and potentially leads to abnormal DLCO in these patients, even in the absence of HF symptoms [14]. None of the prior studies assessed if gas transfer defect in DM is independent of asymptomatic systolic or diastolic dysfunction. Therefore, the objective of the current study is to assess if DLCO is impaired in patients with DM independent of HF, when HF is assessed using more objective clinical and echocardiographic criteria.

2. Materials and methods

After Institutional Review Board approval, we conducted a retrospective review of medical records of 26,578 adults, aged 18–97 years, who had pulmonary function tests (PFT) performed in our institution. In cases of repeat PFT on the same patient (n = 6696), we included only the most recent test. We excluded patients with type 1 DM, patients with diseases known to cause diffusion abnormalities (n = 9051) (Appendix A), and patients with incomplete smoking history or race/ethnicity data (n = 6667). Among 560 patients with type 2 DM (cases), only 335 had an echocardiogram performed within three months of the time of PFT. Cases were matched to patients without DM (controls), on age, sex, race and height. If several control patients were identified for 1 case, one of them was selected at random. Only 323 matches were available, and among these, 20 had incomplete echocardiograms, bringing the study sample to 303 cases and 303 controls.

We abstracted the following data: DLCO (mL/min/mmHg); demographics (age, sex, self-reported race/ethnicity, height and weight); self-reported smoking history; history of diseases known to cause diffusion abnormalities (Appendix A); history of type 2 DM at the time of PFT; history of HF; echocardiographic evidence of systolic [ejection fraction (EF) of less or equal to 40%] or diastolic dysfunction [grade 2 or 3 diastolic dysfunction along with an EF of more than 40%]. The history of a disease was determined using the ICD9 codes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). We defined the HF status based on a combination of history of HF and echocardiographic evidence of systolic or diastolic dysfunction: no HF (no history of HF and no evidence of systolic or diastolic dysfunction); systolic HF (history of HF and systolic dysfunction); diastolic HF (history of HF and diastolic dysfunction); asymptomatic left ventricular (LV) systolic dysfunction (no history of HF, but echocardiographic evidence of systolic dysfunction), and asymptomatic LV diastolic dysfunction (no history of HF, but echocardiographic evidence of diastolic dysfunction).

Baseline characteristics of the cases and controls were compared using t-tests or chi-square tests. The difference in DLCO between cases and controls was first examined using unadjusted raw values (by t-tests), then using multiple regression models with generalized estimating equation (GEE) methodology, adjusting for smoking status (never/former/current), BMI and HF status (no HF, systolic HF, diastolic HF, asymptomatic LV systolic dysfunction, asymptomatic LV diastolic dysfunction). Statistical significance was determined at p < 0.05. All analyses were performed using SAS statistical analysis software (SAS/STAT software, Version 9.2 of the SAS System for Windows OS (Cary, NC, USA).

3. Results

Patients with DM had higher BMI (mean ± SD: 31.4 ± 8.7 vs. 27.8 ± 6.3 kg/m²), were more likely to have ever smoked (39.3% vs. 34.2%), more likely to have systolic (28.4% vs. 9.6%) or diastolic HF (6.6% vs. 3.9%), compared to those without DM (Table 1). The unadjusted mean value of DLCO was significantly lower in patients with DM compared to those without DM (Table 1). This difference attenuated, but remained significant after adjustment for covariates (mean ± SE: 15.5 ± 0.9 vs. 16.4 ± 0.9 mL/min/mmHg, p = 0.01).

4. Discussion

In a diverse urban patient population we found that DLCO is reduced in patients with DM compared to those without DM, independent of HF, when HF is comprehensively defined using a combination of clinical and echocardiographic criteria. In a prior study we found that DLCO reduction in DM was independent of clinical HF when clinical HF was assessed based on ICD9 codes. This study confirms our prior findings, when clinical HF is defined more accurate, based on both ICD9 codes and echocardiographic findings [13]. In addition, it shows that the reduction in DLCO in patients with DM is also independent of asymptomatic LV systolic or diastolic dysfunction (which can cause pulmonary congestion, and therefore reduced DLCO). Overall, our findings contribute to better define the association between DM and gas transfer defect.

The diffusion abnormalities in patients with DM can have clinical implications [15]. For instance, in a previous study we found that reduced DLCO in patients with DM predicted hospitalization for pneumonia, independent of blood glucose control and comorbidities [16]. If future prospective studies will demonstrate that the measurement of DLCO can provide

Table 1 - Baseline characteristics of diabetic and non-diabetic patients included in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DM</th>
<th>Non-DM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>61.7</td>
<td>61.8</td>
<td></td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>58.7</td>
<td>58.7</td>
<td></td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>68.6</td>
<td>68.6</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>22.1</td>
<td>22.1</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.6</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1.6</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Height, mean (SD)</td>
<td>67.5</td>
<td>67.4</td>
<td>0.94</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>31.4</td>
<td>27.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>60.7</td>
<td>65.7</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>9.9</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>29.4</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>28.4</td>
<td>9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>6.6</td>
<td>3.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Asymptomatic systolic dysfunction</td>
<td>0.9</td>
<td>1.3</td>
<td>0.80</td>
</tr>
<tr>
<td>Asymptomatic diastolic dysfunction</td>
<td>1.6</td>
<td>7.3</td>
<td>0.001</td>
</tr>
<tr>
<td>DLCO, mL/min/mmHg, mean (SD)</td>
<td>15.72</td>
<td>17.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
useful clinical information, then screening patients with DM for alveolar microangioopathy should be considered.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Excluded diseases known to cause diffusion abnormalities

Bronchitis
Emphysema
Asthma
Chronic obstructive pulmonary disease (COPD)
Cystic Fibrosis
Pneumonia (within 3 months of PFT)
Alpha-1-antitrypsin deficiency
Sarcoidosis
Myoneural disorders (e.g. myasthenia gravis)
Polyarteritis nodosa
Goodpasture’s syndrome
Wegener’s granulomatosis
Bronchiectasis
Pneumoconioses and other lung diseases due to external agents
Interstitial fibrosis
Postinflammatory pulmonary fibrosis
Idiopathic fibrosing alveolitis/Hamman–Rich syndrome
Pulmonary eosinophilia
Scleroderma
Systemic lupus
Systemic Sclerosis
Rheumatoid arthritis
Kyphosis/Scoliosis
Bronchiectasis

REFERENCES


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