Pulmonary functions in patients with type 2 diabetes mellitus & correlation with anthropometry & microvascular complications

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Background & objectives: The purpose of this study was to evaluate pulmonary functions including respiratory muscle strength in patients with type 2 diabetes mellitus (T2DM) and to determine their correlations with anthropometric profile, glycaemic control, and microangiopathic diabetic complications.

Methods: Twenty nine patients with T2DM and 11 healthy control subjects were divided into the following three groups: (i) T2DM patients with any or a combination of microangiopathy(ies) (retinopathy, nephropathy, and peripheral neuropathy) (group 1, n=12); (ii) T2DM patients without any complications (group 2, n = 17); and (iii) a healthy control group (group 3, n=11). All patients were assessed with anthropometry, glycosylated haemoglobin (HbA1c), and lipid profile. Pulmonary functions were measured by spirometry. Pulmonary diffusion capacity for carbon monoxide (DLco) was measured by the steady state method. The presence of diabetic nephropathy was determined by 24 h protein excretion.

Results: A significant reduction of DLco was observed in group 1 (P<0.001), as compared to the other groups. There were no differences among the three groups for other pulmonary functions; forced vital capacity, forced expired volume in one second, peak expiratory flow rate, and maximal static inspiratory and expiratory pressures. Significant correlations were observed between DLco and the following parameters in group 1; HbA1c (r=0.62, P<0.05), total cholesterol level (r = -0.44, P<0.05) and creatinine clearance (r=0.42, P<0.05).

Interpretation & conclusion: The present study shows that the impairment of pulmonary diffusion capacity for carbon monoxide was common in T2DM Asian Indian patients having microangiopathy. Pathophysiologically, it could be related to glycaemic control or dyslipidaemia. Correlation of % BF with DLCo needs to be explored further.

Key words Asian Indians - diabetic microangiopathy - pulmonary diffusion capacity - pulmonary functions - type 2 diabetes mellitus

There is an alarming increase in the incidence and prevalence of diabetes mellitus particularly in Asian Indians. The major morbidities in type 2 diabetes mellitus (T2DM) are due to its microangiopathic and macroangiopathic complications, which affect eyes, kidneys, nerves, heart, and major vessels. In type 1 diabetes, mellitus, lung function has been investigated in several clinical studies. A study by Marvisi et al on pulmonary functions in patients with T2DM, suggested possible associations between pulmonary function abnormalities and diabetic renal microangiopathy, retinopathy and diabetic control. Isotani et al showed independent changes in pulmonary diffusing capacity for carbon monoxide (DLco) as a manifestation of pulmonary microangiopathy. Theoretically, several pathological changes may affect the lungs in patients with T2DM.
Collagen and elastin changes, which may occur due to small vessel involvement, can lead to significant structural changes. Ljubic et al \(^6\) showed that diabetes could lead to the development of pulmonary complications due to collagen and elastin changes, as well as microangiopathy. Increased non-enzymatic glycation of proteins and peptides of the extracellular matrix at chronic high circulating glucose levels may also have an important role in the pathological changes of the lungs in T2DM patients\(^7\). These studies suggested a relationship between pulmonary complications and other chronic complications in diabetes.

Since the prevalence of diabetes in Asian Indians is among the highest in the world\(^1\), it would be important to study pulmonary functions in this subgroup. Further it is not clear whether pulmonary functions in diabetic patients correlate with anthropometric profile and glycaemic control. The present study was therefore undertaken to investigate pulmonary functions and respiratory muscle strength in patients with T2DM and to look for their correlation with anthropometric profile, glycaemic control and microangiopathic complications.

**Material & Methods**

The patients with T2DM were selected from the outpatient department (OPD) of the Department of Medicine, All India Institute of Medical Sciences, New Delhi during November 2001 to December 2002. Twenty-nine patients (21 males, 8 females) with T2DM and 11 healthy subjects (9 males, 2 females) were divided into three groups; (i) T2DM subjects with retinopathy and/or diabetic nephropathy and/or neuropathy (group 1, n=12); (ii) T2DM patients without any complications (group 2, n=17); and (iii) a control group of healthy non-diabetic subject (group 3, n=11). Informed written consent was taken from all subjects. The respiratory, cardiac and neuromuscular systems were clinically normal as examined by a specialist. All patients had BMI < 30 kg/m\(^2\). Patients having any acute or chronic pulmonary disease, and smokers (defined as smoking of any number of cigarettes or bidis) were excluded.

**Biochemical investigations:** Blood samples were obtained after 12 h overnight fast for the estimation of levels of blood glucose, total cholesterol (TC), serum triglycerides (TG), and high-density lipoprotein cholesterol (HDLC). An oral glucose tolerance test was performed according to the World Health Organization criteria\(^8\). Glycosylated haemoglobin (HbA\(_1c\)) was measured as an indicator of glycaemic control using thiobarbituric acid colorimetry method\(^9\). Levels of TC, TG and HDLC were measured using ELISA kits (Randox Laboratory, San CA, USA) by a semi-automated analyzer (Micro Semi Autoanlyser 2000, C.L. Micromed, Italy). Value of low-density lipoprotein cholesterol (LDLC) was calculated using Friedewald’s formula\(^10\).

**Anthropometric measurements:** Height and weight of all subjects were recorded and BMI was calculated. Waist circumference (WC) and hip circumference (HC) were measured. Mean of three readings of each measurement was taken for the calculation of waist-hip ratio (W-HR). Skinfolds (SF) at four sites (biceps, triceps, subscapular and suprailiac) were measured using Lange skinfolds calipers (Beta Technology Inc, Santa Cruz, CA, USA). Mean of three readings was calculated at each site of measurement. All four skinfolds were added together to obtain sum of four skinfolds (Σ 4SF). Equation of Durnin and Womersley\(^11\) validated for Asian Indians\(^12\) was used for calculation of per cent body fat (BF) from Σ 4SF\(^13\).

**Definitions and cut-offs:** Diabetes mellitus was diagnosed according to the World Health Organization criteria\(^8\). Excess of body fat was defined when >25 per cent in males and >30 per cent in females\(^14\). Normal lipid levels were defined according to the criteria of National Cholesterol Educational Program, Adult Treatment Panel III\(^15\).

**Pulmonary function test and lung diffusing capacity (DLco):** Chest skiagram was done to exclude the presence of structurally obvious pulmonary disease. Pulmonary functions including forced vital capacity (FVC), forced expired volume in one second (FEV\(_1\)) and peak expiratory flow rate (PEFR) were measured by spirometer (Morgan PK, UK) according to the American Thoracic Society criteria\(^16\). The variables were reported in absolute volume as well as the per cent-predicted based on the regression equations. DLco was measured by the steady state method\(^17\). Maximal static inspiratory (MIP) and expiratory pressure (MEP) were
measured in the sitting position. The MIP was measured near residual volume and MEP was measured near total lung capacity. Best of three satisfactory readings was taken for analysis. This technique has been validated in our laboratory and the prediction equations for normal north Indian subjects have been derived and reported previously\textsuperscript{18,19}.

Evaluations for the complications of T2DM: Diabetic retinopathy: An experienced ophthalmologist performed the direct ophthalmoscopic examination on the patients. Retinopathy was defined as mild to moderate non-proliferative, severe non-proliferative and clinically significant macular edema.

Diabetic nephropathy: Excretion of >300 mg of albumin in urine over 24 h was defined as the presence of overt diabetic nephropathy after excluding urinary tract infection and other causes of renal disease. Creatinine clearance was calculated using the following formula: 
\[
\text{\frac{\text{140-age (yr)} \times \text{weight (kg)}}{72}} \times \text{serum creatinine} \]
\textsuperscript{20}.

Diabetic peripheral neuropathy: Peripheral neuropathy was evaluated clinically and was defined as ≥ 2 missing deep tendon reflexes in legs, diminished distal touch (assessed by cotton wool), pinprick or pressure sensation, distal vibratory sensation (assessed by graduated tuning fork of 128 Hz) and joint position sense. Other potential causes of peripheral neuropathy were excluded before attributing the peripheral neuropathy to diabetes.

Macroangiopathy: Histories of previous myocardial infarction or typical angina chest pain along with significant electrocardiographic (ECG) changes were taken as indicative of presence of coronary heart disease (CHD). Cardiac evaluation was completed by clinical examination, electrocardiogram and echocardiograph. Any history of previous stroke or history suggestive of transient ischaemic attack (blindness, dysarthria, or unilateral motor or sensory phenomenon) was taken as evidence of cerebral vascular disease. Peripheral vascular disease was defined as history of intermittent claudication or non-healing foot ulcers and/or absence of ≥ 2 foot pulses.

Statistical analysis: After confirming the approximate normality of data, descriptive statistics for anthropometric, biochemical and lung function parameters were computed by arithmetic mean and standard deviation. One-way analysis of variance (ANOVA) was used to compare mean values in the three groups. In case of overall statistical significance in ANOVA, Scheffe’s post-hoc test was used to compare pairwise means. Pearson correlation coefficient was used to quantify the extent of relationship between DLco and other quantitative variables. STATA 7.0 intercooled version software (STATA Corp., Houston, Texas, USA) was used for statistical analysis. All the statistical tests used for analysis were two-tailed. \(P<0.05\) was considered as statistically significant.

Results

The data on 40 (30 males, 10 females) subjects were analysed. The mean age was 44.4±16.4 yr in healthy controls and 46.7±12.0 yr in patients with T2DM. The mean duration of diabetes was 4.4±6.1 yr (range 0-10 yr). One patient had CHD. None of the patients had cerebral vascular diseases or peripheral vascular disease. Nine patients (23.1%) were hypertensives.

Anthropometric profile and body fat analysis: The duration of diabetes (10.2±7.3 yr, \(P<0.05\)) was significantly higher in group 1, compared to group 2. The mean value of BMI of group 1 (25.2±2.9 kg/m\(^2\)) was significantly higher (\(P<0.05\)) than group 3 (21.9±2.5 kg/m\(^2\)). The mean values of WC (94.1±8.8 cm, \(P<0.01\)) and HC (96.9±10.8 cm, \(P<0.01\)) were significantly higher in group 1 as compared to the group 3. There were no significant differences in the mean values of individual skinfolds and \(\Sigma\)4SF among the three groups (Table I).

Biochemical profile: The mean levels of fasting blood glucose (197.9±83.5 mg/dl, \(P<0.001\)), post-prandial blood glucose (275.5±97.4 mg/dl, \(P<0.001\)), blood urea (33.4±17.1 mg/dl, \(P<0.01\)) and HbA\(_1c\) (8.7±1.1%, \(P<0.001\)) were significantly higher in group 1 as compared to the other two groups. Mean serum levels of TG, TC, LDL-C and HDL-C were statistically comparable among the groups (Table II).

Diabetic microangiopathies: Eight patients had peripheral neuropathy, 4 had nephropathy, and 7 patients had any grade of retinopathy in group 1.
Pulmonary functions: The mean value of DLco was significantly lower in group 1 (15.8±3.1 cc/min/mmHg, P<0.001) as compared to the other groups. Mean values of FVC, FEV₁, PEFR, MIP and MEP were statistically comparable among the groups (Table III).

In group 1 patients, significant correlations were observed between DLco and HbA1c (r=0.62, P<0.05), total cholesterol level (r=-0.44, P<0.05) and creatinine clearance (r=0.42, P<0.05). Significant negative correlation was also observed between DLco and percent body fat (r=-0.75, P<0.05) in group 2 patients.
The significant observation in the present study was impairment of DLco in T2DM patients with microangiopathy(ies). Marvisi et al. also observed a significant reduction in DLco in patients with diabetic microangiopathy. Ljubic et al. suggested a relationship between diabetic complications, particularly microangiopathy with collagen and elastin changes in lungs. In another study, on a larger number of patients with T2DM (n=80) a reduction of DLco in patients with diabetic microangiopathy was observed. DLco was reported to be significantly lower in patients with proliferative retinopathy vs patients with background retinopathy. Similar to the present study, Isotani et al. carefully excluded patients with other risk factors, which could affect pulmonary flow volume curves. Absence of correlation between pulmonary function tests and the presence of microangiopathy or glycaemic control has also been reported. No significant respiratory muscle weakness was observed in patients with microangiopathy in the present study. Respiratory muscle weakness has been observed in patients with type 1 diabetes mellitus. A significant correlation between reduction of DLco and the grade of albuminuria demonstrated a relationship of diffusion capacity derangement with other diabetic microangiopathic complications as well. The findings of the present study showed a close correlation of microangiopathies and decrease in DLco. No other correlation was seen in lung functions, suggesting changes in the intestine of the lung as a part of diabetic microangiopathies.

The possible pathophysiological mechanism(s) remains speculative and requires further studies. Since pulmonary bed has an extensive capillary bed, it is reasonable to expect that it could be affected in diabetes. To support, thickened alveolar epithelial and pulmonary capillary basal laminae have been observed in patients with T2DM on postmortem examination. A simple explanation could be deterioration of pulmonary gas exchange due to thickening of alveolar and small vessel walls. It is also reasonable to expect that a decrease in DLco may occur with the increasing duration of diabetes, when prevalence of microangiopathic complications also increases. Whether subtle neuromuscular respiratory muscle involvement due to diabetic neuropathy of the thoracic nerves additionally contributes to the respiratory dysfunction remains to be ascertained.

The limitation of the present study was small number of subjects in each group. Further, the negative correlation between per cent BF and decrease in DLco observed in patients of group 2 could not be explained. A possible link could be the presence of insulin resistance and dyslipidaemia in the patients with excess BF, which might cause endothelial dysfunction and thus decrease blood flow due to effect on small arteries supplying alveoli and pulmonary septae. This preliminary observation remains to be studied in future.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=12)</th>
<th>Group 2 (n=17)</th>
<th>Group 3 (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>80.4±10.7</td>
<td>80.7±15.8</td>
<td>94.1±16.1</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>81.0±9.4</td>
<td>80.1±16.2</td>
<td>83.5±14.0</td>
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<td>PEFR (% predicted)</td>
<td>83.3±18.2</td>
<td>84.1±25.3</td>
<td>69.1±19.6</td>
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<tr>
<td>DLco (cc/min/mmHg)</td>
<td>15.8±3.1*</td>
<td>17.5±2.1</td>
<td>20.1±1.5</td>
</tr>
<tr>
<td>MIP (mmHg)</td>
<td>85.6±21.7</td>
<td>104.7±28.5</td>
<td>93.7±2.0</td>
</tr>
<tr>
<td>MEP (mmHg)</td>
<td>96.5±34.1</td>
<td>104.6±28.6</td>
<td>93.0±25.8</td>
</tr>
</tbody>
</table>

Values are mean ±SD
FVC, lung forced vital capacity; FEV1, forced expired volume in one second; PEFR, peak expiratory flow rate; DLco, lung diffusion capacity for carbon monoxide; MIP and MEP, maximal static inspiratory and expiratory pressures
*P<0.001 compared to groups 2 and 3
studies, particularly in view of high prevalence of metabolic syndrome in Asian Indians.

In conclusion, the present study showed impairment of DLco in patients with T2DM with microangiopathies. The present observations further suggested that hyperglycaemia and dyslipidaemia might have a contributory role in its pathogenesis.

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References


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