Original Article

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Lung: Another Victim of the Silent killer Diabetes- A Cross-sectional Study

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ABSTRACT

Introduction: Diabetes is a multisystem disorder with well known complications involving various organs in the body. The presence of abundant connective tissue and microvasculature raises the possibility that lung may also be affected in diabetes.

Aim: To evaluate the pulmonary function parameters in patients with diabetes mellitus and to determine their correlation with glycaemic control, duration of diabetes and other microvascular complications.

Materials and Methods: This is a cross-sectional study done between September 2018 and March 2019. A total of 300 type 2 diabetic patients, aged 30-70 years, with duration of diabetes more than 1 year, were included in the study. Thorough history was taken regarding the duration of diabetes and symptoms of the complications. All of them were evaluated for diabetic microangiopathies: nephropathy (by 24 hour urinary protein excretion), retinopathy (by direct ophthalmoscopy) and neuropathy (by clinical examination). Glycosylated Haemoglobin (HbA1c) was measured as an indicator of glycaemic control. Spirometry and single breath diffusion capacity for carbon monoxide were performed on all the subjects. Pulmonary Function Test (PFT) parameters of each subject were compared with the normal values. Unpaired t-test and one-way analysis of variance (ANOVA) were used. Correlation and regression studies were used to find out the strength of association between Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) and the following: the duration of disease, HbA1c and presence of other microvascular complications.

Results: Pulmonary function parameters like Forced Expiratory Volume in first second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Forced Rate (PEFR) and DLCO were below the normal values in 53% of diabetic patients included in the study. Majority of them had a restrictive ventilation pattern. The diffusion capacity corrected for Alveolar Volume (VA) as measured by DLCO/VA was significantly reduced in those with longer duration of diabetes and in those with other microvascular complications. However, the poor lung functions had no correlation with the HbA1C values.

Conclusion: This study demonstrated that lungs are indeed affected in patients with type 2 diabetes. The presence of extrapulmonary microangiopathy and duration of the disease may predict the incidence and the severity of the lung function abnormality.

Keywords: Diffusion capacity, Microvascular complications, Spirometry

INTRODUCTION

Diabetes Mellitus (DM) is a significant public health problem worldwide [1]. It is an endocrine disorder characterised by persistent hyperglycaemia, abnormal metabolism of carbohydrates, proteins and lipids resulting from absolute or relative insulin deficiency. This metabolic disorder precipitates a number of microvascular pathologies like nephropathy, neuropathy and retinopathy as well as macrovascular pathologies like coronary artery disease, cerebrovascular accident and peripheral vascular disease. These complications may be related to chemical alterations in collagen, elastin and other connective tissue constituents. It is also due to microangiopathy caused by non-enzymatic glycosylation of proteins induced by chronic hypoglycaemia [2].

Given the impact of diabetes on the retinal and glomerular microvasculature, it is reasonable to expect that diabetes would also involve the lung. The alveolar-capillary network in the lung is a large microvascular unit and may be affected by microangiopathy [3]. It is usually under-diagnosed because of its large reserve due to which even a substantial loss of microvascular bed may be well tolerated without dyspnoea [4].

Due to an alarming increase in the incidence and prevalence of diabetes particularly in the world, it would be important to study pulmonary functions in diabetic patients. Many authors have documented restrictive, obstructive or mixed ventilatory abnormalities in patients with diabetes. However, the findings are not consistent and studies involved a relatively small number of diabetic patients considering the burden of the disease [5-8].

Several mechanisms have been postulated in the pathogenesis of diabetic lung. These are microangiopathy of the alveolar capillaries and pulmonary arterioles, chronic low grade inflammation, autonomic neuropathy involving the respiratory muscles, loss of elastic recoil secondary to collagen glycosylation of lung parenchyma and hypoxia-induced resistance [2,4,6]. However, the exact pathophysiological mechanism and magnitude of the association between the reduced lung function and diabetes is not well established.

This study was thus conducted to determine the pattern of pulmonary function abnormalities among the patients with diabetes mellitus and its correlation with the incidence of other microangiopathic complications, duration of the disease and glycaemic control.

MATERIALS AND METHODS

This cross-sectional study was carried out at Kempegowda Institute of Medical Sciences, Bangalore from September 2018 to March 2019. Written informed consent taken from all the subjects and institutional ethical committee approved the study (Letter number-82591938027, dated 16-9-2018).

Total 300 patients with type 2 diabetes mellitus, both inpatients and outpatients, aged 30-70 years, duration of diabetes more than 1 year, were **included** in the study. Patients with history of smoking, significant exposure to dust, with history of chest or abdominal surgeries, age more than 80 years, body mass index more than 30 kg/m^2, known case of asthma, chronic obstructive pulmonary disease and heart disease were **not included**. Patients with evidence of any acute or chronic lung diseases as determined by examination and chest radiograph were **excluded** from the study.

Interviewer administered questionnaire was used to obtain detail history including duration of diabetes and relevant clinical examination concentrating on complications of diabetes. A fasting blood sample was drawn for the HbA1c levels.

After demonstrating the technique for carrying out PFT, the subjects were made to perform thrice in front of trained personnel in a sitting position. Best of the three readings were taken. DLCO, pulmonary function parameters such as FVC, FEV1 and PEFR were measured for all the participants using a single breath Carbon Monoxide (CO) diffusion test and computerised spirometer. The pulmonary function parameters were then compared to the normal values and interpreted as either of the following- obstructive, restrictive or mixed ventilatory pattern. When FEV1 and FEV1/FVC ratio and PEFR were markedly reduced, it was categorised as obstructive pattern. When FVC was markedly decreased, FEV1 was normal/slightly decreased and FEV1/FVC ratio and PEFR were normal/increased, it was known as restrictive pattern. Mixed pattern refers to decreased FEV1, decreased FEV1/FVC ratio, decreased FVC along with decreased PEFR [9].

The presence of diabetic nephropathy was determined by initially testing for albuminuria in urine. Those with positive results were further confirmed by measuring 24 hour protein excretion rate by semi-automated analyser. An albumin excretion rate between 30-300 mg per day was considered as indicative of microalbuminuria. Fundus examination was done using direct ophthalmoscope and the diabetic retinopathy was graded according to the disease severity scale as recommended by the American academy of ophthalmology. The presence of diabetic neuropathy was diagnosed based on clinical examination of sensory, motor and autonomic nervous system.

STATISTICAL ANALYSIS

All the data were collected and tabulated in Microsoft Excel. Statistical Analysis was done with SPSS version 15.0 software. Approximate normality of data was confirmed and descriptive analysis of arithmetic means of lung function test values was evaluated. Continuous variable data was used. Pearson correlation was used. Correlation and regression studies were used to examine the strength of association between glycaemic status, duration of diabetes and presence of microvascular complications with DLCO/VA. All the statistical tests used for analysis were two tailed. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 300 diabetic patients were included in the study. Among them 167 were males and 133 were females. The age range of the subjects was 30 to 70 years, with a mean 53.24±6.31 years. The mean duration of diabetes was 13.54±5.47 years [Table/Fig-1].

Variable	Mean±standard deviation
Age (years)	53.24±6.31
Body mass index (kg/m^2)	25.8±1.9
Duration of diabetes (years)	13.54±5.4
Fasting blood glucose (mg/dL)	131±18
Post prandial blood sugar (mg/dL)	243±17
Glycosylated Haemoglobin (%)	9.8±2.1
Number of patients with atleast one of the microvascular complications	118
Number of patients with neuropathy	32
Number of patients with retinopathy	79
Number of patients with nephropathy	64

[Table/Fig-1]: Baseline characteristics of patients included in the study.

Out of 300 diabetics included in the study, 159 (53%) patients had a significant abnormality in their PFT. FEV1, FVC, PEFR and DLCO were reduced in these patients when compared to normal values adjusted to their age. The ventilatory dysfunction was predominantly restrictive as shown by preserved FEV1/FVC% and reduced DLCO [Table/Fig-2].

Pattern of abnormality	n (%)
Restrictive pattern	77 (26)
Obstructive	26 (8)
Mixed	56 (19)
Total abnormal tests	159 (53)

[Table/Fig-2]: Patterns of abnormality in Pulmonary Function Test (PFT) among diabetics (n=300).

Among 300 patients included in the study, 122 had diabetes for longer than 10 years and the rest with duration less than 10 years. On correlating DLCO/VA with the duration of diabetes in the patients, there was a significant difference in the values in those who had a longer duration of diabetes when compared with those who have shorter duration of the disease (Spearman, s r=-0.805, p=<0.05). However, no such association was found between DLCO/VA and HbA1c [Table/Fig-3].

	r-value	p-value
DLCO/VA and duration of diabetes	-0.805	<0.05*
DLCO/VA and glycosylated haemoglobin	-0.287	0.8**
DLCO/VA and presence of microvascular complications	-0.993	<0.001*

[Table/Fig-3]: Correlation of DLCO with duration of diabetes, HbA1c and presence of other microvascular complications.
*=significant, **=not significant
DLCO/VA=DLCO corrected for alveolar volume (VA)
Above results are according to correlation studies and regression analysis between DLCO/VA and various parameters

Out of 300 subjects included in the study, 118 patients had either of the three microvascular complication (nephropathy, retinopathy or neuropathy). This study showed these patients had statistically significant lower values of DLCO/VA compared to those who do not have the above mentioned complications [Table/Fig-3].

DISCUSSION

Diabetes is a disease with profound multi-organ damage and several studies locally and internationally had attempted to evaluate relationship between diabetes and lung functions.

This study showed that the pulmonary function parameters were significantly lower than predicted, in diabetic patients. These findings are comparable to many other studies done before [1,2,5,6]. Most of the patients in this study showed restrictive type of ventilatory pattern similar to the pattern widely reported in literature [2]. One study showed mixed obstructive-restrictive pattern of dysfunction [5] while few others published that there is no significant difference in PFT parameters in diabetics as compared to controls [7,8].

This study also showed that the reduction in lung function is more pronounced in patients with other microvascular complications. The study by Kaminsky DA speculates that abnormal lung function may precede the diagnosis of diabetes, suggesting that lung may contribute to or at least be commonly affected by factors involved in the pathogenesis of diabetes [10]. Sinha S et al., also observed a significant change in lung function in diabetic patients with microangiopathy [7]. Marvisi M et al., found a significant reduction in DLCO in diabetic patients with microangiopathy [11].

Persistent hyperglycaemia causes non-enzymatic glycosylation of proteins in the lungs and chest wall which makes the collagen resistant to proteolysis. This leads to its accumulation in connective tissue of the lung [8-11]. This proposition is further strengthened by the post mortem studies which showed thickening of both alveolar epithelial and pulmonary basal laminae in patients with diabetes [3,12-16].

The advanced glycation products are formed by both enzymatic as well as direct processes in the periphery leading to vascular endothelial dysfunction and changes in the elasticity and properties of ground substances leading to inability of the vascular smooth muscle to dilate adequately. In normal endothelial cells, active vasodilator substances are formed which lead to dilation of the micro and macrovasculature. In diabetics due to dysfunction of the endothelial cells, such vasodilation does not occur [5]. Hyperglycaemia induced oxidative stress, elevated levels of free fatty acids; chronic low grade inflammation may also cause some damage to the endothelium of the alveoli and may ultimately lead to predominantly restrictive with or without obstructive changes in the lung. Autonomic neuropathy related to respiratory muscles and insulin resistance syndrome may also play a role in causing a restrictive pathology [11,17].

In this study, similar to several others [12,14,16], longer duration of diabetes was associated with lower DLCO. Longer the duration of diabetes, longer is the exposure of the lung to inflammatory processes and end glycation products which is the main physiology of diabetic consequences.

According to this study glycaemic control as determined by HbA1c was not noted to be associated with the PFT parameters. This is understandable as it only evaluates the glycaemic control over preceding 2-3 months which may not be long enough to make a reasonable impact on the lung function. However, strict glycaemic control from the beginning along with reduction of metabolic syndrome may be helpful in preventing the progression of pulmonary abnormalities.

This study implies that frequent PFT should be done to detect the early restrictive changes, especially with a longer duration of diabetes and in those with other microvascular complications. Pre-anaesthetic check up of patients with type 2 diabetes may also include PFT to determine the baseline pulmonary function for better monitoring during surgeries.

Limitation(s)

This study was performed at a tertiary level hospital with a specific socio-demographic profile. So, the results may not be generalisable. Furthermore, there was no blinding of the clinician or the patients, which would introduce bias in the observations. Hence, a larger double blinded randomised control studies are warranted in future to confirm the findings.

CONCLUSION(S)

The complications related to diabetes pose a significant healthcare burden and disrupt the overall quality of life. Hence, it needs to be diagnosed and treated at an early stage. Microangiopathy which occurs during the course of diabetes not only affects eyes, kidney and nervous system but also affects the alveolar basement membrane which results in restrictive disease more than obstructive pattern in the lung. This detrimental effect caused by hyperglycaemia is more pronounced in patients with other microvascular complications and those with longer duration of the disease.

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