Pulmonary Function Test by Spirometry in Patients with Diabetes Mellitus and Correlation with Disease Duration and Hba1c Level: A Case Control Study

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ABSTRACT

Introduction: Diabetes mellitus is a multisystem disorder with different microvascular and macrovascular complications. The presence of extensive microvascular circulation and abundant connective tissue in the lungs raises the possibility that lung may be a "target organ" in diabetes patients. Study objective was to study pulmonary function by spirometry in patients with diabetes mellitus and compare with non-diabetic healthy controls and to study association of pulmonary function in diabetes patients to disease duration and Hba1c level.

Material and methods: The study was a hospital based case control study conducted from July 2018 to June 2019. 45 diabetes patients diagnosed for more than 5 years and 45 controls of similar age group, sex and with similar exclusion criteria as the study group were included in the study. Spirometry was performed for all the cases and controls.

Results: Cases had low FVC (2.98 ± 0.59 vs 3.23 ± 0.57), FEV1 (2.45 ± 0.49 vs 2.70 ±0.50), FEV1/FVC (0.82 ± 0.02 vs 0.84 ± 0.02) and PEF (7.31 ± 1.34 vs 7.90 ± 1.64) compared to controls and the difference was statistically significant. Negative correlation was found between spirometry with Hba1c level and disease duration but the correlation was weak and not significant.

Conclusion: Our study showed that there is significant pulmonary function impairment in diabetes patients as compared to controls. More than fifty percent of patients had restrictive pattern of pulmonary dysfunction. However, no significant association was found between the pulmonary dysfunction with Hba1c level and duration of diabetes in our study.

Keywords: Diabetes Mellitus, Spirometry, Hba1c, Disease Duration

INTRODUCTION

Diabetes mellitus is a metabolic disorder with heterogeneous etiologies characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] It is accompanied by wide spread biochemical, morphological and functional abnormalities which may precipitate complications that affect the renal, cardio-vascular, nervous systems and also skin, liver, collagen and elastic fibres. Thus diabetes mellitus is a multisystem disorder that affects many organs of the body.[2]

Unlike other organs like eyes and kidney, lung has not been considered as a seat of target organ damage and hence management protocols do not include pulmonary function test as a routine screening procedure in diabetic patients. There is extensive micro vascular circulation and abundant connective tissue in the lungs which raises the possibility that lung tissue may be affected by microangiopathy process and non-enzymatic glycosylation of tissue proteins, induced by chronic hyperglycemia, thereby rendering the lung a "target organ" in diabetic patients.[3]

The alveolar capillary network is the largest microvascular organ (surface area 140 m2) and receives the entire cardiac output. As the pulmonary reserves are larger, the symptoms and disability from diabetes develop earlier in other organs than in lung. Hence pulmonary function abnormalities remain clinically undetectable in diabetic patients for a long time. If patients exhibit subclinical PFT abnormalities then in context of acute or chronic lung diseases or pulmonary edema, the loss of pulmonary reserve may become clinically important. Hence, routine measures of airflow limitation may predict morbidity and mortality in patients with diabetes and concurrent lung disease.

Current research aimed to study pulmonary function by spirometry in patients with diabetes mellitus and compare with non-diabetic healthy controls and to study association of pulmonary function in diabetes patients to disease duration and Hba1c level.

MATERIAL AND METHODS

The study was a hospital-based case-control study, done between 1st July, 2018 and 30th June, 2019 in the Department of Medicine of Assam Medical College and Hospital. Prior to commencement of the study approval from the Institutional Ethics Committee (H) of Assam Medical College and Hospital, Dibrugarh was taken.

Forty five patients who were diagnosed cases of Diabetes Mellitus admitted in Department of Medicine in Assam

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Medical College & Hospital, Dibrugarh were taken as cases. Controls were forty five non-diabetic apparently healthy individuals with similar characters as cases, regarding age group, sex and with similar exclusion criteria as the study group.

All the cases and controls were given an explanation of the study and informed written consent were taken from them or their attendants before enrollment into the study.

Inclusion criteria
- Diagnosed cases of diabetes mellitus for duration of more than 5 years

Exclusion criteria
- History of smoking,
- Acute or chronic respiratory disease,
- History of occupational exposure affecting lung function,
- Neuromuscular, cardiovascular or end stage kidney disease
- Physical disability that may affect lung function as kyphoscoliosis, pectus excavatum and pectus carinatum.
- Obese persons (BMI more than 30 kg/m2).
- Patients contraindicated for doing spirometry such as recent myocardial infarction, pneumothorax, haemoptysis of unknown origin, recent eye, thorax or abdominal surgery, presence of an acute disease process that might interfere with test performance (e.g. nausea, vomiting)
- Patients who refused to give written informed consent.

A detailed clinical history, physical examination and investigations were done in all the patients and filled-up in a predesigned proforma. An elaborate history was taken in each patient with special reference to the points concerning diabetes mellitus, duration of diabetes, age of onset of diabetes, complications of diabetes, to rule out any acute or chronic respiratory illness, cardiac and neuromuscular abnormality. History of smoking, occupational exposure history affecting lung function, history of recent myocardial infarction, pneumothorax, haemoptysis of unknown origin, recent eye, thorax, abdominal surgery were enquired.

A detailed general physical examination was carried out with special emphasis on weight, height and BMI. Systemic examination was done with weightage on every system affected by diabetes.

FBS, PPBS, HbA1c levels, Electrocardiogram and Echocardiography and chest x-ray was done for every patient. Spirometry was done for both cases and controls.

Estimation of blood glucose was done by Glucose oxidase and Peroxidase method in vitros 5600 integrated system.

Estimation of Glycated Hemoglobin (HbA1c) by high-performance liquid chromatography (HPLC assay) using the Biorad D10 Analyzer which employs cation – exchange chromatography.

Spirometry was performed by using a computerized system, Spirolab II (made in Italy), MIR. It was performed according to the recommendations by the American Thoracic Society regarding the technical considerations, standardization between laboratories and maneuver in a quiet room in sitting position.[4] Tests were repeated for minimum 3 times and best values for interpretation were taken. Measured parameters were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF). The FEV1/FVC ratio was calculated. The values expressed as percentage of the predicted normal value were calculated for these parameters. The test result with the highest sum of the forced vital capacities (FVC) and forced expiratory volume in 1 second (FEV1) from individual maneuvers was included in the data analysis.

STATISTICAL ANALYSIS

The statistical analysis of data was performed using the computer program, Statistical Package for Social Sciences (SPSS for Windows, version 20.0. Chicago, SPSS Inc.) and Microsoft Excel 2010. Results on continuous measurements are presented as mean ± standard deviation are compared using student t test. Discrete data are expressed as number (%) and are analysed using Chi square test and Fischer's exact test (where the cell counts were <5 or 0). Pearson's correlation coefficient (r) was used to measure the associations among continuous variables. For all analyses, the statistical significance was fixed at 5% level (p value <0.05).

RESULTS

The mean age for all cases was 44.24 ± 13.10 years, whereas the mean age for all controls was 44.33 ± 13.96 years. The maximum age and the minimum was 70 years and 16 years for cases and 72 years and 15 years for control respectively. The percentage of the male and female in both the groups were 64.44% (29) and 35.56%(16) respectively. The male: female ratio in both the groups was 1.81:1. The mean BMI of cases was 22.33±3.95 kg/m2 and controls was 23.43±2.37 kg/m2 and the difference was statistically insignificant. Out of 45 diabetes patients, 34 (75.56%) were diagnosed for 5 - ≤10 years and 11 (24.44%) were diagnosed for >10 year. 11 (24.44%) were Type 1 DM and 34 (75.56%) were Type 2 DM. 10 (22.22%) cases were with well controlled diabetes (HbA1c ≤ 7) whereas 35 (77.78%) cases were having uncontrolled diabetes (HbA1c >7). The mean HbA1c was 9.75 ± 2.62.

The spirometry parameters were significantly reduced in diabetic subjects compared with controls. 57.78% of cases had restrictive type of spirometry and none had obstructive or mixed pattern of spirometry and the rest had normal pulmonary function.

Patients with duration of diabetes >10 years had higher ventilator dysfunction than the patients with duration of diabetes of 5 – ≤10 years, although there was no significant difference. A negative correlation was found between the PFT parameters and duration of diabetes but the correlation was weak and not significant.

Regarding Hba1c level, there was a no significant difference

		Case	Control	P value
Age		44.24±13.10years	44.33±13.96years	0.97
BMI		22.33±3.95kg/m2	23.43±2.37kg/m2	0.11
Gender	Male	29(64.44%)	29(64.44%)	-
	Female	16(35.56%)	16(35.56%)	-
Hba1c	≤7	10 (22.22%)	-	-
	7	35 (77.78%)	-	-
Duration of	5 - ≤10 years	34 (75.56%)	-	-
Diabetes	>10 years	11 (24.44%)	-	-
Table-1: Physical characteristics of subjects				

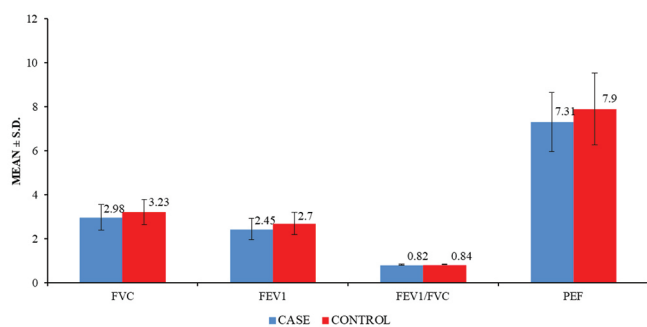| PFT parameters	Case (Mean±S.D.)	Control (Mean±S.D.)	p value
FVC	2.98 ± 0.59	3.23 ± 0.57	0.0418
FEV1	2.45 ± 0.49	2.70 ± 0.50	0.0179
FEV1/FVC	0.82 ± 0.02	0.84 ± 0.02	0.0036
PEF	7.31 ± 1.34	7.90 ± 1.64	0.0272
Table-2: Comparison of spirometry parameters in case and control			

PFT parameters	Duration of diabetes		P value
	5—≤10 years (Mean ± S.D.)	> 10 years (Mean ± S.D.)	
FVC	3.00 ± 0.52	2.93 ± 0.78	0.7784
FEV1	2.47 ± 0.44	2.40 ± 0.64	0.7471
FEV1/FVC	0.82 ± 0.02	0.82 ± 0.01	0.6410
PEF	7.38 ± 1.32	7.11 ± 1.44	0.5915
Table-3: Spirometry in cases according to the duration of diabetes			

PFT parameters	HBA1C		P value
	≤7 (Mean ± S.D.)	> 7 (Mean ± S.D.)	
FVC	2.84 ± 0.58	3.04 ± 0.59	0.3524
FEV1	2.33 ± 0.51	2.51 ± 0.49	0.3308
FEV1/FVC	0.82 ± 0.02	0.82 ± 0.02	0.2868
PEF	6.87 ± 1.39	7.47 ± 1.31	0.2439
Table-4: Spirometry in cases according to HBA1C level			

Figure-1: Comparision of spirometry parameteres in case and control

in spirometry parameters revealed no significance between patients with Hba1c level >7 and patients with Hba1c level≤7. Although a negative correlation was found between the spirometry parameters and Hba1c level but the correlation was weak and not significant.

DISCUSSION

The link between diabetes mellitus and pulmonary function is not fully understood. The association between diabetes mellitus and pulmonary function has been attributed to a number of suggested mechanisms including chronic inflammation, non-enzymatic glycosylation of proteins, microangiopathy of the alveolar capillaries, mechanical effects of central obesity and changes in body composition and impaired nitric oxide metabolism.

Defective pulmonary function seen in diabetes can be due to diabetic microangiopathy in lungs. This is evidenced by autopsy findings in human diabetic subjects which show thickening of alveolar epithelia, pulmonary capillary basal lamina, centrilobular emphysema, and pulmonary microangiopathy.[5] The diffusing capacity for carbon monoxide is reduced in diabetes. This may be due to thickened alveolar epithelium and pulmonary capillary basal laminae in diabetic patients.[6]

The potential mechanism of decreased lung function can also be non-enzymatic glycosylation of proteins, such as collagen in the lungs and chest wall. This glycosylation leads to irreversible collagen cross-linking, rendering to decreased proteolysis and accumulation of collagen in lung connective tissue.[7] The glycosylation process occurs in the early stages of diabetes, when hyperglycemia is most pronounced until new equilibrium is reached at lower turnover rate of collagen. Chronic hyperglycemia causes fibrous tissue formation in the chest wall and bronchial tree protein by non-enzymatic glycation. This may cause reduced compliance of the lungs.[8] Diabetes mellitus is also associated with poor skeletal muscle strength due to increased protein catabolism. Thus, respiratory muscle endurance decreases in diabetes mellitus. The patients with diabetes complicated by autonomic neuropathy may have decreased lung function due to impaired control of bronchomotor tone. Resting vagal tone is depressed which explains the depressed bronchoconstrictory response to both cholinergic stimuli and hyperventilation with cold air.[7] Thus, there is a complex alteration of both control of ventilation and bronchomotor tone in diabetic patients with automatic neuropathy.

Hyperglycemia causes over production of mitochordrial superoxides and reduction in anti-oxidant defence of the lungs.[8] The glycation of proteins can lead to oxidative stress by direct release of O_2 and H_2O_2, and activation of phagocytes through a specialized receptor for advanced

glycosylation end products. Oxidants include reactive oxygen species (ROS), reactive nitrogen species, sulphur centered radicals and others. Phagocytic cells generate large amounts of NO and ROS. In diabetes there are alterations in antioxidant enzymes, impaired glutathione metabolism, and decreased ascorbic acid levels. Nitric oxide is produced by nitric oxide synthase (NOS). Three different forms of NOS expressed in lungs are neuronal (n NOS), endothelial (e NOS), and inducible (i NOS). Excessive NO produced by i NOS and its potent oxidative derivative peroxynitrate via oxidation, hydroxylation, and nitration is involved in acute lung injury which may also be an explanation of decreased lung function.[8]

In our study the mean value of FVC, FEV1, and PEF in cases were found to be less than the control group and the difference was statistically significant. A negative correlation was found between the PFT parameters and Hba1c level and duration of diabetes but the correlation was weak and not significant.

There is cumulative data that demonstrate a pattern of ventilator dysfunction in T2DM with proportional decreases in forced vital capacity (FVC) and forced expiratory flow in 1s (FEV1) that are directly related to hyperglycemia.

In the study by Sreeja C.K et al., pulmonary function test was carried out in 20 Type 2 Diabetes mellitus and 20 Type 1 Diabetes mellitus patients and 40 subjects as controls. There was a significant reduction in FEV1/FVC% in both diabetes mellitus groups compared with controls.[9]

In a study by Muhammad Irfan et al., 128 subjects who were non-smokers and had no acute or chronic pulmonary disease were recruited. 64 of these subjects had DM and 64 were healthy matched controls. Diabetes patients showed a significant reduction in the forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and slow vital capacity (SVC), relative to non-diabetic controls.[10]

Mohankumar and Arulmozhi in 2005 studied pulmonary complications in elderly diabetics. They reported that in DM patients, total lung capacity, lung volume, and lung compliance are reduced, the central and peripheral airflows are reduced, and acceleration of aging process in pulmonary connective tissue is seen.[11]

Meta-analysis by van den Borst, et al., showed that Diabetes is associated with statistically significant impaired pulmonary function in a restrictive pattern. Results were irrespective of body mass index (BMI), smoking, diabetes duration, and HbA1c levels.[12]

The study by Shravya Keerthi G et al. in 2012, 50 Type 2 Diabetes Mellitus patients were taken as cases and 50 staff of Narayana medical college as control. The mean FVC, FEV1, FEV1/FVC, PEFR, FEF25-75%, MVV values are low in diabetics (p value <0.001) compared to non-diabetics and female diabetics showed greater decrease in PFT values than male diabetics.[13]

In the Korea National Health and Nutrition Examination Survey 2011 to 2013 by Hee Yeon Kim et al, 8,784 participants (including 1,431 diabetics) aged ≥ 40 years were studied. Subjects with diabetes had a higher prevalence of restrictive (18.4% vs. 9.4%, p < 0.001) and obstructive impairments (20% vs. 12.6%, p < 0.001) than those without diabetes. However, diabetes duration or glycated hemoglobin were found to have no association with pulmonary impairment in diabetes.[14]

Amal Abd El-Azeem et al. in 2013, concluded that predominant reduction in all the spirometric parameters in diabetic patients toward the restrictive pattern as well as there was significant deterioration in DLCO in comparison with healthy controls. FVC (p< 0.01), and FEV1/FVC% (p<0.001) were significantly lower in type1 diabetic patients in comparison to those of type II. Impairment of lung functions was obvious with a longer duration of diabetes.[15]

In a study by Swati H. Shah et al. in 2013, pulmonary function tests (PFTs) of 60 type 2 diabetic male patients and 60 normal healthy male controls aged 40-60 years were compared and associations between FVC and FEV1 and HbA1c and duration of illness in diabetic patients were analyzed. It was found that the PFTs were significantly decreased in diabetic patients compared with the healthy controls except FEV1/FVC. There was no correlation found between FVC and FEV1 and duration of illness as well as HbA1c.[16]

Dhiraj Kapoor et al in 2015 studied 90 cases and 90 matched controls. Patients with type 2 DM patients as compare to its controls were observed to have restrictive pattern of lung dysfunction. In addition it was found that long duration of DM was significantly (r: 0.39; P = 0.00) positively correlated with lung dysfunction.[17]

Simran Kaur et al in 2016 studied 50 diabetics and 50 matched apparently healthy volunteers. It was seen that there was significant reduction in all the PFT parameters (FVC%, FEV1% and FEV1/FVC) in diabetics as compared to controls. Also strong positive correlation was seen between fasting blood sugar and FEV1/FVC in diabetics.[18]

Limitation of the study is, spirometry was the only tool used to assess the pulmonary function. The whole range of tests for assessing pulmonary function would have yield better result, especially when done for a larger population.

Our study showed that there is significant pulmonary function impairment in diabetes patients as compared to controls. More than fifty percent of patients had restrictive pattern of pulmonary dysfunction. However, no significant association was found between the pulmonary dysfunction with Hba1c level and duration of diabetes in our study.

CONCLUSION

So, we may conclude that patients with diabetes mellitus have underlying pulmonary dysfunction and the assessment of pulmonary function is an important investigation. Early detection of functional impairment and its appropriate treatment will probably help to reduce morbidity and mortality especially in situation of acute on chronic lung diseases.

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